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THYROID SURGERY

Editors: Wen Tian, MD; Emad Kandil, MD, FACS, FACE

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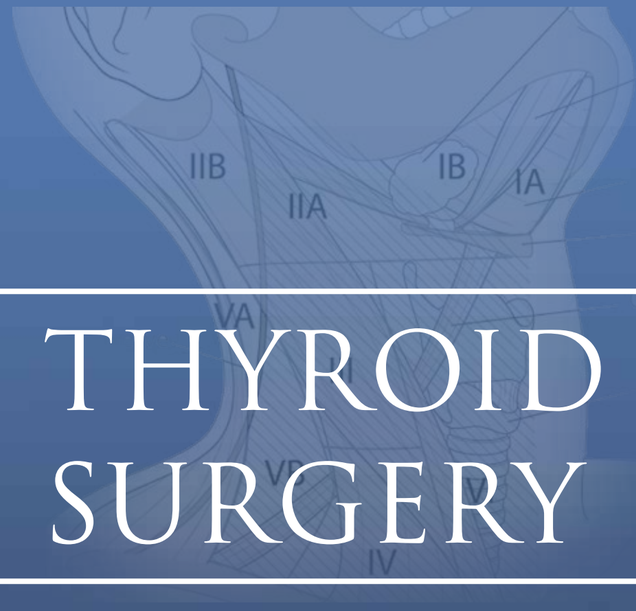

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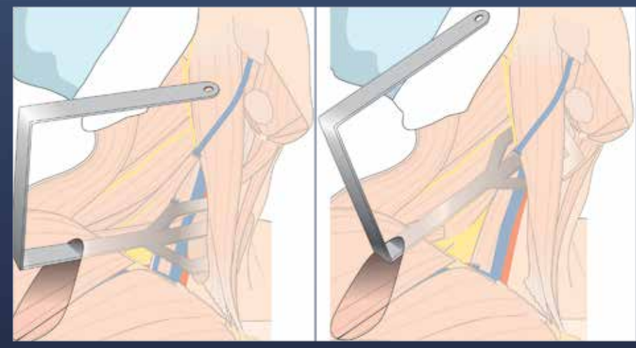

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Thyroid Surgery

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Foreword

Thyroid disease is one common and frequently occurring disease, which is very harmful to human health. Thyroid cancer is one of the most common endocrine malignancies, and also one of the few malignancies with ascending occurrence rates. Rapid development of economy in recent years has advanced the progress of medical technology, making more and more novel technologies widely applied. The treatments for thyroid disease have been also constantly updated and improved, of which surgery plays a quite significant role.

Over the last decade there has been a rapid expansion in the number of different surgical approaches available to patients undergoing thyroid/parathyroid surgery. These articles from the book *Thyroid Surgery* were written by the world known experts in the field of thyroid surgery. Specially, multiple articles are covering the range of most widely adopted remote access techniques and minimally invasive procedures. Several related procedures are also discussed, including robotic lateral neck dissection.

This book does not contain that definitive data that well establish the role of *Thyroid Surgery* in the very field, while providing readers with the up-to-date knowledge and advanced techniques in the area of thyroid surgery, adding the precious experience of experts across the world. From the advance of the basic research of thyroid disease to the spectacular progress of thyroid surgery, from neck dissection in differentiated thyroid carcinoma to video-assisted and robotic-assisted thyroid/parathyroid surgery, the book will show readers a vivid picture of the recent progress of thyroid surgery.

I'm of great honor to be invited to write this preface for this fantastic new book on thyroid surgery and here would like to congratulate the editors, Profs. Tian and Kandil, as well as the authors on the success of this forthcoming book. I believe this comprehensive collection of articles will be a valuable resource for all thyroid related practitioners, medical personals and scientists who devote their professions to science and patients. I also wish that readers could always find an article of your interest from this book.

Rong Li, MD
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Foreword

The last few decades have witnessed a continuous increase in the incidences of thyroid nodule and thyroid cancer. For instance, an estimated 62,450 new cases of thyroid cancer will be diagnosed in the United States in 2015, accounting for 3.8% of all the new tumor cases. Fortunately, the development and applications of new technology and diagnostic/therapeutic approaches have dramatically promoted the basic research and surgical procedures for thyroid cancer. Many novel thyroid surgeries (e.g. video-assisted surgeries and robotic surgeries) have emerged, and an increasing number of patients have received such surgeries in more hospitals. However, neck lymph node dissection for differentiated thyroid cancer remains a controversial procedure in terms of prophylactic central neck dissection, range of lateral neck dissection, and use of molecular markers (e.g. BRAF) for guiding dissection. Thus, a thorough understanding and awareness of these controversial issues will be helpful to inform the clinicians to develop the optimal treatment protocol and thus benefit the patients.

This new book, *Thyroid Surgery*, delivers the latest findings on thyroid nodules and thyroid cancer. Contributed by many top international experts, the book details the most debatable issues in this field. It is intended to update the knowledge and skills of thyroid surgery for physicians from departments of thyroid surgery, endocrine, nuclear medicine, and pathology. We hope our readers will find this book interesting and informative.

Lin Chen, MD
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Preface

We are very pleased to announce the launch of the book Thyroid Surgery, with the collective effort from the eminent thyroid experts around the world.

Since its first introduction, thyroid Surgery has developed for more than 100 years. Particularly in the past few decades, the technique of thyroid surgery becomes more and more matured and refined.

It is inspiring to witness thyroid Surgery has become the main treatment for thyroid cancer. However, limited by current understanding and evidence, thyroid Surgery still faces quite a lot of challenges. For example, it remains controversial regarding how to avoid the potential damage of recurrent laryngeal nerve during surgery and what is the indication for Subtotal thyroidectomy and total thyroidectomy. It is time for us to take a retrospective journey on thyroid Surgery with an outlook on its future.

Keeping that in mind, the book on thyroid cancer aims to be an operative manual and reference in clinical practice. Instead of only focusing on thyroid surgery and being didactic and pedantic, the book gives an overview on current evidence and the state-of-art in thyroid surgery with case presentation.

From basic Research of thyroid tumors to efficacy analysis of different surgical treatment, the book will also facilitate the translation from basic research to clinical practice.

We believe this textbook will set a basis for future consensus and guideline in thyroid surgery. Finally our sincere thanks go to all the authors for their valuable input that makes this collective work possible.

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Thyroid Surgery
(FIRST EDITION)

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Guideline

A benign genomic classifier for thyroid nodules with indeterminate cytology: a critical appraisal

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Alexander and colleagues recently published, in the New England Journal of Medicine, a 19 month prospective multicenter genomic classifier validation study for benign thyroid nodules with indeterminate cytology, involving 49 clinical sites, 3,789 patients, and 4,812 fine needle aspiration biopsy (FNAB) specimens. This study was sponsored by Veracyte Incorporated (Veracyte Inc. South San Francisco California U.S.A.) (1). The development of the FNAB-trained genomic classifier utilized was described in a prior Veracyte sponsored study published 2 years earlier, and was composed of 167 genes (142 genes in the main classifier and 25 genes to filter out rare neoplasms) (2). FNAB were sent to Veracyte for genomic analysis that was carried out on custom-built arrays, and performance on these custom arrays was validated with data from the Affymetrix Human Exon ST 1.0 arrays (the genomic profiling platform upon which the classifier was originally developed) (Affymetrix, Santa Clara California U.S.A.). A total of 367 FNABs (47 benign, 55 cancer, and 265 indeterminate (129 atypia or follicular lesion of undetermined significance, 81 follicular or Hurthle cell neoplasm, 55 suspicious for malignancy) were evaluated by the genomic classifier. For the 312 cases that had genomic data and reference standard data available their genomic classifier had a sensitivity of 87% (79-93%) and a specificity of 53% (46-60%), PPV 47% (39-54%), and NPV 90% (83-94%) for diagnosing thyroid lesions as "suspicious" for cancer. When the 265 indeterminate FNABs are considered alone, the classifier correctly identified 78 of 85 cancers as being "suspicious" for cancer and 93 of 180 benign lesions as being benign. Thus, in the indeterminate FNAB group the classifier had a sensitivity of 92% (84-97%), specificity of 52% (44-59%), a PPV of 47% (40-55%), and a NPV of 93% (86-97%). The reasons for the observed reduction in their genomic classifier specificity, when compared to their prior study (specificity 83.9%), was not elucidated upon by the authors. These investigators concluded that a more conservative, or a less surgically aggressive, management approach should be considered for most individuals who have indeterminate FNAB results and a benign genomic classifier diagnosis.

Based upon a sensitivity of 92%, there will be 8% of FNABs diagnosed as benign by the genomic classifier that will actually be cancer (false negatives). In their report the authors showed that 6/7 false negatives were due to inadequate sampling of thyroid nodules. It is not clear whether this is an inherent limitation of the FNAB based genomic test or if changes in their operating procedures could reduce this number. Based upon a test specificity of 52%, there will be 48% of patients that will be incorrectly diagnosed as "suspicious" for cancer (false positive) when they actually have benign disease. Thus, the high sensitivity (92%) and low specificity (52%) could lead to close to half of individuals with an indeterminate FNAB diagnosis, being given a false positive "suspicious" for cancer diagnosis. Therefore, a key question is whether a "suspicious" for cancer genomic classifier diagnosis lead to an increase in thyroid operations? Another major drawback of the genomic classifier is that its low positive predictive value (47%) does not allow surgeons to have confidence in tailoring their operative approach (i.e., total thyroidectomy and central neck dissection) for cancer. As well, will individuals classified as being "suspicious" for cancer by a genomic classifier, with a 47% PPV, undergo inappropriately aggressive thyroid surgery and central neck lymph node dissection?

In another recent study, also sponsored by Veracyte

Inc., Duick *et al.* reported on how a benign diagnosis from their genomic classifier (now named Afirma) influenced the decision of the endocrinologists and patients to proceed with a thyroid operation (3). Their genomic classifier is now termed the 'Afirma Gene Expression Classifier' (AGEC) and is described by these authors as a proprietary diagnostic test developed by Veracyte that is offered through a sole source, Clinical Laboratory Improvement Amendments (CLIA)-certified reference laboratory. As mentioned above the genomic classifier test classifies thyroid nodules diagnosed as being indeterminate by cytology as either benign (NPV 93%) or "suspicious" for cancer (PPV 47%). This study was carried out through survey of 51 endocrinologists at 21 practice sites that had requested >/= 3 molecular classifier tests from Veracyte. They found that the historical operative rate of 74% for cytologically indeterminate nodules fell to 7.6% after the molecular classifier was adopted into their practice (P<0.001). The rate of surgery on cytologically indeterminate nodules that were diagnosed as benign by the genomic classifier did not differ from the historically reported rate of operation on benign thyroid nodules (P=0.41). In this report the influence of a molecular classifier test with a "suspicious" for cancer diagnosis was not specifically evaluated, though the authors commented that the cost savings from not operating on the genomic classifier 'benign' patients may partially offset the costs of any possible increase in the rate of operation for genomic classifier diagnosed "suspicious" for cancer patients. This comment is worrisome, and the impact of their molecular classifier "suspicious" for malignancy diagnosis on rates of thyroid surgery and costs, given the genomic classifier specificity being 53%, is concerning and warrants further study.

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Overall, the report by Alexander *et al.* that describes a multicenter clinical study evaluating a benign thyroid tumor genomic classifier for lesions with an indeterminate FNAB diagnosis, despite its limitations, is exciting not only because it serves to validate a diagnostic test with a high NPV, but because it is one of the few published studies that demonstrates the feasibility of conducting a multicenter thyroid cancer diagnostic molecular marker trial. While ultimately the clinical acceptance, implementation, and economic impact of this or some other thyroid cancer molecular diagnostic test are yet to be determined, it seems likely that such tests for thyroid cancer are here to stay, and over time will likely become important adjuncts to traditional thyroid cytomorphology.

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References

1. Alexander EK, Kennedy GC, Baloch ZW, et al. Preoperative Diagnosis of Benign Thyroid Nodules with Indeterminate Cytology. N Engl J Med 2012;367:705-15.
2. Chudova D, Wilde JI, Wang ET, et al. Molecular classification of thyroid nodules using high-dimensionality genomic data. J Clin Endocrinol Metab 2010;95:5296-304.
3. Duick DS, Klopper JP, Diggans JC, et al. The Impact of Benign Gene Expression Classifier Test Results on the Endocrinologist-Patient Decision to Operate on Patients with Thyroid Nodules with Indeterminate Fine-Needle Aspiration Cytopathology. Thyroid 2012. [Epub ahead of print].

Preoperative diagnosis of benign thyroid nodules with intermediate cytology

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Thyroid nodules are very common and are diagnosed in over 7% of the adult population. However, most thyroid nodules are benign and only 5% harbor malignancy. Therefore it is of utter importance to develop safe and accurate tools that distinguish between benign nodules and malignant ones. At present, fine needle aspiration biopsy (FNAB) is considered the gold standard diagnostic tool for thyroid nodules. Despite a specificity of over 95%, indeterminate FNAB results are obtained in 15-30% of the cases. Indeterminate FNAB results include follicular lesions of unknown significance (FLUS), follicular lesions or neoplasms (FL or FN), and suspicious for malignancy. These specific FNAB results carry a malignancy risk of 5-15%, 15-30%, and 60-75% respectively (1). Such indeterminate FNAB results face both the patient and the surgeon with a treatment dilemma and in most cases patients undergo diagnostic surgery even though the majority of the cases turn out to be benign. The development of new and more accurate preoperative diagnostic techniques in such cases can eliminate the need of unnecessary diagnostic surgery. This article is a research highlight of the new and developing diagnostic techniques for such lesions.

Immunohistologic biomarkers lack the sensitivity & specificity to differentially characterize the FNA indeterminate cytopathologic subgroups of atypia/FLUS from FN or from suspicious for malignancy categories. Additionally, there is significant overlap of immunohistologic markers between cytopathologically indeterminate nodules and differentiated thyroid cancer (2).

The first method that demonstrated improved accuracy was ***testing for genetic alterations***. Papillary thyroid carcinomas contain BRAF and RAS point mutations, as well as RET/PTC and TRK rearrangements. These mutations are identified in up to 70% of papillary thyroid cancers (PTCs). About 70-75% of follicular thyroid cancers (FTCs) also carry mutually exclusive genetic alterations, namely, RAS point mutations or PAX8/PPARγ rearrangements. A recent meta-analysis revealed that out of 581 BRAF-positive thyroid FNAB samples, 580 (99.8%) were papillary carcinomas. Moreover, 15-39% of reported BRAF-positive FNAB samples were indeterminate or nondiagnostic on cytology, suggesting that BRAF also aids in the diagnosis of malignancy in nodules with indeterminate cytology. In FNAB samples, the detection of clonal RET/PTC is a strong indicator of papillary carcinoma, which is especially helpful for samples that are indeterminate on cytology or inadequate for cytologic evaluation (3). To assess the role of ancillary molecular studies in the diagnosis of thyroid lesions with "follicular lesion of undetermined significance/atypia of undermined significance" (FLUS/AUS) cytology, Ohori *et al.* evaluated 117 thyroid FNAB samples for BRAF and RAS mutations and RET/PTC and PAX8/PPARγ rearrangements. Molecular analysis and subsequent surgical resections demonstrated that the cancer probability for FLUS/AUS with molecular alteration was 100% while that without molecular alteration was 7.6%. These findings suggest that molecular testing of FNAB samples may refine FLUS/AUS cases into low- and high-risk categories, thereby increasing diagnostic accuracy (4).

More recently, numerous reports discussed the role of ***microRNA (miR) biomarkers*** in malignant thyroid cancer. miRs are short non coding RNA molecules that usually

function as negative regulators for the expression of protein encoding genes and are involved in cell development and apoptosis and may act as tumor suppressor genes or oncogenes. Dysregulation of different miRs have been described in various thyroid cancers including PTC, FTC, Medullary thyroid cancer (MTC), and anaplastic thyroid cancer (ATC). miRs can characterize aberrantly activated metabolic pathways in malignant thyroid nodules. Protocols for miRs profile analysis are available for snap frozen tissues, formalin fixed paraffin embedded samples, and even cells obtained from FNAB (5). For miR analysis to be of diagnostic value, it should be extracted from cells obtained from FNAB. In a recent study using a panel of six miRs on a sample of 27 ex vivo FNAB, the accuracy for predicting PTC was 98% (6). Nevertheless, the accuracy for FTC is not as high and ranges between 70% and 90%. The added value of miR analysis in the evaluation of thyroid nodules with indeterminate FNAB results was also investigated with encouraging results that exceed the relatively low accuracy cytology results for these problematic scenarios. Yu *et al.* identified upregulated miRs in the serum of PTC patients and further demonstrated that levels decreased significantly after tumor excision (7). The diagnostic utility of miRs extracted from FNAB samples or from patients' serum is promising, however, it is limited by the high costs associated with the process.

One novel diagnostic technique that measures the expression of 167 genes has shown promise in improving preoperative risk assessment. A ***gene expression classifier (GEC)*** has been found to help identify nodules that are benign rather than malignant. The GEC uses the expression of 167 genes to classify nodules as either benign or suspicious. In a recent large prospective multicenter trial the GEC results were compared to histopathology of poperated nodules. The technique had a negative predictive value of 95% for aspirates classified as atypia of undetermined significance and 94% for aspirates classified as follicular neoplasms or suspicious for follicular neoplasms (8). This implied that thyroid nodules with these cytologic abnormalities and benign GEC results have a post test result probability of malignancy that is similar to the probability for nodules with cytologically benign features on FNA. The negative predictive value for aspirates with features of malignancy was lower (85%), and although the sensitivity was 100% for cytologically benign and cytologically malignant lesions, a specificity of 70% limits the use of the test in samples with benign cytologic features (8).

A unique technique of analysis is measurement of the ***Thyrotropin Receptor mRNA (TSHR mRNA)***. This technique measures the TSHR mRNA levels in the *blood* (derived from circulating thyroid cancer cells) and not on material obtained from a thyroid nodule by FNAB. This technology was combined with diagnostic thyroid ultrasonography and ultrasound guided FNAB and utilized to aid preoperative diagnosis of differentiated thyroid cancer. Eventually, the use of TSHR mRNA was reported for postoperative surveillance in follicular cell derived thyroid cancer to detect thyroid cancer persistence and recurrence. More recently, a large prospective study reported the validation of data for TSHR mRNA in both preoperative management of follicular neoplasms and the utility of the biomarker for thyroid cancer surveillance. It was found that when used in combination with diagnostic ultrasound and a FNAB result of follicular neoplasm, it has a sensitivity of 97% and specificity of 88% for predicting thyroid cancer (9).

To summarize, the preoperative evaluation of a thyroid nodule still relies on FNAB and indeterminate FNAB cytology results pose a diagnostic and management challenge. Diagnostic surgery is most commonly performed for such indeterminate results and turns out to be unnecessary in the majority of the cases. However, the above mentioned technologies and techniques seem to be promising and may very well replace diagnostic surgery in the near future.

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References

1. Cibas ES, Ali SZ. The Bethesda System for Reporting Thyroid Cytopathology. Thyroid 2009;19:1159-65.
2. Duick DS. Overview of molecular biomarkers for enhancing the management of cytologically indeterminate thyroid nodules and thyroid cancer. Endocr Pract 2012;18:611-5.
3. Bhaijee F, Nikiforov YE. Molecular analysis of thyroid tumors. Endocr Pathol 2011;22:126-33.
4. Ohori NP, Singhal R, Nikiforova MN, et al. BRAF mutation detection in indeterminate thyroid cytology specimens: Underlying cytologic, molecular, and pathologic characteristics of papillary thyroid carcinoma. Cancer Cytopathol 2012. [Epub ahead of print].
5. Mazeh H. MicroRNA as a Diagnostic Tool in Fine-

Needle Aspiration Biopsy of Thyroid Nodules. Oncologist 2012;17:1032-8.
6. Mazeh H, Mizrahi I, Halle D, et al. Development of a microRNA-based molecular assay for the detection of papillary thyroid carcinoma in aspiration biopsy samples. Thyroid 2011;21:111-8.
7. Yu S, Liu Y, Wang J, et al. Circulating microRNA profiles as potential biomarkers for diagnosis of papillary thyroid carcinoma. J Clin Endocrinol Metab 2012;97:2084-92.
8. Alexander EK, Kennedy GC, Baloch ZW, et al. Preoperative Diagnosis of Benign Thyroid Nodules with Indeterminate Cytology. N Engl J Med 2012;367:705-15.
9. Milas M, Shin J, Gupta M, et al. Circulating thyrotropin receptor mRNA as a novel marker of thyroid cancer: clinical applications learned from 1758 samples. Ann Surg 2010;252:643-51.

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The role of noncoding RNA in thyroid cancer

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Abstract: Increasing noncoding RNAs (ncRNAs) were found to show abnormal expression patterns in various human cancers. Based on size, ncRNAs are generally grouped into two categories, short noncoding RNAs and long noncoding RNAs (lncRNAs) of greater than 200 nt. Small noncoding RNAs include microRNAs, piRNAs, snoRNAs, and endogenous siRNAs, out of the role of miRNAs in development and cancer biology has been extensively studied. In contrast to small noncoding RNAs like miRNAs, long noncoding RNAs are much less known concerning their functions in human cancers especially in thyroid cancer. The present review highlighted the roles of miRNAs and newly discovered lncRNAs in thyroid development, tumorigenesis, metastasis, and their clinical implication.

Keywords: MicroRNA; long noncoding RNA; thyroid cancer

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Introduction

Less than 2% the mammalian genome are protein coding genes and over 90% of genome represent noncoding RNAs (ncRNA) which are transcribed but do not encode proteins. Despite of initial controversy regarding their biological characters, increasing evidence had showed that ncRNAs are highly regulated and functional (1). Two categories of ncRNA were grouped according to their size, short ncRNAs and long ncRNAs (lncRNA). The short ncRNA includes transcripts such as miRNAs, transfer RNAs (tRNAs), small interfering RNAs (siRNAs), piwi-interacting RNAs (piRNAs) and some ribosomal RNAs, out of which miRNAs were most extensively studied in human cancers. Although being not well understood in human cancers, long noncoding RNAs (>200 nt) have recently forwarded to the forefront of noncoding RNA research. Thyroid cancer is the most common malignant tumor of the endocrine organs whose incidence has been steadily increased over the past few decades (2). The deregulation of ncRNA expression is believed to be an important regulator of tumor development and progression of thyroid cancer. The present review highlighted the roles of miRNAs and newly discovered lncRNAs in thyroid development, tumorigenesis, metastasis, and their clinical implication.

MiRNAs and thyroid cancer

MicroRNAs (miRNAs) represent a class of short endogenous noncoding RNAs regulating gene expression at mRNA post-transcriptional level in many biological and pathological processes, including proliferation, apoptosis, and differentiation (3). Increasing evidence has revealed the involvement of mi-RNA in human malignancies. The deregulation of miRNA expression is believed to be an important regulator of tumor development and progression. Due to its repression effect, deregulation of specific mi-RNA could lead to the repression of tumor suppressor gene and/or increase of oncogene expression. Consequently, these molecular changes favor cell proliferation, differentiation and apoptosis. MicroRNA expression profiling of human tumors has identified signatures associated with diagnosis, staging, prognosis, and response to treatment (4). MiRNA expression profiles resulted in being different not only between tumors and normal tissues but also between different subtypes of tumors and between primary tumors

and metastatic tumors.

A comprehensive analysis by microarray found that a significant miRNA signature with thyroid cancers. Out of numerous differentially expressed miRNAs in thyroid cancer, three miRNAs including miR-221, -222 and -181b were extensively studies in thyroid cancers (5). Studies demonstrated that miR-221, -222, and -146 are transcriptionally up-regulated in PTC tumors in comparison with normal thyroid tissue (6). Functional study showed that miR-221 and miR-222 are endogenous regulators of $P27^{Kip1}$ protein expression, which represents a very important regulator of cell cycle (7). What is concomitant with up-regulation of the three miRNAs is the dramatic loss of KIT transcript and Kit protein, both of which involves in the pathogenesis of thyroid cancer. Microarray analysis of PTCs showed numerous genes were directly and indirectly regulated by miR-221 and studies both *in vitro* and *in vivo* using the bioluminescence imaging system confirmed the down-regulation of HOXB5 by endogenous or exogenous miR-221 (8). Significant down-regulation of miR-1 was detected in a panel of thyroid tumors compared with normal thyroid tissues and miR-1 as a tumor suppressor targeting CCND2, CXCR4, and SDF-1 genes, suggesting its ability to inhibit thyroid carcinoma cell proliferation and migration (9).

In contrast to mRNAs, mature miRNAs are comparatively stable and remain largely intact in routinely collected, formalin-fixed paraffin-embedded (FFPE) clinical tissues (10). The ability to detect miRNA profiles in FFPE tissues implicated a great opportunity to perform the large retrospective analyses necessary to confirm the diagnostic role and investigate the prognostic significance of miRNA profiles. Numerous studies have demonstrated that the potential diagnostic value of mi-RNA expression signatures in thyroid cancer, especially for indeterminate results on fine-needle aspiration biopsy (FNAB) samples. FNAB is currently the most widely used tool for the preoperative diagnosis of thyroid lesions with limitation for up to 30% indeterminate cases (11). Investigation of miRNA expression pattern for differential diagnosis of thyroid neoplasms in fine needle aspiration biopsy samples is feasible and may improve the accuracy of FNAB cytology. Pallante *et al.* (5) investigated that expression of miR-221, -222 and -181b had 5- to 35-fold differential in FNAB samples of PTCs compared with other thyroid nodules. Overexpression of four miRNAs (miR-100, miR-125b, miR-138, and miR-768-3p) was detected in malignant samples of follicular origin and only miR-125b was significantly overexpressed in FTC samples (12). These findings suggested that specific miRNAs can be potential diagnostic tools with high accuracy in both surgical and preoperative FNA samples. Mazeh *et al.* (13) found that miR-221 was the most favorable miRNA in differentiating benign from malignant thyroid pathology with specificity (100%), negative (96%) and positive (100%) predictive value, and accuracy (98%) respectively. Given the high negative predictive value of miR-7 (100%), patients may benefit from the result based on the predictor and avoid an immediate diagnostic thyroidectomy.

Mi-RNA expression profiles have a close association with clinicopathological features which help determine optimum management of thyroid cancer. A recent study suggested that miRNA signature can distinguishes the degree of PTC aggressiveness (14). The results showed that four miRNAs (miR-146b, miR-222, miR-34b, miR-130b) were differentially expressed in aggressive in comparison with nonaggressive PTCs. Additionally, miR-146b was demonstrated to have a close association with aggressive behavior of PTC among BRAF-positive tumors, which further refine the prognostic importance of BRAF. Similar correlation was observed between downregulated miRNAs (miR-34b and miR-1) and higher MET expression in aggressive PTC. Chou *et al.* (15) uncovered that overexpression of miR-146b, miR-221, and miR-222 were significantly associated with extra-thyroidal invasion in PTCS. MiRNA-100 was observed to have a significantly expression level between T1 and T4 tumors (16). Schwertheim *et al.* (17) reported that poorly differentiated thyroid carcinoma had a distinct mi-RNA expression profile in comparison with both PTC and ATC, suggesting that deregulation of some miRNAs may take part in selecting a subset of PTC progressing to PDTC.

LncRNAs and thyroid cancer

Increasing studies suggest that lncRNAs constitute an important component of tumor biology, representing regulatory functions including modulation of apoptosis and invasion, reprogramming of induced pluripotent stem cells, marker of cell fate and parental imprinting. Deregulation of individual lncRNA expression not only involve in development and progression of specific cancers, but also be significant molecules for clinical implication (18). LncRNAs utilize varied mechanism to regulate gene expression. In general, the mechanism lncRNA regulating gene expressing could be transcriptional or post-

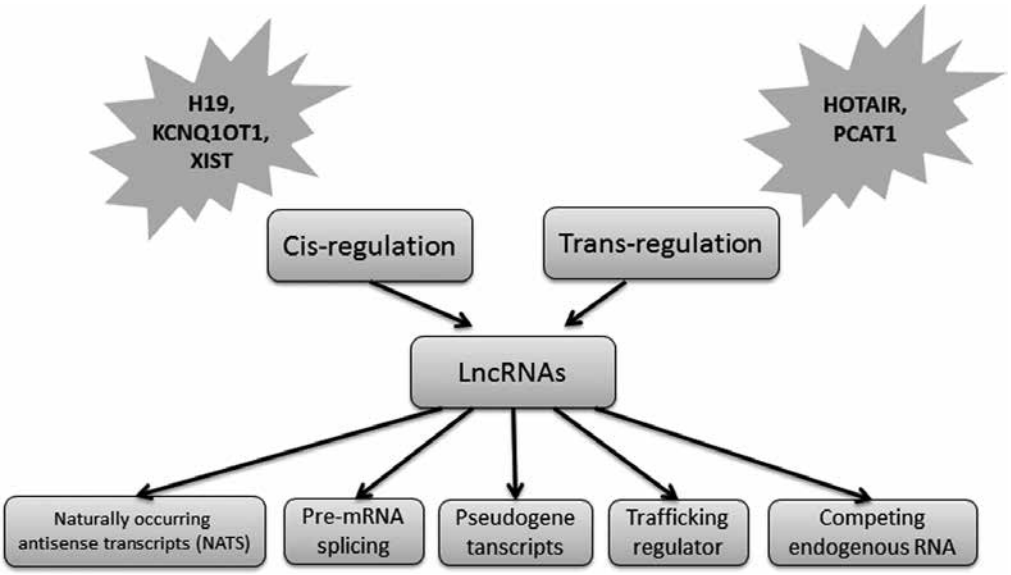

Figure 1 Schematic mechanisms of lncRNAs function. Generally, lncRNAs can regulate gene expression transcriptionally or post-transcriptionally. Under cis- and trans-regulatory mechanism, lncRNAs target genomically local and distant genes respectively. The post-transcriptional mechanisms include naturally occurring antisense transcripts (NATS), pre-mRNA splicing, pseudogene trascripts, trafficking regulator and competing endogenous RNA

transcriptional. Cis- and trans-regulation are two main transcriptional regulations, under which lncRNAs can target genomically local and distant genes respectively. The post-transcriptional regulatory mechanism is involved in post-transcriptional processing of mRNAs, including splicing, editing, trafficking, translation and degradation. Recently, a new regulatory mechanism has been revealed that lncRNA can function as competing endogenous RNA (termed ceRNA) for shared miRNAs (19,20). ceRNAs showed a post-transcriptional regulatory role in miRNA molecules' distribution on the targets. The schematic of lncRNAs was illustrated in *Figure 1*.

Out of numerous lncRNAs, a few well characterized lncRNAs to date such as HOTAIR, H19, MALAT1, Xist, KCNQ1OT1, AIR, and Evf-2 were extensively studied in human cancers. HOTAIR (HOX Antisense Intergenic RNA) can distally regulate the chromosomal domain on HOXD locus via physical interaction of its 5' domain with PRC2 methylase and in turn result in silencing of the HOXD gene (21). HOTAIR is found to be significantly up-regulated in breast cancer and hepatocellular carcinoma and can be served as an independent predictor of prognosis (18,22). H19, one of the imprinting-associated lncRNAs, has been observed to be deregulated in hepatocellular and bladder cancer and involve in both oncogenic and tumor suppressive qualities. The diverse roles of H19 in cancers may be demonstrated due to its direct activation by cMYC and down-regulation by p53 (23,24). Abnormal expression of MALAT1 was investigated in various human cancers including breast, lung, pancreas, prostate, liver, colon, and ovarian cancer (25,26). Silencing of MALAT1 expression in lung cancer cells can impair cell migration ability by regulation of motility-related genes.

The role of lncRNAs in thyroid cancer is just beginning to be elucidated and there is a long way to go. Most recently, a genome-wide association studies (GWAS) addressed the predisposition to papillary thyroid cancer (PTC), out of which two SNPs (rs965513 and rs944289) were addressed to have highly significant association with PTC located in 9q22.33 and 14q13.3 respectively (27-30). A long noncoding RNA gene termed Papillary Thyroid Carcinoma Susceptibility Candidate 3 (PTCSC3) located 3.2 kb downstream of rs944289 at 14q.13.3 (31). PTCSC3 expression was found to be strictly thyroid-specific and be dramatically down-regulated in both thyroid tumor tissues and thyroid cell lines. However, the function of PTCSC3 in thyroid cancer is still unclear. Yoon *et al.* (32) reported that down-regulation of a novel gene, NAMA (noncoding RNA associated with MAP kinase pathway and growth arrest) was highly associated with the activating BRAF mutation

V600E in papillary thyroid cancer.

Up to date, only a small portion of lncRNAs has been identified and the implication of lncRNAs in tumorigenesis, metastasis, and progression remain to be further investigated. LncRNAs have emerged as important regulatory molecules in development and progression of thyroid cancer. Given the expression profiling of lncRNAs in human cancers is not fully reported, study of lncRNAs in thyroid cancer is becoming an attractive field, which will lead to new markers of cancer diagnosis, prognosis as well as novel therapeutic targets.

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References

1. ENCODE Project Consortium, Birney E, Stamatoyannopoulos JA, et al. Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project. Nature 2007;447:799-816.
2. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. JAMA 2006;295:2164-7.
3. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell 2004;116:281-97.
4. Lu J, Getz G, Miska EA, et al. MicroRNA expression profiles classify human cancers. Nature 2005;435:834-8.
5. Pallante P, Visone R, Ferracin M, et al. MicroRNA deregulation in human thyroid papillary carcinomas. Endocr Relat Cancer 2006;13:497-508.
6. He H, Jazdzewski K, Li W, et al. The role of microRNA genes in papillary thyroid carcinoma. Proc Natl Acad Sci U S A 2005;102:19075-80.
7. Visone R, Russo L, Pallante P, et al. MicroRNAs (miR)-221 and miR-222, both overexpressed in human thyroid papillary carcinomas, regulate p27Kip1 protein levels and cell cycle. Endocr Relat Cancer 2007;14:791-8.
8. Kim HJ, Kim YH, Lee DS, et al. In vivo imaging of functional targeting of miR-221 in papillary thyroid carcinoma. J Nucl Med 2008;49:1686-93.
9. Leone V, D'Angelo D, Rubio I, et al. MiR-1 is a tumor suppressor in thyroid carcinogenesis targeting CCND2, CXCR4, and SDF-1alpha. J Clin Endocrinol Metab 2011;96:E1388-98.
10. Tetzlaff MT, Liu A, Xu X, et al. Differential expression of miRNAs in papillary thyroid carcinoma compared to multinodular goiter using formalin fixed paraffin embedded tissues. Endocr Pathol 2007;18:163-73.
11. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167-214.
12. Vriens MR, Weng J, Suh I, et al. MicroRNA expression profiling is a potential diagnostic tool for thyroid cancer. Cancer 2012;118:3426-32.
13. Mazeh H, Mizrahi I, Halle D, et al. Development of a microRNA-based molecular assay for the detection of papillary thyroid carcinoma in aspiration biopsy samples. Thyroid 2011;21:111-8.
14. Yip L, Kelly L, Shuai Y, et al. MicroRNA signature distinguishes the degree of aggressiveness of papillary thyroid carcinoma. Ann Surg Oncol 2011;18:2035-41.
15. Chou CK, Chen RF, Chou FF, et al. miR-146b is highly expressed in adult papillary thyroid carcinomas with high risk features including extrathyroidal invasion and the BRAF(V600E) mutation. Thyroid 2010;20:489-94.
16. Vriens MR, Weng J, Suh I, et al. MicroRNA expression profiling is a potential diagnostic tool for thyroid cancer. Cancer 2012;118:3426-32.
17. Schwertheim S, Sheu SY, Worm K, et al. Analysis of deregulated miRNAs is helpful to distinguish poorly differentiated thyroid carcinoma from papillary thyroid carcinoma. Horm Metab Res 2009;41:475-81.
18. Gupta RA, Shah N, Wang KC, et al. Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. Nature 2010;464:1071-6.
19. Salmena L, Poliseno L, Tay Y, et al. A ceRNA hypothesis: the Rosetta Stone of a hidden RNA language? Cell 2011;146:353-8.
20. McCarthy N. Regulatory RNA: layer by layer. Nat Rev Genet 2011;12:804.
21. Rinn JL, Kertesz M, Wang JK, et al. Functional demarcation of active and silent chromatin domains in human HOX loci by noncoding RNAs. Cell 2007;129:1311-23.
22. Gibb EA, Brown CJ, Lam WL. The functional role of long non-coding RNA in human carcinomas. Mol Cancer 2011;10:38.
23. Barsyte-Lovejoy D, Lau SK, Boutros PC, et al. The c-Myc oncogene directly induces the H19 noncoding RNA by allele-specific binding to potentiate tumorigenesis. Cancer Res 2006;66:5330-7.

24. Lee MP, DeBaun MR, Mitsuya K, et al. Loss of imprinting of a paternally expressed transcript, with antisense orientation to KVLQT1, occurs frequently in Beckwith-Wiedemann syndrome and is independent of insulin-like growth factor II imprinting. Proc Natl Acad Sci U S A 1999;96:5203-8.
25. Lai MC, Yang Z, Zhou L, et al. Long non-coding RNA MALAT-1 overexpression predicts tumor recurrence of hepatocellular carcinoma after liver transplantation. Med Oncol 2012;29:1810-6.
26. Lin R, Maeda S, Liu C, et al. A large noncoding RNA is a marker for murine hepatocellular carcinomas and a spectrum of human carcinomas. Oncogene 2007;26:851-8.
27. Gudmundsson J, Sulem P, Gudbjartsson DF, et al. Common variants on 9q22.33 and 14q13.3 predispose to thyroid cancer in European populations. Nat Genet 2009;41:460-4.
28. Gudmundsson J, Sulem P, Gudbjartsson DF, et al. Discovery of common variants associated with low TSH levels and thyroid cancer risk. Nat Genet 2012;44:319-22.
29. Takahashi M, Saenko VA, Rogounovitch TI, et al. The FOXE1 locus is a major genetic determinant for radiation-related thyroid carcinoma in Chernobyl. Hum Mol Genet 2010;19:2516-23.
30. He H, Nagy R, Liyanarachchi S, et al. A susceptibility locus for papillary thyroid carcinoma on chromosome 8q24. Cancer Res 2009;69:625-31.
31. Jendrzejewski J, He H, Radomska HS, et al. The polymorphism rs944289 predisposes to papillary thyroid carcinoma through a large intergenic noncoding RNA gene of tumor suppressor type. Proc Natl Acad Sci U S A 2012;109:8646-51.
32. Yoon H, He H, Nagy R, et al. Identification of a novel noncoding RNA gene, NAMA, that is downregulated in papillary thyroid carcinoma with BRAF mutation and associated with growth arrest. Int J Cancer 2007;121:767-75.

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Expressions of D2-40, CK19, galectin-3, VEGF and EGFR in papillary thyroid carcinoma

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Objective: To investigate the expressions of D2-40, CK19, galectin-3, VEGF, and EGFR in papillary thyroid carcinoma and their clinical significances.

Methods: The expressions of D2-40, CK19, galectin-3, VEGF, and EGFR in 38 cases of papillary thyroid carcinoma and 12 cases of thyroid papillary hyperplasia were detected by immunohistochemical staining.

Results: The positive expression rates of D2-40, CK19, Galectin-3, VEGF and EGFR in patients with papillary thyroid carcinoma were all significantly higher than those in patients with thyroid papillary hyperplasia (all $P<0.05$). The expressions of D2-40, VEGF, and EGFR in papillary thyroid carcinoma with lymph node metastasis were significantly higher than those without lymph node metastasis ($P<0.05$). The expressions of GK19 and galectin-3 showed no significant differences between the papillary thyroid carcinomas with and without lymph node metastasis ($P>0.05$).

Conclusions: The detection of D2-40, CK19, galectin-3, VEGF, and EGFR is helpful for the diagnosis and differential diagnosis of papillary thyroid carcinoma and thyroid papillary hyperplasia.

Keywords: Thyroid neoplasms; papillary carcinoma; D2-40; CK19; galectin-3; VEGF; EGFR; immunohistochemis

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Introduction

Thyroid carcinoma accounts for 1% in systemic malignancies tumors (1), and they cause more deaths than all endocrine organs cancers. Early diagnosis and prompt treatment of thyroid cancer may maximize the survival rate and prolong survival time of patients. Papillary thyroid carcinoma (PTC) is the most common type of thyroid malignancies, approximately 75-85% of thyroid cancers are papillary carcinoma (1). It originates from the thyroid follicle cells. However, distinguishing papillary thyroid carcinoma from thyroid papillary hyperplasia is extremely challenging due to tumor heterogeneity. On occasion cases of papillary thyroid hyperplasia, in particular solitary nodules with papillary change, can simulate papillary thyroid carcinoma and cause a diagnostic dilemma (2). In addition, PTC gives frequently rise to nodal metastases via lymphatic vessels. Metastases occur in 20% of patients. Most commonly, they metastasize to the lungs, bones, liver and the brain.

In the recent years, the development of PTC is influenced by many factors including genetic alterations, growth factors, and physical agents such as radiation. Useful prognostic factors are needed for determining biologic behavior, providing an initial assessment. And a large number of molecular alterations have been used in differential diagnosis of papillary thyroid carcinoma. These biomarkers, such as D2-40, cytokeratin 19 (CK19), galectin-3, Vascular endothelial growth factor (VEGF), and epidermal growth factor receptor (EGFR) have been translated into clinical practice which offered significant improvement in the preoperative diagnosis of thyroid cancer (3-9).

D2-40 is a newly identified monoclonal antibody that

specifically binds to a 40,000 asialoglycoprotein M2A (tumor embryonic antigen). M2A is often used to mark lymphatic vessels distinguishably from vascular endothelial cells in laboratory settings as it is expressed in lymphatic endothelial cells instead of the vascular endothelium, so it is considered the most specific lymphatic marker (10). CK19 is a low molecular weight cytokeratin, and there have been several reports on its role in the diagnosis and differential diagnosis of thyroid benign and malignant lesions (11,12). Some investigators (13,14) also noted focal expression of CK19 in benign thyroid lesions. Galectin-3, a member of the B galactosil binding lectin family, for which normal functions include cell-cell regulation, growth, and differentiation in some studies. Finding that the sensitivity and specificity of galectin-3 were 93% and 100%, respectively, for papillary thyroid carcinoma, Finley (15) suggested that galectin-3 could contribute to the differentiation between benign and malignant thyroid papillary hyperplasia. His view was supported by Cvejić (16). VEGF is a main promoter of endothelial growth and migration, many studies have shown a correlation between expression of it and prognosis in several cancers, including well-differentiated thyroid cancer (7,17). Several aspects of the relationship between thyroid cancer and VEGF expression have been studied (18), including prognosis and the presence of metastasis. EGFR is a member of the Erb family of receptors which is abnormally activated in many epithelial tumors and is one of the receptors often found up-regulated in human carcinomas and often related to poor prognosis or advanced pathological stages (19). Yeh *et al*. have shown that EGFR is involved in cancer cell invasion (20).

However, few efforts have been made for a systematic detection of multiple antibodies. In this study, the purpose was to assess the significances of D2-40, CK19, galectin-3, VEGF and EGFR expression in the diagnosis and differential diagnosis of papillary thyroid carcinoma.

Materials and methods

Specimens and general information

The surgical specimens were collected from 38 patients with papillary thyroid carcinoma and 12 patients with benign thyroid disease with papillary hyperplasia in the Department of Pathology, Jilin City Central Hospital from January 2008 to December 2009. All of the thyroid lesion specimens were pathologically confirmed and classified according to the WHO classification criteria for thyroid tumors. The subjects were divided into: (I) papillary carcinoma group: 12 men and 26 women, at the age from 31 to 64 years (mean 49.7); (II) papillary hyperplasia group: 3 men and 9 women, at the age from 25 to 54 years (mean 42.4 years). All patients were treatment-naive and had complete clinical and pathological data. Each section was reviewed by two pathologists at the level of deputy director or above.

Experimental methods

Immunohistochemical method

Specimens were fixed in 10% neutral buffered formalin, processed conventionally, embedded in paraffin, cut into 4μm sections and stained with hematoxylin and eosin (HE). The immunohistochemical SP assay was conudcted following the instructions in the kit insert. Reagents used in this study included mouse anti-human D2-40, CK19, galectin-3, VEGF and EGFR (ready-for-use agents). All of the reagents, SP broad-spectrum ultra-sensitive kits and diamino benzidine (DAB) staining kits were purchased from Fuzhou Maixin Company. Phosphate buffered saline (PBS) was used as negative control in place of the primary antibody.

Determination of results

The galectin-3 positive signal was recognized when brownish-yellow granules were present in the cytoplasm, CK19-positive signal when in both the cytoplasm and cell membrane; EGFR-positive signal when in the cell membrane and cytoplasm, and VEGF-positive signal when in the cytoplasm. The positive status was further graded according to the proportion of positive cells as described in the Beesley classification method and the staining intensity, with a stained cell count =0 or <10% as negative, 10-25% as (+), 26-50% as (++), and >50% as (+++). The D2-40 interpretation was performed according to the Weidner method (21) in a select region with the highest density of lymphatic vessels at low magnification, where a single endothelial cell or a cluster of endothelial cells stained brownish-yellow represented a positive lymphatic vessel. The numbers of lymphatic vessels in five random fields under the light microscope (×200) were then counted and averaged as the micro-lymphatic vessel density (MLVD). All of the sections were reviewed by senior pathologists in a double-blind fashion .

Statistical analysis

The data were processed in SPSS10.0 software using Chi-square tests to compare intragroup differences. A P value less than 0.05 was considered statistically significant.

Results

Expression of CK19, galectin-3, VEGF and EGFR in the two kinds of thyroid tissue

In tissues of papillary thyroid carcinoma (papillary carcinoma), CK19 expression was mainly found in the cell membrane and cytoplasm, with a positive rate of 100% (*Figure 1A*), whereas in papillary thyroid hyperplasia (papillary hyperplasia), the CK19 positive rate was only 9.1%. The difference between the two groups was significantly different (P<0.05). All specimens of papillary carcinoma with lymph node metastasis showed moderate to intense staining with a positive rate of 100%, and those without lymph node metastasis had similar staining intensity with a same positive rate of 100%, without difference between groups (P>0.05). The positive expression of galectin-3 was mostly in the cytoplasm in papillary carcinoma (*Figure 1B*), with a higher positive rate of 97.4% than that of 16.7% in papillary hyperplasia (P<0.05). Similarly, all specimens of papillary carcinoma with lymph node metastasis showed moderate to highly intense staining with a positive rate of 100%, and those without lymph node metastasis had a positive rate of 96.9%, without significant difference (P>0.05). VEGF, mainly located in the cytoplasm, had mild to intense staining in papillary carcinoma (*Figure 1C*), with a positive rate of 78.9%, higher than that in papillary hyperplasia of 25.0% (P<0.05). The positive rate in the group of papillary carcinoma with lymph node metastasis (83.3%) was higher than that of papillary carcinoma without lymph node metastasis (78.1%, P<0.05). Positive EGFR, mostly in the cell membrane and cytoplasm, showed mild to intense staining in papillary carcinoma (*Figure 1D*), with a positive rate of 73.7%; higher than that of 20.0% (P<0.05). The positive rate in the group of papillary carcinoma with lymph node metastasis (83.3%) was higher than that of papillary carcinoma without lymph node metastasis (71.9%) (P<0.05) (*Table 1*).

D2-40 expressions

Positive expression of D2-40 was located in the membrane and cytoplasm of lymphatic endothelial cells. Since stained micro-lymphatic vessels (MLV) did not primarily exist in papillary thyroid carcinoma, the staining of the stroma and capsule should be taken into account. The micro-lymphatic vessel density (MLVD) in the 38 cases of papillary carcinoma was (13.8±3.7) per field (*Figure 2*), and that in the 12 cases of papillary hyperplasia was (4.3±2.34) per field, with a significant difference between the two groups (P<0.05). The MLVDs of the 6 cases of papillary carcinoma with lymph node metastasis and 32 cases without lymph node metastasis were respectively (14.4±2.13) and (8.6±3.21) per field, with a significant difference between the two groups (P<0.05) (*Table 2*).

Combined test results for D2-40, CK19, galectin-3, VEGF and EGFR expressions

Of the 38 cases with papillary carcinoma, 28 subjects (73.7%) were simultaneously positive for CK 19, galectin-3, VEGF and EGFR, with a MLVD of (13.8±3.7) per field in D2-40 expression. Only one in the 12 cases (8.3%) with thyroid papillary hyperplasia was positive for the above indicators, with a MLVD of (4.3±2.34) per field in D2-40 expression. The difference was significant (P<0.05). Of the six subjects of papillary carcinoma with lymph node metastasis, five were positive for both VEGF and EGFR, accoutning for 83.3% (5/6), with a MLVD of (14.4±2.13) per field in D2-40 expression. Of the 32 subjects of papillary carcinoma without lymph node metastasis, 29 were positive for both VEGF and EGFR, accounting for 71.9% (23/32), with a MLVD of (8.6±3.21) per field. The intragroup differences in both proportions were significant (P<0.05). The positive rates of CK19 and galectin-3 expressions in papillary carcinoma patients with and without lymph node metastasis were 100% (6/6), 100% (6/6), 100% (32/32) and 96.9% (31/32), respectively, without significant difference between the two groups (P>0.05).

Discussion

Lymph node metastasis plays a critical role in the determination of staging, treatment options and prognosis of papillary thyroid carcinoma. Although immunohistochemistry has been widely recognized as an effective adjunct tool for the detection, there has been controversy over the most effective antibody or the need for combined use of antibodies.

The usefulness of CK19 in diagnosing PTC has been studied extensively (11,12), with most studies showing

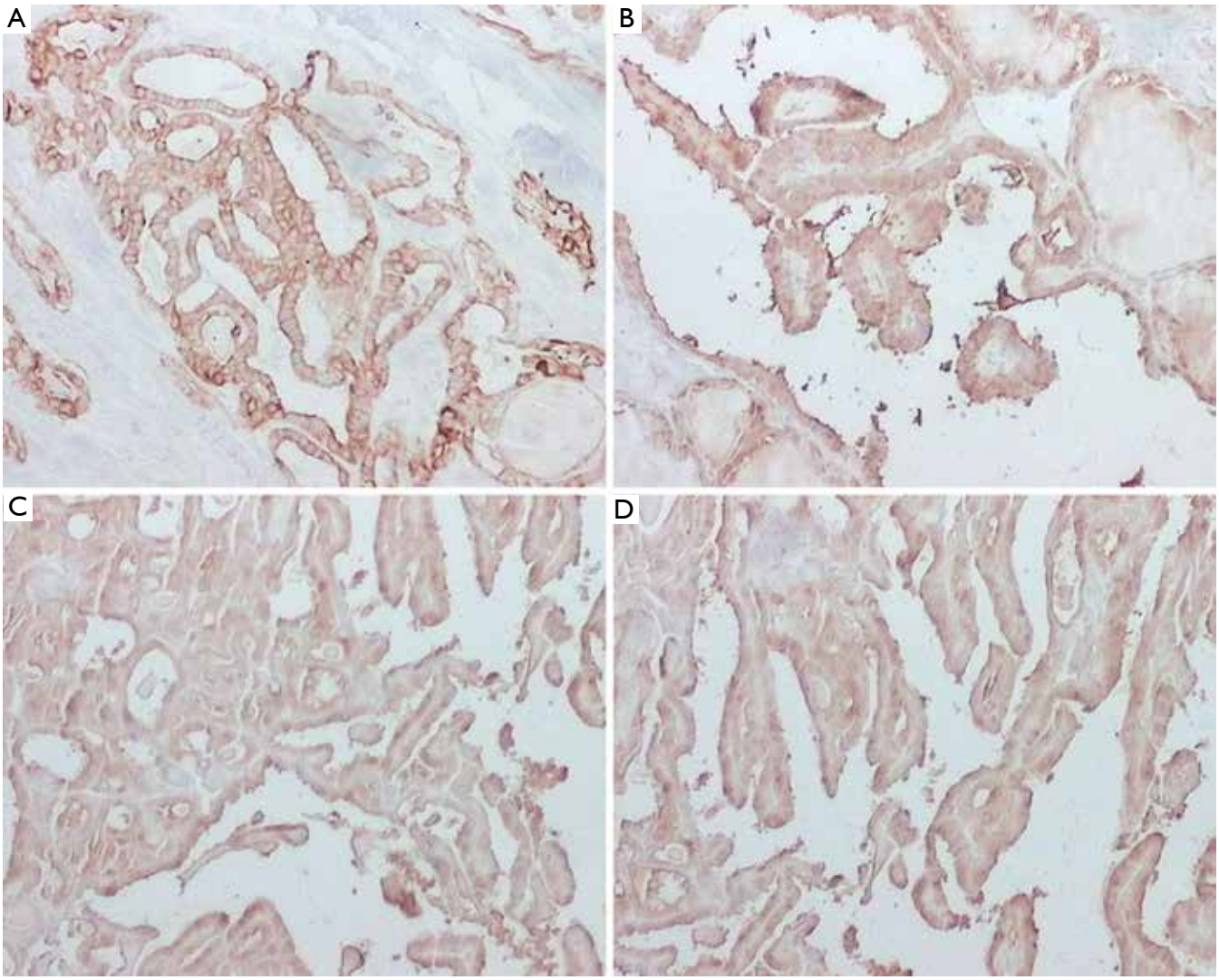

Figure 1 Expressions of CK19, galectin-3, VEGF, and EGFR in papillary thyroid carcinoma (SP ×400). A: CK19; B: galectin-3; C: VEGF; D: EGFR

Table 1 Expressions of CK19, galectin-3, VEGF, and EGFR in papillary thyroid carcinoma and thyroid papillary hyperplasia

Tissue	n	CK19				Positive rate (%)	Galectin-3				Positive rate (%)	VEGF				Positive rate (%)	EGFR				Positive rate (%)
		(-)	(+)	(++)	(+++)		(-)	(+)	(++)	(+++)		(-)	(+)	(++)	(+++)		(-)	(+)	(++)	(+++)	
Thyroid papillary hyperplasia	12	11	1	0	0	(9.1)*	10	2	0	0	(16.7)*	9	1	2	0	(25.0)*	10	2	0	0	(2 0.0)*
Papillary thyroid carcinoma	38	0	0	12	26	(100)	1	1	22	14	(97.4)	8	4	18	8	(78.9)	10	3	15	10	(73.7)
With lymph node metastasis	6	0	0	2	4	(100)	0	0	1	5	(100)	1	2	3	0	(83.3)	1	3	2	0	(83.3)
Without lymph node metastasis	32	0	0	10	22	(100)	1	1	21	9	(96.9)	7	2	15	8	(78.1)**	9	0	13	10	(71.9)**

Note: *P<0.05, compared with papillary thyroid carcinoma group; **P<0.05, compared with "with lymph node metastasis" group.

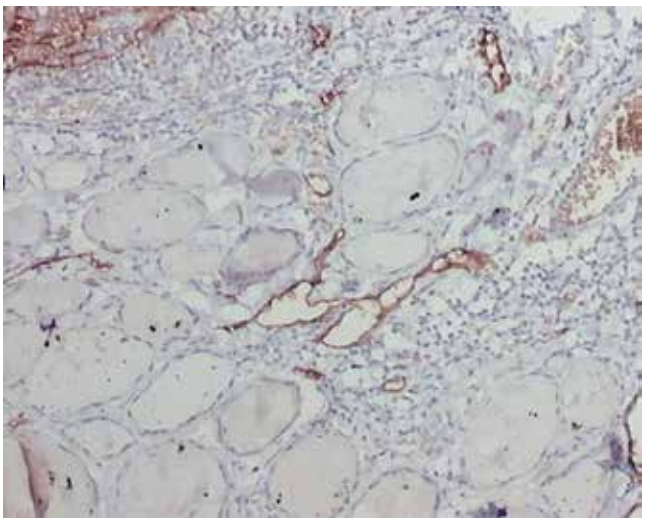

Figure 2 Expression of D2-40 in papillary thyroid carcinoma (SP×100)

Table 2 Relationship between thyroid papillary hyperplasia/ papillary thyroid carcinoma and MLVD

Group	n	MLVD (per field) ($\bar{x}\pm s$)	P
Thyroid papillary hyperplasia	12	4.30±2.34	<0.05
Papillary thyroid carcinoma	38	13.80±3.70	
With lymph node metastasis	6	14.40±2.13	
Without lymph node etastasis	32	8.60±3.21	

strong diffuse expression of CK19 in the majority of PTCs (22,23). In this study, the positive rates of CK19 expression were 100% in papillary carcinoma, 9.1% in papillary hyperplasia (P>0.05), and 100% in papillary carcinoma either with or without lymph node metastasis. Those findings suggested that CK19 was a highly sensitive indicator of thyroid papillary carcinoma, which could be used for the differential diagnosis between papillary carcinoma and papillary hyperplasia, though it added little value to prediction of lymph node metastasis associated with the tumor.

A member of the lectin protein family, galectin-3 is a polypeptide consisting of the amino acid terminal region and the carbohydrate identification zone at the hydroxyl terminal, providing a new option for the detection of angiogenesis (24). Studies have shown that galectin-3 are key to the differential diagnosis of papillary thyroid carcinoma (25). In this study, the positive rates of galectin-3 were 97.4% in papillary thyroid carcinoma and 16.7% in papillary hyperplasia, though as high as 100% and 96% in papillary carcinoma with and without metastasis, respectively. Hence, we believed that galectin-3 could be a valuable antibody for the differential diagnosis of papillary thyroid carcinoma and papillary hyperplasia (26,27), though it was of little significance in predicting lymph node metastasis.

VEGF is a vascular endothelial cell-specific heparin-binding growth factor that can induce angiogenesis in vivo. As a highly conserved homodimeric glycoprotein, it promotes the proliferation of vascular endothelial cells and increases vascular permeability by specifically binding to the three vascular endothelial growth factor receptors (VEGFR-1, -2 and -3). Fellmer and coworkers (28) noted a significantly increased level of VEGF expression in papillary thyroid carcinoma, which was closely linked with the lymph node metastasis yet negatively or weakly present in papillary hyperplasia. In this study, the positive rates of VEGF expression were 78.9% in papillary carcinoma, 25.0% in papillary hyperplasia, and 83.3% and 78.1% in papillary carcinoma with and without lymph node metastasis, respectively, consistent with the findings in the study by Zhang *et al*. (29). We believed that VEGF could induce tyrosine kinase phosphorylation of the lymphatic endothelial cell receptor VEGFR-3 via paracrine or autocrine signaling. The resultant proliferation or expansion of the lymphatic vessels inside or surrounding solid tumors (30) created an open access for invasion by tumor cells and contributed to lymph node metastasis in the region dominated by malignant cells. It could also explain the trend toward lymph node metastasis in papillary thyroid carcinoma. Hung (31) noted a significantly higher level of VEGF expression in papillary thyroid carcinoma with increased potential for lymph node metastasis than in normal tissues and papillary hyperplasia lesions, suggesting that VEGF could be used as an indicator for differentiation between papillary thyroid carcinoma and papillary hyperplasia, as well as the presence of regional lymph node metastasis.

EGFR is the product of the expression of proto-oncogene C-erbB-1, a membrane protein with a molecular weight of 170 kD that consisted of an extracellular functional area for binding to EGF, a short transmembrane domain and an intracellular component that has tyrosine acid activity. EGFR are highly effective in activating tyrosine kinase, and can also exert the activity of this enzyme (32) to cause residue phosphorylation of a specific tyrosine. Through kinase cascade amplification, the signals caused a series of biological effects such as activation of protein kinase and increased synthesis of proteins and DNA, eventually leading

to cell growth and division. As shown in this study, the positive rates of EGFR expression were 73.7% in papillary thyroid carcinoma, 20% in papillary thyroid hyperplasia, and 83.3% and 71.9% in papillary carcinoma with and without lymph node metastasis, respectively, suggesting significantly increased EGFR expression in thyroid papillary carcinoma compared to papillary thyroid hyperplasia. That pattern of EGFR overexpression in tumor tissues was also supported by the study results of Haugen (33). Of all subjects positive for papillary thyroid carcinoma, the expression was also higher in cases with lymph node metastasis than those without, suggesting a close link between EGFR expression and the metastasis.

D2-40 is thought to be a specific marker for lymphatic vessels. Because D2-40 has shown selective immunoreactivity for lymphatic endothelium, its proposedc linical uses include testing for lymphatic invasion by primary tumors (34). As shown in this study, D2-40 specifically located in the lymphatic endothelial cells of the thyroid tissue, making it a more accurate and sensitive indicator applicable for a wider range compared to other lymphatic markers. That was consistent with the findings of Fukunaga (35). Tumor-induced lymphangiogenesis is an important step in lymphatic metastasis. Newborn lymphatic vessels are composed of monolayer cells. The absence of the basal layer, tight junctions between cells, a large number of potential lacunae and other factors are conducive to the entry of tumor cells into the lymphatic vessels. Lymphangiogenesis and the resultant increased lymphatic vessel density contribute to the invasion of tumor cells into regional lymph nodes through lymphatic capillaries, and thus the occurrence of lymphatic metastasis. In this study, the MLVD was significantly higher in papillary carcinoma labeled with D2-40 than in papillary hyperplasia, and also higher in tumors with lymph node metastasis than those without. D2-40 is a more sensitive and specific indicator of tumor lymphatic vessel density and has higher reliability for predicting lymph node metastasis. It is expected to become an indicator for differential diagnosis of papillary thyroid carcinoma and papillary hyperplasia and predictor for lymph node metastasis.

Some studies (22,36) suggested a combination of valuable antibodies to improve the sensitivity and specificity of the differential diagnosis of thyroid cancer. In this study, the expressions of five antibodies (D2-40, CK19, galectin-3, VEGF and EGFR) were significantly higher in papillary carcinoma than in papillary hyperplasia; the expressions of D2-40, VEGF and EGFR were higher in papillary carcinoma with lymph node metastasis than in those without the metastasis, but there was no different in the expressions of CK19 and galectin-3. In conclusion, the combination of D2-40, CK19, galectin-3, VEGF and EGFR is more accurate in the differential diagnosis of papillary carcinoma and papillary hyperplasia and the prediction of lymph node metastasis than a single antibody or double antibody combination. Hence, it is believed that the combination of the five antibodies could be a more reliable tool for the differential diagnosis than single-antibody detection.

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References

1. Erdem H, Gündogdu C, Sipal S. Correlation of E-cadherin, VEGF, COX-2 expression to prognostic parameters in papillary thyroid carcinoma. Exp Mol Pathol 2011; 3:12-7.
2. Casey MB, Lohse CM, Lloyd RV. Distinction between papillary thyroid hyperplasia and papillary thyroid carcinoma by immunohistochemical staining for cytokeratin 19, galectin-3, and HBME-1. Endocr Pathol 2003;14:55-60.
3. Sethi K, Sarkar S, Das S, et al. Biomarkers for the diagnosis of thyroid cancer. J Exp Ther Oncol 2010;8:341-52.
4. Ito Y, Miyauchi A, Kakudo K, et al. Prognostic significance of ki-67 labeling index in papillary thyroid carcinoma. World J Surg 2010;34:3015-21.
5. Chiu CG, Strugnell SS, Griffith OL, et al. Diagnostic utility of galectin-3 in thyroid cancer. Am J Pathol 2010;176:2067-81.
6. Barut F, Onak Kandemir N, Bektas S, et al. Universal markers of thyroid malignancies: galectin-3, HBME-1, and cytokeratin-19. Endocr Pathol 2010;21:80-9.
7. de Araujo-Filho VJ, Alves VA, de Castro IV, et al. Vascular endothelial growth factor expression in invasive papillary thyroid carcinoma. Thyroid 2009;19:1233-7.
8. Fassnacht M, Kreissl MC, Weismann D, et al. New targets and therapeutic approaches for endocrine malignancies. Pharmacol Ther 2009;123:117-41.
9. Wang SL, Li SH, Chen WT, et al. Expression of D2-40 in adjunct diagnosis of papillary thyroid carcinoma. APMIS 2007;115:906-10.
10. Kaiserling E. Immunohistochemical identification of

lymph vessels with D2-40 in diagnostic pathology. Pathologe 2004;25:362-74.
11. Miettinen M, Kovatich AJ, Kärkkäinen P. Keratin subsets in papillary and follicular thyroid lesions. A paraffin section analysis with diagnostic implications. Virchows Arch 1997;431:407-13.
12. Baloch ZW, Abraham S, Roberts S, et al. Differential expression of cytokeratins in follicular variant of papillary carcinoma: an immunohistochemical study and its diagnostic utility. Hum Pathol 1999;30:1166-71.
13. Casey MB, Lohse CM, Lloyd RV. Distinction between papillary thyroid hyperplasia and papillary thyroid carcinoma by immunohistochemical staining for cytokeratin 19, galectin-3, and HBME-1. Endocr Pathol 2003;14:55-60.
14. Cameron BR, Berean KW. Cytokeratin subtypes in thyroid tumours: immunohistochemical study with emphasis on the follicular variant of papillary carcinoma. J Otolaryngol 2003;32:319-22.
15. Finley DJ, Arora N, Zhu B, et al. Molecular profiling distinguishes papillary carcinoma from benign thyroid nodules. J Clin Endocrinol Metab 2004;89:3214-23.
16. Cvejić D, Savin S, Petrović I, et al. Differential expression of galectin-3 in papillary projections of malignant and non-malignant hyperplastic thyroid lesions. Acta Chir Iugosl 2003;50:67-70.
17. Fenton C, Patel A, Dinauer C, et al. The expression of vascular endothelial growth factor and the type 1 vascular endothelial growth factor receptor correlate with the size of papillary thyroid carcinoma in children and young adults. Thyroid 2000;10:349-57.
18. Klein M, Vignaud JM, Hennequin V, et al. Increased expression of the vascular endothelial growth factor is a pejorative prognosis marker in papillary thyroid carcinoma. J Clin Endocrinol Metab 2001;86:656-8.
19. Lam AK, Lau KK, Gopalan V, et al. Quantitative analysis of the expression of TGF-alpha and EGFR in papillary thyroid carcinoma: clinicopathological relevance. Pathology 2011;43:40-7.
20. Yeh MW, Rougier JP, Park JW, et al. Differentiated thyroid cancer cell invasion is regulated through epidermal growth factor receptor-dependent activation of matrix metalloproteinase (MMP)-2/gelatinase A. Endocr Relat Cancer 2006;13:1173-83.
21. Weidner N. Intratumor microvessel density as a prognostic factor in cancer. Am J Pathol 1995;147:9-19.
22. Casey MB, Lohse CM, Lloyd RV. Distinction between papillary thyroid hyperplasia and papillary thyroid carcinoma by immunohistochemical staining for cytokeratin 19, galectin-3, and HBME-1. Endocr Pathol 2003;14:55-60.
23. Cameron BR, Berean KW. Cytokeratin subtypes in thyroid tumours: immunohistochemical study with emphasis on the follicular variant of papillary carcinoma. J Otolaryngol 2003;32:319-22.
24. Zhang T,Wan S,Ding Y, et al. Influence of galectin-3 on proliferation of endothelial cells induced from bone marrow mesenchymal stem cells. Chinese Journal of General Surgery 2010;19:1005-9.
25. Chen Y, Shen D, Sun K, et al. Expression of Galectin-3,CK19,HBME-1 and CD56 and their significance in papillary thyroid microcarcinoma. Chinese Journal of Clinical and Experimental Pathology 2010;26:425-8.
26. Rossi ED, Raffaelli M, Mule' A, et al. Simultaneous immunohistochemical expression of HBME-1 and galectin-3 differentiates papillary carcinomas from hyperfunctioning lesions of the thyroid. Histopathology 2006;48:795-800.
27. Beesley MF, McLaren KM. Cytokeratin 19 and galectin-3 immunohistochemistry in the differential diagnosis of solitary thyroid nodules. Histopathology 2002;41:236-43.
28. Fellmer PT, Sato K, Tanaka R, et al. Vascular endothelial growth factor-C gene expression in papillary and follicular thyroid carcinomas. Surgery 1999;126:1056-61;discussion 1061-2.
29. Zhang H, Wei Q. Expression of vascular endothelial growth factor-C and its receptor Flt-4 in papillary thyroid carcinoma. Journal of Chinese Physician 2005;7:1465-7.
30. Kitadai Y, Amioka T, Haruma K, et al. Clinicopathological significance of vascular endothelial growth factor (VEGF)-C in human esophageal squamous cell carcinomas. Int J Cancer 2001;93:662-6.
31. Hung CJ, Ginzinger DG, Zarnegar R, et al. Expression of vascular endothelial growth factor-C in benign and malignant thyroid tumors. J Clin Endocrinol Metab 2003;88:3694-9.
32. Liu X, Pu P, Gao Z. Study on expression of epidermal growth factor receptor gene in human gliomas. Chinse Journal of Neurosurgery 1998;14:71-6.
33. Haugen DR, Akslen LA, Varhaug JE, et al. Demonstration of a TGF-alpha-EGF-receptor autocrine loop and c-myc protein over-expression in papillary thyroid carcinomas. Int J Cancer 1993;55:37-43.
34. Schacht V, Dadras SS, Johnson LA, Up-regulation of the lymphatic marker podoplanin, a mucin-type transmembrane glycoprotein, in human squamous cell

carcinomas and germ cell tumors. Am J Pathol. 2005 Mar;166(3):913-21
35. Fukunaga M. Expression of D2-40 in lymphatic endothelium of normal tissues and in vascular tumours. Histopathology 2005;46:396-402.
36. Cheung CC, Ezzat S, Freeman JL, et al. Immunohistochemical diagnosis of papillary thyroid carcinoma. Mod Pathol 2001;14:338-42.

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Abnormality of pl6/p38MAPK/p53/Wipl pathway in papillary thyroid cancer

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Objective: To investigate the expression of the pl6/p38MAPK/p53/Wipl pathway in patients with papillary thyroid cancer (PTC) and its clinical significance.

Methods: The protein expressions of Wipl, p53, p38MAPK, and p16 in 70 cases of PTC tissues and 20 cases of normal thyroid tissues were detected by immunohistochemical staining. The correlations of Wipl protein high-expression with p53, p38MAPK, and pl6 protein expressions were analyzed.

Results: The high-expression rate of Wipl protein in the PTC tissue was 64.3% (45/70), which was significantly different than that in normal thyroid tissue (0/20) (P<0.01). There were no significant differences between the paired groups in terms of age, gender, tumor size, and lymph node metastasis (all P>0.05). The Wipl protein high-expression was negatively correlated with the expressions of p38MAPK, p53 and pl6 (r value was –0.620, 0.356 and 0.550, respectively, and all P<0.01).

Conclusions: The pl6/p38MAPK/p53/Wipl pathway is abnormal in PTC, and this abnormality may possibly be associated with the aberrantly up-regulated Wipl, which can induce inhibition of p38MAPK, p53 and pi6.

Keywords: Thyroid neoplasms; wild-type p53-induced phosphatase 1; carcinoma, papillary; immunohistochemistry

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Introduction

Wild-type p53 induced phosphatase 1 (Wip1) is a member of the PP2C family of evolutionarily conserved protein phosphatases and a novel proto-oncogene (1,2). Originally described as a p53-regulated gene. In recent years, analysis of Wip1 has focused primarily on its role in tumorigenesis because of its overexpression in human tumors. Overexpression or activation of Wip1, as commonly seen in primary human tumors, could have a more general effect on multiple signaling pathways contributing to deregulation of several molecular networks.

p53 and p16 are key anti-oncogenes, whereas p38 mitogen-activated protein kinase (MAPK) is a key cell cycle regulator (3). Wip1 is a major inhibitor of p53 functions. The mutation or missing of p53 gene is the cause of many tumors (4) which is a main carcinogenic mechanism of Wip1. Wip1 has been implicated as a negative regulator of p53 via its ability to attenuate p38 MAPK activity (5,6). p16, also known as mitotic inhibitor or multiple tumor suppressor gene, is one of the cell cycle regulator. p16 is a key anti-oncogene. Moreover, higher Wip1 expression is associated with lower p16 levels in primary human mammary carcinomas (7). And Wip1 can potently down-regulate p16 expression by suppressing p38MAPK (8). However the downregulation of p53 and the DNA damage and DNA repair responses by WIP1 has cancer implications, particularly since the DNA damage response has recently been shown to play a crucial role as an early anti-cancer barrier (9-11). It is known that p38 mitogen-activated protein (MAP) kinase controls cellular pathways for proliferation, differentiation, development of the inflammatory response, and apoptosis. Wip1 also negatively regulates the stress responsive p38 MAPK pathway by

directly inactivating p38 through dephosphorylation (12). However phosphorylated p38 MAP kinase phosphorylates and activates p53 to cause cell cycle arrest or apoptosis. And Wip1 can control a feedback loop in the p38 MAP kinase-p53 signaling pathway (12). Thus, pl6/p38MAPK/p53/Wipl signal transduction pathways may play a crucial role in human tumors.

Not surprisingly, Wip1 has been implicated as an oncogene and Wip1 gene amplification and/or protein overexpression have been reported in a variety of human tumors including breast cancer, neuroblastoma, pancreatic cancer, ovarian cancer, and gastric cancer (7,13). However, its expression in papillary thyroid carcinoma (PTC) remains unclear. Up to now few studies have explored the role of pl6/p38MAPK/p53/Wipl pathway in the occurrence and development of PTC. In this study, by detecting the protein expressions of Wipl, p53, p38MAPK, and p16 in 70 cases of PTC tissues and 20 cases of normal thyroid tissues using immunohistochemical staining and analyzing their mutual correlation, we investigated the role of pl6/p38MAPK/p53/Wipl pathway in PTC. To our knowledge, this is the first report establishing the existence of the signaling pathway in PTC and may be a potential target for therapeutic intervention for treatment of PTC.

Materials and methods

Specimens and general information

PTC group

The specimens and clinical data of 70 patients with pathologically confirmed PTC who were treated in our hospital from March 2010 to December 2010 were retrospectively collected. There were 16 males and 54 females aged 15-64 years (mean: 41 years). Lymph node metastasis was noted in 33 patients, while 37 patients had no lymph node metastasis. TNM staging showed 39 cases in stage I, 12 in stage II, 14 in stage III, and 5 in stage IV. All patients were naive to chemotherapy and radiotherapy before the surgery. PTC specimens were obtained from these tissues immediately after surgical resection.

Control group

Pathologically confirmed normal thyroid tissues were obtained from 20 cases. There were 4 males and 16 females aged 20-55 years (mean: 42.3 years).

Main reagents

The main reagents included rabbit anti-human Wip1 polyclonal antibody (Santa Cruze); rabbit anti-human p-p38MAPK monoclonal antibody (Cell Signaling); and mouse anti-human p53/p16 monoclonal antibody and streptavidin-proxidase (SP) reagent kit (Fuzhou Maxim Biotech Inc., China).

Experimental methods

Immunohistochemical staining

Specimens were fixed in 10% neutral buffered formalin, embedded in paraffin, cut into 4 μm sections and stained with hematoxylin and eosin (HE) or SP methods. Known positive sections were used as a positive control and phosphate buffer saline (PBS) was substituted for the primary antibody for a negative control.

Determination of results

The positive protein expression of Wip1 was mostly in nucleus and only a few in cytoplasm. Positive protein expressions of p-p38MAPK, p53, and p16 were found in the nucleus as brown/yellow granules (diamino benzidine (DAB) staining). The numbers of positive cells in five random high-definition fields under the light microscope (×400) were then counted, and their proportions relative to the total cells were calculated. Wip1: a stained cell count =0 or <10% as negative (–), 10-30% as (+), and >30% as (++); negative (–) to (+) was regarded as low expression and (++) as high expression. p53, p38, and p16: a stained cell count =0 or <10% as negative (–) and ≥10% as positive (+).

Statistical analysis

Data were analyzed using SPSS 13.0 software. Rates were compared using Chi square test and correlation was analyzed with Spearman's rank correlation coefficient. $P<0.05$ was considered significantly different.

Results

Expression of Wip1 in normal thyroid tissues and PTC tissues

The immunohistochemical staining of Wip1 was negative or weak in the follicular epithelial cells of normal thyroid tissues (*Figure 1A*), whereas the positive expression of Wip1 in PTC tissues was mostly in nucleus (*Figure 1B*). The

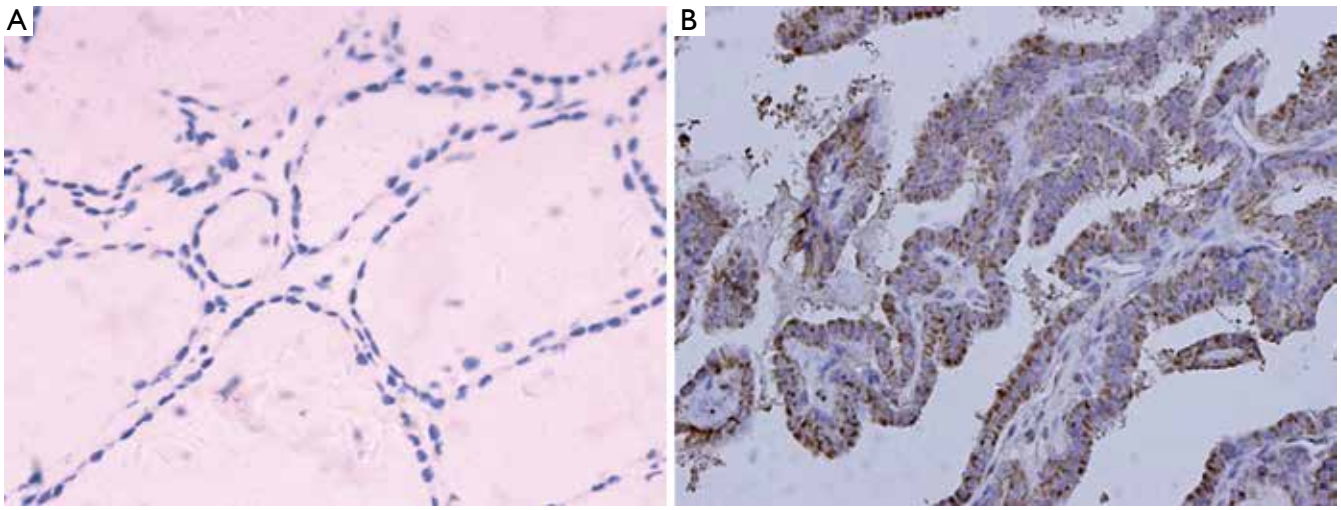

Figure 1 Expression of Wip1 (DAB staining, ×400). A: Noraml thyroid tissue, without Wip1 positive expression; B: PTC tissue, with Wip1 positive expression (mostly in nucleus).

high-expression rate of Wipl protein in the PTC tissue was 64.3% (45/70), which was significantly higher than that in normal thyroid tissue (0/20) (χ^2=25.714, P=0.00039).

Wip1 high expression and its relationship with the clinopathological factors of thyroid carcinoma

Wip1 high expression showed no correlation with age, gender, tumor size, lymph node metastasis, and pathological stage (all P>0.05). These factors also showed no significant difference among the groups (χ^2=0.311, 0.029, 0.002, 0.796, and 0.194, respectively; P=0.577, 0.865, 0.961, 0.372, and 0.659, respectively) (*Table 1*).

Protein expressions of p38MAPK, p53, and p16 in PTC tissues their correlations with the Wip1 high expression

The positive protein expressions of p38MAPK, p53, and p16 in PTC tissues were all in nucleus (*Figure 2*). The Wipl protein high-expression was negatively correlated with p53, p38MAPK, and pl6 protein expressions (*Table 2*).

Discussion

Previous study has shown that the occurence and development of human tumors are closely associated with the changes in intracellular genome, among which the activation of proto-oncogenes, the inactivation or missing of anti-oncogenes, and the changes in the functions of many cell cycle regulatory genes play key roles (14). As shown in our current study, the high-expression rate of Wipl protein in the PTC tissue was 64.3% (45/70), which was significantly higher than that in normal thyroid tissue (P<0.01), indicating that Wip1 is involved in the progression of PTC. Correlation analysis showed that Wip1 high expression was not correlated with the clinopathological factors including age, gender, tumor size, lymph node metastasis, and pathologic stage, which are consistent with our previous findings (15). Therefore, Wip1 can not be used to predict the prognosis.

Also in our study, the high protein expression of Wip1 in PTC tissues was negatively correlated with the protein expressions of p38MAPK, p53, and p16; in other words, PTC tissues with Wip1 high protein expression were often associated with the depletion of the protein expression of p38MAPK, p53, or p16, and vice versa. As a stress regulator, Wip1 can inactivate p38MAPK (6,16). p38MAPK, a key cell cycle regulator, plays an important role in controlling the G1/S and G2/M checkpoints; the inactivation of p38MAPK increases the risk of tumorigenesis (3). p53, as one of the most important anti-oncogenes, plays an important role in the apoptosis induced by DNA damage (17,18). p53 has two subtypes: wild type and mutant type. The subtype detected by immunohistochemical methods is mainly mutant type. As shown in our study, by inhibiting the functions of p53,

Table 1 Wip1 high expression and its relationship with the clinopathological factors of thyroid carcinoma

Clinopathological factors	n	Wip1 high expression		χ^2	P
		n	(%)		
Age					
<45	45	30	66.7	0.311	0.577
≥45	25	15	60.0		
Gender					
Male	16	10	62.5	0.029	0.865
Female	54	35	64.8		
Tumor size					
>40 mm	11	7	63.6	0.002	0.961
≤40 mm	59	38	64.4		
Lymph node metastasis					
Yes	33	23	69.7	0.796	0.372
No	37	22	59.5		
TNM stage					
Stage I - II	51	32	62.7	0.194	0.659
Stage III - IV	19	13	68.4		

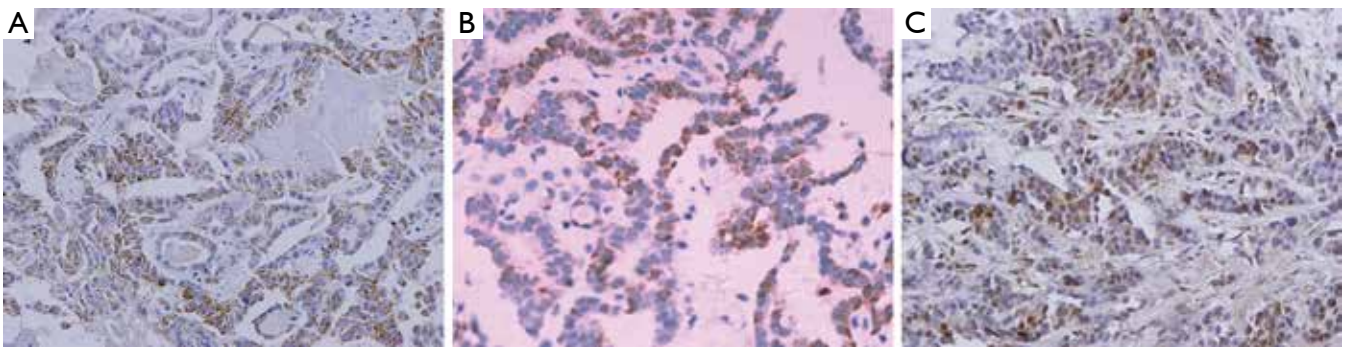

Figure 2 Immunohistochemical staining of p38MAPK, p53, and p16 in PTC tissues (DAB staining, ×400). A: positive expression of p38MAPK; B: positive expression of p53; and C: positive expression of p16.

Table 2 Correlation of Wipl protein high-expression with p53, p38MAPK, and pl6 protein expressions in PTC tissues

Wip1	p38		p53		p16	
	(+)	(–)	(+)	(–)	(+)	(–)
(++)	9	36	14	31	12	33
(–)-(+)	21	4	17	8	21	4
r	-0.620		-0.356		-0.550	
P	<0.01		<0.01		<0.01	

Wip1 reduced the selective mutation of p53 gene.

As a key anti-oncogene, p16 can specifically inhibit CDK4/6 and thus prevent the transition of a cell from G1 to S phase. It adjusts the mitosis via negative feedback and prevents the abnormal proliferation of cells. And its inactivation or missing can dramatically accelerate the growth of cells, therefore play a crucial role in the progression of PTC.

In addition, we found that the pl6/p38MAPK/p53/Wipl pathway is abnormal in PTC, and this abnormality may possibly be associated with the aberrantly up-regulated Wipl, which can induce inhibition of p38MAPK, p53 and p16. It is therefore speculated that Wip1 may be a therapeutic target for PTC; particularly, the inhibition of Wip1 function may enhance the activities of anti-oncogenes and thus exert therapeutic effect on PTC. Research also has shown that arsenic trioxide can inhibit Wip1, during which Wip1 is served as the direct molecular target. Currently, arsenic trioxide is mainly used for the treatment of acute promyelocytic leukemia (19). The prevalence of thyroid cancer has shown an increasing trend in China in recent years (20); unfortunately, this disease is not sensitive to conventional chemotherapy drugs.

In conclusions, the pl6/p38MAPK/p53/Wipl pathway is abnormal in PTC, and this abnormality may possibly be associated with the aberrantly up-regulated Wipl, which can induce inhibition of p38MAPK, p53 and pi6. The arsenic trioxide may exert its anti-tumor efficacy in the targeted therapy for thyroid cancer.

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References

1. Bulavin DV, Demidov ON, Saito S, et al. Amplification of PPM1D in human tumors abrogates p53 tumor-suppressor activity. Nat Genet 2002;31:210-5.
2. Li J, Yang Y, Peng Y, et al. Oncogenic properties of PPM1D located within a breast cancer amplification epicenter at 17q23. Nat Genet 2002;31:133-4..
3. Bulavin DV, Higashimoto Y, Popoff IJ, et al. Initiation of a G2/M checkpoint after ultraviolet radiation requires p38 kinase. Nature 2001;411:102-7.
4. Liu Peng, Liu Yan, Sun Hui. Correlation between expression of p53 and bcl-2/bax in breast cancer. Chinese Journal of Experimental Surgery 2007;24:176-8.
5. Bulavin DV, Phillips C, Nannenga B, et al. Inactivation of the Wip1 phosphatase inhibits mammary tumorigenesis through p38 MAPK-mediated activation of the p16(Ink4a)-p19(Arf) pathway. Nat Genet 2004;36:343-50.
6. Lu X, Nguyen TA, Moon SH, et al. The type 2C phosphatase Wip1: an oncogenic regulator of tumor suppressor and DNA damage response pathways. Cancer Metastasis Rev 2008;27:123-35.
7. Yu E, Ahn YS, Jang SJ, et al. Overexpression of the wip1 gene abrogates the p38 MAPK/p53/Wip1 pathway and silences p16 expression in human breast cancers. Breast Cancer Res Treat 2007;101:269-78.
8. Lee JS, Lee MO, Moon BH, et al. Senescent growth arrest in mesenchymal stem cells is bypassed by Wip1-mediated downregulation of intrinsic stress signaling pathways. Stem Cells 2009;27:1963-75.
9. Halazonetis TD, Gorgoulis VG, Bartek J. An oncogene-induced DNA damage model for cancer development. Science 2008;319:1352-5.
10. Bartkova J, Horejsí Z, Koed K, et al. DNA damage response as a candidate anti-cancer barrier in early human tumorigenesis. Nature 2005;434:864-70.
11. Nguyen TA, Slattery SD, Moon SH, et al. The oncogenic phosphatase WIP1 negatively regulates nucleotide excision repair. DNA Repair (Amst) 2010;9:813-23.
12. Yamaguchi H, Durell SR, Feng H, Development of a substrate-based cyclic phosphopeptide inhibitor of protein phosphatase 2Cdelta, Wip1. Biochemistry 2006;45:13193-202.
13. Le Guezennec X, Bulavin DV. WIP1 phosphatase at the crossroads of cancer and aging. Trends Biochem Sci 2010;35:109-14.
14. Zhang Bo, Lu Jian-hua, Liu Ke, et al. DBC2 negatively regulates the proliferation of breast cancer cells and induces apoptosis. Chinese Journal of Experimental Surgery 2010;27:345-7.
15. Yang Dehua, He Jiaan, Li jian, et al. Expression of proto-oncogene Wipl in breast cancer and its clinical significance. National Medical Journal of China 2010;90:519-22.
16. Fuku T, Semba S, Yutori H, et al. Increased wild-type p53-induced phosphatase 1 (Wip1 or PPM1D) expression correlated with downregulation of checkpoint kinase 2 in human gastric carcinoma. Pathol Int 2007;57:566-71.
17. Liu G, Chen X. Regulation of the p53 transcriptional activity. J Cell Biochem 2006;97:448-58.
18. Gorgoulis VG, Vassiliou LV, Karakaidos P, et al. Activation of the DNA damage checkpoint and genomic instability in

human precancerous lesions. Nature 2005;434:907-13.
19. Yoda A, Toyoshima K, Watanabe Y, et al. Arsenic trioxide augments Chk2/p53-mediated apoptosis by inhibiting oncogenic Wip1 phosphatase. J Biol Chem 2008;283:18969-79.
20. Wang Y, Wang W. Increasing Incidence of Thyroid Cancer in Shanghai, China, 1983-2007. Asia Pac J Public Health 2012 Mar 16.

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Does nodule size predict compressive symptoms in patients with thyroid nodules?

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Background: Thyromegaly and thyroid nodules are known to cause compressive symptoms, but the exact relationship between nodule size and development of compressive symptoms is unclear. We sought to determine whether compressive symptoms are directly related to nodule size.

Methods: A retrospective analysis of 99 patients who underwent thyroidectomy by a single surgeon was performed. Patients were placed into one of two cohorts: those who experienced preoperative compressive symptoms (N=51) and those who did not (N=48). Compressive symptoms were defined as experiencing neck fullness, dysphagia, choking, or dyspnea. Nodule size, thyroid lobe size, and the presence of visible thyromegaly were compared between the two groups.

Results: Average nodule size in patients with compressive symptoms was 3.8 versus 2.2 cm in asymptomatic patients (P<0.0001). Average lobe diameter was 6.2 cm in patients with compressive symptoms versus 4.9 cm in asymptomatic patients (P<0.001). Visible thyromegaly was present in 65.2% of patients with compressive symptoms and 15.4% of asymptomatic patients (P<0.0001). The most common symptom was dysphagia, occurring in 80% of patients, followed by neck fullness (69%), choking (49%), and dyspnea (32%). Of patients who underwent surgery for compressive symptoms, 92.7% had improvement in their symptoms postoperatively. Of patients with a thyroid nodule greater than 1.5 cm, 97% showed improvement in symptoms postoperatively.

Conclusions: Thyroid nodule size and lobe size appear to directly correlate with compressive symptoms. Of patients with compressive symptoms and a thyroid nodule >1.5 cm, 97% experienced improvement in symptoms postoperatively.

Keywords: Thyroid; nodule; compressive; symptoms; predict

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Introduction

Thyroid nodules are present in as much as 65% of the population (1). Patients with thyroid nodules often complain of compressive symptoms, including neck fullness, dysphagia, odynophagia, choking, and dyspnea (2). Compressive symptoms may occur in both benign as well as malignant thyroid nodules (3). Surgery for large thyroid nodules or for diffuse thyromegaly often relieves compressive symptoms (4). Several authors have investigated the relationship between compressive symptoms and thyroid lobe volume (5). The exact relationship between thyroid nodule size, however, and compressive symptoms remains unclear. We hypothesized that compressive symptoms would be more likely to occur in patients with larger thyroid size and larger dominant thyroid nodules. We sought to determine whether compressive symptoms are directly related to nodule size and lobe size, and furthermore, to determine whether patients who undergo thyroidectomy for moderate-sized thyroid nodules experience resolution of symptoms postoperatively.

Materials and methods

A retrospective analysis was based on data acquired from an IRB-approved patient database and electronic records at Robert Wood Johnson University Hospital (New Brunswick, NJ, USA). A total of 99 consecutive patients who underwent thyroidectomy or thyroid lobectomy by a single surgeon between July 2008 and January 2012 were identified. These patients had uniform documentation on the presence or absence of compressive symptoms, (specifically of dysphagia, dyspnea, choking sensation, and/or neck fullness) and the presence or absence of visible thyromegaly on physical examination.

Patients were placed into one of two cohorts: those who experienced preoperative compressive symptoms (N=51) and those who did not (N=48). Compressive symptoms were defined as experiencing neck fullness, dysphagia, choking, or dyspnea. Odynophagia and globus were not included, as these were not uniformly identified on patient notes. Nodule and lobe sizes were obtained from preoperative thyroid ultrasound reports and compared between cohorts. We chose to define nodule size by the largest diameter obtained either in transverse, sagittal, or coronal plane. We used this as an alternative to thyroid lobe volume, given the variability in ultrasound technique and radiographic reporting among our various referring radiology centers. In patients with multiple nodules, we chose to focus on the largest diameter of the largest thyroid nodule. We felt that taking into account multiple, often subcentimeter, thyroid nodules would not provide a good assessment of thyroid bulk. Instead, we used the thyroid lobe diameter as a surrogate for thyroid bulk (i.e., multiple small nodules together resulting in thyroid lobe enlargement would be identified by an enlarged thyroid lobe size).

For patients with symptoms of dysphagia thought to be unrelated to the thyroid, diagnostic workup included a barium swallow, direct laryngoscopy and endoscopy, and computed tomography (CT) [or magnetic resonance imaging (MRI)] to rule out other causes of compressive symptoms. Only after other possible causes had been ruled out would thyroid surgery be offered for a <2.0 cm thyroid nodule when a patient insisted that the compressive symptoms were severe.

An assessment of resolution of symptoms on postoperative visits was also recorded. Descriptive statistics were calculated using SAS version 9.1, including student's *t*-tests for continuous variables, chi-squared tests for categorical data, and Wilcoxon-Mann-Whitney rank sum tests for ordinal variables.

Results

Patient demographics are shown in *Table 1*. The most common diagnosis in both asymptomatic and symptomatic groups was multinodular goiter (31.3% and 70.6% of patients respectively), with more patients in the symptomatic group diagnosed with multinodular goiter (P<0.0001). Mean thyroid nodule size in symptomatic patients was 3.8 cm [95% confidence interval (CI): 3.3-4.3 versus 2.2 cm (95% CI: 1.9-2.6) in asymptomatic patients (P<0.0001). Mean lobe diameter was 6.2 cm (95% CI: 5.7-6.7) in symptomatic patients versus 4.9 cm (95% CI: 4.6-5.2) in asymptomatic patients (P<0.001), *Table 2*. CIs and ranges of nodule size and diameter between groups are shown in *Figures 1* and *2*, respectively. Visible thyromegaly was present in 65.2% of patients with compressive symptoms compared to 15.4% of asymptomatic patients (P<0.0001), also shown in *Table 2*.

The most common symptom was dysphagia, occurring in 80% of patients in the cohort, followed by globus (69%), choking (49%), and dyspnea (32%). Patients in which the left lobe was enlarged or had an enlarged left-sided nodule trended towards experiencing more symptoms of dysphagia than those on the right; however, these differences were not statistically significant (P=0.354, P=0.435 respectively). Of patients who underwent surgery for compressive symptoms, 92.7% had relief of their symptoms postoperatively (P<0.0001). Of patients where the largest thyroid nodule was greater than 1.5 cm, 97% showed improvement in symptoms postoperatively. Of three patients with compressive symptoms with a negative barium swallow and dysphagia workup, and with a thyroid nodule <1.5 cm, only two of the three experienced resolution of compressive symptoms.

Discussion

Compressive symptoms are a common finding in patients with thyroid nodules (6,7). In two large series, compressive symptoms ranged between 11% and 22% of patients (6,7). Surgery for compressive symptoms for patients with marked thyromegaly has been shown to be effective (4,5,8). A study analyzing outcomes in 29 patients with marked thyromegaly who underwent thyroidectomy, of which 25 had compressive symptoms, found that all 25 patients in this group reported improvement in symptoms after surgery (4). Of note, 18 of these patients had evidence of tracheal compression and 19 had evidence of substernal extension preoperatively (4). Other studies have also shown that thyromegaly in the

Table 1 Patient demographics

	Asymptomatic	Symptomatic	P value
N	48.0	51.0	
Mean age (range)	48.0 (19.0-87.0)	49.7 (18.0-78.0)	0.551
Number female (%)	37.0 (77.1)	44.0 (86.3)	0.236
Diagnosis (%)			
Diffuse hyperplasia	1.0 (2.1)	1.0 (2.0)	0.965
Focal nodular hyperplasia	3.0 (6.3)	3.0 (5.9)	0.939
Follicular adenoma	3.0 (6.3)	3.0 (5.9)	0.939
Follicular carcinoma	5.0 (10.4)	–	0.018
Hurthle cell adenoma	1.0 (2.1)	1.0 (2.0)	0.965
Hyperplastic change/nodule	5.0 (10.4)	4.0 (7.8)	0.656
Medullary carcinoma	1.0 (2.1)	–	0.300
Multinodular goiter	15.0 (31.3)	36.0 (70.6)	<0.0001
Neuroendocrine carcinoma	1.0 (2.1)	–	0.300
Other	3.0 (6.3)	4.0 (7.8)	0.757
Papillary carcinoma	12.0 (25.0)	5.0 (9.8)	0.045
Papillary microcarcinoma	5.0 (10.4)	3.0 (5.9)	0.408
Thyroiditis	7.0 (14.6)	6.0 (11.8)	0.678

Table 2 Comparison of nodule size, lobe size, and thyromegaly between groups

	Asymptomatic	Symptomatic	P value
N	48.0	51.0	
Mean largest nodule, cm (SD)	2.2 (1.3)	3.8 (1.9)	<0.0001
Mean largest lobe, cm (SD)	4.9 (1.1)	6.2 (1.9)	<0.001
Visible thyromegaly, N (%)	4.0 (15.4)	30.0 (65.2)	<0.0001

SD, standard deviation.

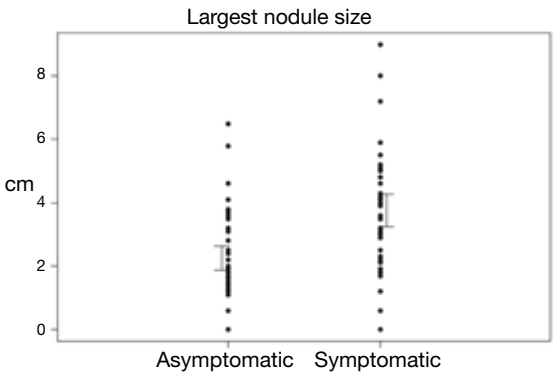

Figure 1 Largest nodule size in the asymptomatic versus symptomatic cohorts. Error bars represent 95% confidence intervals for the mean.

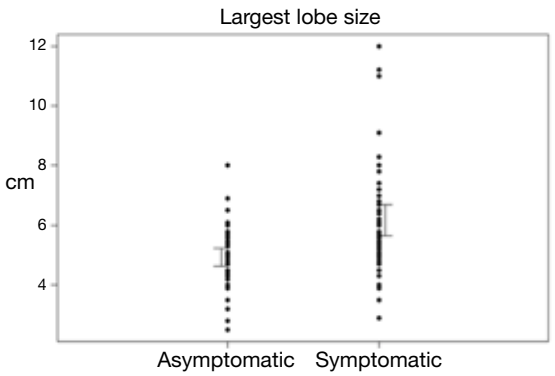

Figure 2 Largest lobe size in the asymptomatic versus symptomatic cohorts. Error bars represent 95% confidence intervals for the mean.

setting of tracheal compression, deviation, or substernal extension is often associated compressive symptoms, which improve with surgery (4,5,8,9).

The efficacy of thyroid surgery for compressive symptoms from smaller thyroid nodules is less well defined. A more recent study, and the only series to compare thyroid volume and compressive symptoms, analyzed 333 consecutive patients who underwent thyroidectomy (for all indications). The study found that as many as 52% of patients experienced some form of compressive symptoms preoperatively when adequately questioned during initial interview (5). The most common compressive symptom was dysphagia, found in 39% (131 patients), followed by dyspnea in 25% (83 patients), and globus found in 10% (32 patients). On average, patients with compressive symptoms were found to have a larger thyroid gland compared to asymptomatic patients (75.5 *vs*. 37.1 mL) (5). The authors, however, did not examine whether nodule size or volume correlated with compressive symptoms.

In our study, compressive symptoms were present preoperatively in 51.5% of our patients. The most common symptom was dysphagia, occurring in 80% of patients, followed by globus (69%), choking (49%), and dyspnea (32%). Patients with compressive symptoms were more likely to have larger thyroid lobes [6.2 cm (95% CI: 5.7-6.7) *vs*. 4.9 cm (95% CI: 4.6-5.2), P<0.001] and larger thyroid nodules [3.8 cm (95% CI: 3.3-4.3) *vs*. 2.2 cm (95% CI: 1.9-2.6), P<0.0001)].

In the study by Banks *et al*., 92% of patients with compressive symptoms who underwent thyroidectomy had improvement in their symptoms, however, 8% had persistent compressive symptoms (5). Interestingly, the average volume of thyroid gland removed in those patients whose compressive symptoms improved compared to those whose symptoms did not improve was statistically the same. In their series, the presence of anaplastic thyroid carcinoma, a history of subglottic stenosis, and the development of a postoperative hematoma was associated with the persistence of postoperative compressive symptoms (5).

In our study, 93% of patients experienced resolution of symptoms postoperatively. When excluding patients with thyroid nodules <1.5 cm, 97% of patients experienced resolution of symptoms postoperatively. Of three patients with compressive symptoms with a negative barium swallow and dysphagia workup, and with a thyroid nodule <1.5 cm, only two of three experienced resolution of compressive symptoms.

We chose visible thyromegaly as a physical exam finding to provide gross assessment of thyroid bulk despite its limitations, as this was an easily obtained finding, and because the World Health Organization and the International Council for the Control of Iodine Deficiency Disorders has already proposed a grading system for endemic goiter (10). In addition, there is published data mostly from the endemic goiter literature that shows good correlation between "visible goiter" physical examination findings with compressive symptoms (11). Banks *et al*. also investigated whether "marked thyroid enlargement" predicted compressive symptoms. The authors defined "marked thyroid enlargement" as a thyroid volume >40 mL for a lobe or >80 mL for bilateral lobes (5). They found that 31% of patients with compressive symptoms had marked thyromegaly compared to only 17% of patients without compressive symptoms (5). In our study, we instead chose to distinguish "visible thyromegaly" from "palpable thyromegaly" based on a physical examination findings rather than a calculated sonographic measurement. We found that visible thyromegaly was present in 65.2% of symptomatic patients and in only 15.4% of asymptomatic patients (P<0.0001).

Banks *et al*. demonstrated that compressive symptoms occurred most frequently in patients with lymphocytic thyroiditis (72%) and anaplastic thyroid carcinoma (71%), followed by multinodular goiter (60%). Only 20% of patients with papillary thyroid carcinoma experienced compressive symptoms (5). Unfortunately, their study did not control for nodule size. Therefore, it is unclear whether patients with papillary thyroid carcinoma experienced less compressive symptoms than those with multinodular goiter, for example, because of the malignant nature of the nodule or because of a probable smaller nodule size. In our series, we found that 71% of symptomatic patients had multinodular goiter while 16% has papillary thyroid carcinoma, and only 12% had thyroiditis. In our analysis, only multinodular goiter was associated with more compressive symptoms.

We also investigated whether nodules on the left were more likely to cause compressive symptoms, especially dysphagia. We hypothesized that as the cervical esophagus normally lies in the left neck (posterolaterally to the left thyroid lobe), left sided thyroid nodules might be more likely to cause dysphagia. However, there was no difference in compressive symptoms of right *vs*. left sided thyroid nodules.

We acknowledge several limitations of this study. First, as a retrospective study, the design introduces selection bias and limits the ability to determine whether the relationship between nodule size and compressive symptoms is causal

or predictive. In addition, patient factors such as ethnicity, height or body habitus, potentially contributing to the presence of compressive symptoms, were not assessed. Next, while our study was adequately powered to demonstrate significant improvement in compressive symptoms in patients with thyroid nodules >1.5 cm, our study does have a relatively small cohort of patients. Further, we did not evaluate whether thyroid nodules were calcified or not (ostensibly, calcified thyroid nodules might cause more compressive symptoms), nor did we qualify whether the thyroid nodules were in an anterior or posterior location (ostensibly, posterior left sided thyroid nodules might be more likely to cause dysphagia compared to anterior left sided thyroid nodules). Much of this information was not readily available from the sonography reports.

Conclusions

Nodule size and lobe size directly correlate with compressive symptoms. Of patients with compressive symptoms and a thyroid nodule >1.5 cm, 97% will experience improvement in symptoms postoperatively.

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References

1. Dean DS, Gharib H. Epidemiology of thyroid nodules. Best Pract Res Clin Endocrinol Metab 2008;22:901-11.
2. Greenblatt DY, Sippel R, Leverson G, et al. Thyroid resection improves perception of swallowing function in patients with thyroid disease. World J Surg 2009;33:255-60.
3. Moumen M, Mehhane M, Kadiri B, et al. Compressive goiters. Apropos of 80 cases. J Chir (Paris) 1989;126:521-6.
4. McHenry CR, Piotrowski JJ. Thyroidectomy in patients with marked thyroid enlargement: airway management, morbidity, and outcome. Am Surg 1994;60:586-91.
5. Banks CA, Ayers CM, Hornig JD, et al. Thyroid disease and compressive symptoms. Laryngoscope 2012;122:13-6.
6. Lacoste L, Gineste D, Karayan J, et al. Airway complications in thyroid surgery. Ann Otol Rhinol Laryngol 1993;102:441-6.
7. Alfonso A, Christoudias G, Amaruddin Q, et al. Tracheal or esophageal compression due to benign thyroid disease. Am J Surg 1981;142:350-4.
8. Netterville JL, Coleman SC, Smith JC, et al. Management of substernal goiter. Laryngoscope 1998;108:1611-7.
9. Wormer BA, McHenry CR. Hashimoto's thyroiditis: outcome of surgical resection for patients with thyromegaly and compressive symptoms. Am J Surg 2011;201:416-9; discussion 419.
10. WHO, UNICEF, ICCIDD. Indicators for assessing Iodine Deficiency Disorders and their control through salt iodization. Geneva: WHO, 1994.
11. Agarwal A, Agarwal S, Tewari P, et al. Clinicopathological profile, airway management, and outcome in huge multinodular goiters: an institutional experience from an endemic goiter region. World J Surg 2012;36:755-60.

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Is there a case for selective, rather than routine, preoperative laryngoscopy in thyroid surgery?

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Background: According to some authors, routine preoperative laryngoscopy should be the standard of care in all patients undergoing thyroid surgery. The rationale for this approach is (I) the risk that a patient has a preoperative vocal cord palsy (VCP) without symptoms; (II) the presence of VCP preoperatively is suggestive of invasive malignancy; (III) it is relevant for the use of intraoperative nerve monitoring; and (IV) surgical strategy may be better defined if a paralysed vocal cord is detected preoperatively.

Methods: This is a review of studies of patients who underwent routine preoperative laryngoscopy to anticipate preoperative VCP and that evaluated related risk factors, including previous surgery, voice function complaints, and a diagnosis of malignancy. The estimated risk of sustaining preoperative VCF in the absence of these factors was determined. The relevant current guidelines from different professional bodies are also addressed.

Results: The level of evidence that supports routine preoperative laryngoscopy is weak. The risk of harboring preoperative VCP in the absence of previous neck or other risk-related surgery, advanced malignancy or voice symptoms is very low (0.5% of cases).

Conclusions: Selective rather than routine use of preoperative laryngoscopy may be acceptable provided that the risk of undetected paralysis is as low as can be reasonably ascertained from the available literature.

Keywords: Laryngoscopy; thyroidectomy; vocal cord paralysis; preoperative period

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Introduction

Recent data on surgery for thyroid malignancies show an annual incidence of 7-9 per 100,000 inhabitants (1-3). Since malignant thyroid tumors account for 25-30% of all thyroid procedures, the number of procedures carried out for all thyroid diseases may easily be as high as 30-40 per 100,000 habitants. When performed by experienced surgeons, thyroidectomy is a highly safe procedure, with a low risk of injury to the recurrent laryngeal nerves (RLN). Although preoperative and postoperative laryngeal function assessment has been proposed as the standard of practice in patients scheduled for thyroid surgery, its routine use is controversial and the data are conflicting (4,5).

Much attention has been directed to postoperative voice changes due to vocal fold palsy (VCP) secondary to injury to the RLN. The prevalence of VCP immediately after surgery varies between published series but may be as high as 9-10% (6). Most of these cases are temporary and patients recover within 12 months after surgery. Permanent postoperative VCP occurs in 2-3% of patients undergoing thyroid surgery. However, prevalence figures greatly vary depending on the adopted policy regarding postoperative laryngeal exam, as they are roughly twice as high if a laryngeal exam is performed routinely rather than only in those patients with postoperative hoarseness (7). Thus, the rates of postoperative VCP reported in the literature may underestimate the real prevalence.

The use of routine postoperative laryngoscopy has been further endorsed by the progressive implementation of

intraoperative neural monitoring (IONM) of the RLN. Postoperative laryngoscopy provides additional information allowing maximum interpretation of the data obtained from IONM, rules out many cases of postoperative voice changes in which vocal cord function is normal, and has implications regarding the safety of future, contralateral surgery. All of these reasons have been cited in recommending the routine use of laryngoscopy after thyroid surgery as the standard of care (8).

The rationale for the use of preoperative routine laryngoscopy as the standard of care in thyroid surgery use is based on four arguments:

(I) There is a significant risk of detecting a preoperative VCP in patients with normal phonatory function;
(II) VCP may preoperatively suggest invasive malignancy;
(III) When found at surgery, a nerve invaded by tumor may be better managed if there is previous knowledge of its functional state;
(IV) The data provide an accurate baseline for postoperative laryngeal assessment.

In addition to identifying VCP due to invasive thyroid malignancy, preoperative laryngoscopy can aid in identifying patients with VCP of idiopathic origin or due to previous neck surgery or other, unusual causes. Preoperative detection of VCP also safeguards the surgeon from potential postoperative litigation when the condition first manifests postoperatively (9). Furthermore, the use of IONM requires knowledge of preoperative vocal cord function as an optimal basis for accurate intraoperative monitoring (8). Finally, an accurate surgical quality assessment through a postoperative vocal cord examination relies on precise knowledge of preoperative vocal cord function.

Direct fiber-optic laryngoscopy can be easily performed with very little training such that all endocrine surgeons should be competent at vocal cord evaluation. In fact, the American Association of Endocrine Surgeons is in the process of developing courses in basic laryngeal fiber-optic evaluation (10). This can be interpreted as a clear change in policy, as in their 2001 and 2010 guidelines there is no mention of a preoperative endoscopic evaluation (11,12).

Nonetheless, there is also substantial support for a more selective preoperative approach, given that patients without risk factors are highly unlikely to harbor a preoperative VCP (13-16). Additionally, most units do not have the appropriate equipment to carry out a preoperative direct laryngoscopy. Moreover, surgeons involved in high-volume practices and thus lacking the time to perform the procedure routinely would need to refer a considerable number of patients to an otorhinolaryngology department, which may delay surgery. An alternative is indirect laryngoscopy by mirror examination, which in most cases is a very simple procedure that provides an indirect view of the vocal cords.

Here we apply an evidence-based approach to analyze the prevalence of preoperative VCP and the risk factors that may predict it. We also review the recommendations provided by different professional bodies.

Etiology of vocal cord paralysis

Functional impairment of the RLN may result from a variety of causes and the damage or injury sustained can occur anywhere along their anatomical course. The etiology of RLN paralysis can be divided into three main causes: surgery-related, tumor invasion, and idiopathic. This was confirmed in a review published by Myssiorek *et al*., in which surgical injury was the most frequent etiology (30-45% of the cases), followed by direct nonlaryngeal tumor invasion (15-30%), and other causes including idiopathic injury (10-25%) (17).

Carotid endarterectomy, thyroid surgery, an anterior approach to the cervical spine, cardiothoracic surgery, and skull-base surgery are the most common operations causing a RLN injury. Although thyroid surgery remains the single most common operation associated with paralysis, the improved techniques for thyroid surgery and the increasing implementation of the other, above-mentioned non-thyroid procedures have increased the relative incidence of the latter as the major cause (18). The prevalence of postoperative VCP in patients undergoing carotid endarterectomy is 2-6%, with functional improvement or complete recovery ranging from 50% to most of these patients.

Events associated with endotracheal intubation are also worth considering. Endotracheal intubation due to different mechanisms accounted for 7% to 11% of RLN paralysis in several larger series, although most patients recovered spontaneously within 6 months (17).

Other, less frequent etiologies of VCP include viral infections, drug induced, jugular vein thrombosis, central venous access procedures, stroke and diabetic neuropathy. Laryngeal dysfunction may also occur with infarcts of the brain, especially of the medulla. This is usually accompanied by dysfunction of the pharyngeal and laryngeal branches of cranial nerves IX and X along with ipsilateral VCP, leading to swallowing difficulty and aspiration. In a series of patients who underwent thyroid surgery, the preoperative

Table 1 Prevalence of preoperative VCP from series of patients with routine preoperative laryngoscopy

Studies	Prevalence	% (95% CI)*	Design
Franch-Arcas, 2014†	7/484	1.4 (0.70-2.95)	Retrospective cohort
Lorenz *et al*. (20)	285/8,128	3.5 (3.13-3.93)	Retrospective cohort
Xin *et al*. (21)	39/1,515	2.6 (1.89-3.50)	Retrospective cohort
Lee *et al*. (22)	11/464	2.4 (1.33-4.19)	Retrospective cohort
Lang *et al*. (16)	7/302	2.3 (1.13-4.71)	Prospective cohort
Wong *et al*. (23)	0/204	0.0 (0.00-1.85)	Prospective cohort
Nam *et al*. (24)	6/500	1.2 (0.55-2.59)	Prospective cohort. Previous neck surgery excluded
Shin *et al*. (25)	7/198	3.5 (1.72-7.12)	Retrospective cohort. All patients with benign thyroid
Wang *et al*. (26)	12/187	6.4 (3.71-10.8)	Retrospective cohort
Goretzki *et al*. (27)	8/1,333	0.6 (0.30-1.18)	Retrospective cohort
Roh *et al*. (28)	29/319	9.1 (6.40-12.7)	Prospective cohort. All patients with malignancy
Schlosser *et al*. (15)	13/695	1.9 (1.10-3.17)	Retrospective cohort
Randolph *et al*. (9)	16/365	4.4 (2.71-7.00)	Retrospective cohort, 14 VCP cases with invasive malignancy
Farrag *et al*. (29)	22/340	6.5 (4.31-9.60)	Retrospective cohort
Chan *et al*. (30)	20/709	2.8 (1.83-4.32)	Retrospectively cohort. All patients with malignancy
Steurer *et al*. (31)	14/563	2.5 (1.49-4.13)	Prospective cohort
Yeung *et al*. (14)	1/160	0.6 (0.11-3.45)	Prospective cohort
Rowe-Jones *et al*. (32)	29/2,408	1.2 (0.84-1.72)	Retrospective cohort. Previous thyroid surgery excluded
Järhult *et al*. (13)	2/174	1.1 (0.32-4.09)	Prospective cohort
Curley *et al*. (33)	25/1,740	1.4 (0.98-2.11)	Retrospective cohort
Holl-Allen *et al*. (34)	13/1,200	1.1 (0.63-1.84)	Prospective cohort

†, unpublished data from the author; *CI, confidence intervals calculated using Wilson's method (35). VCP, vocal cord palsy.

prevalence of VCP was 10-fold higher in those with diabetic neuropathy (19). This relationship should be taken into account during the preoperative workup of patients undergoing thyroid surgery.

Finally, there are also a considerable number of cases of VCP without obvious cause. These idiopathic cases account for 10-20% of all VCPs.

Reported prevalence of preoperative vocal cord paralysis

The prevalence of VCP in patients who underwent routine laryngoscopy as part of the preoperative workup for thyroid surgery has been retrospectively reviewed in several case series. The data reported in those studies greatly vary, given that the characteristics of the included patients (e.g., the proportion with a malignant thyroid tumor and the inclusion of patients with revision procedures or previous neck surgery) may modify the determined preoperative risk of VCP.

This review considers 20 case series in which patients scheduled for thyroid surgery underwent routine preoperative laryngoscopy (9,13-16,20-34). Most of the included series are retrospective. We also made use of data extracted from the database of endocrine surgery patients treated in our department from 2007 to 2013 (Franch-Arcas *et al*., unpublished data). Because all of the reviewed data involve series with small numbers of patients, the prevalence should be interpreted with caution. Data from the included studies are summarized in *Table 1*. Excluding series with <200 patients and others based only on patients with malignancies, the prevalence of preoperative VCP ranges from 1% to 6%.

Asymptomatic vocal fold palsy

Patients with VCP may be asymptomatic, due to variable remaining vocal cord function as well as variability in the position of the paralyzed vocal cord and functional compensation by the contralateral vocal cord. Slow-growing

tumors that infiltrate or surround the nerve generally allow compensation for paralysis such that even in the presence of an immobile cord, symptoms may not be evident. Similarly, in patients with long-standing benign goiter, progressive stretching of the laryngeal nerve may allow for functional compensation. Even in the case of a permanent symptomatic VCP, the symptoms may improve with time and even disappear, falsely suggesting that the paralysis has resolved. In a study of 98 patients with paralyzed cords of different etiologies, as many as 19 patients were asymptomatic (36). Data on the prevalence of asymptomatic VCP among all reported cases of VCP were available for 13 out of the 20 studies included in this review (*Table 2*). They show that asymptomatic VCP is not rare at all and may account for >50% of all VCPs.

Table 2 Prevalence of asymptomatic VCP with regard to all reported VCP (from those studies with available data)

Studies	Asymptomatic/all VCP	% [95% CI]*
Franch-Arcas G, 2014†	4/7	57 [25-84]
Lee *et al*. (22)	3/8	37 [13-69]
Lorenz *et al*. (20)	36/285	13 [9-17]
Lang *et al*. (16)	4/7	57 [25-84]
Xin *et al*. (21)	34/39	87 [73-94]
Shin *et al*. (25)	0/7	0 [0-35]
Roh *et al*. (28)	5/14	36 [16-61]
Schlosser *et al*. (15)	5/13	38 [17-64]
Randolph *et al*. (9)	11/16	56 [33-77]
Farrag *et al*. (29)	7/22	32 [16-53]
Chan *et al*. (30)	0/20	0 [0-16]
Steurer *et al*. (31)	6/14	43 [21-67]
Yeung *et al*. (14)	1/1	100 [21-100]
Curley *et al*. (33)	0/25	0 [0-13]

†, unpublished data from the author; *CI, confidence intervals calculated using Wilson's method (35); VCP, vocal cord palsy.

There is some debate on whether the definition of "voice symptoms" should be considered as those complaints referred by the patient or the subjective evaluation by the surgeon. In the study by Lee *et al*. the prevalence of preoperative voice symptoms was 39% of patients if any voice complaint referred by the patient was registered as "voice symptoms", whereas this prevalence dropped to 4% if only surgeon-documented voice abnormalities were considered (22). Recent guidelines from the American Academy of Otolaryngology-Head and Neck Surgery Foundation recommends the use of more objective methods for assessing patient's preoperative voice, including patient self-report scores, audio-perceptual judgment and acoustic measurement of audio recordings (37).

The sensitivity and specificity of the presence of voice symptoms as a screening test for preoperative VCP is shown in *Table 3*. In most of the studies, sensitivity did not reach 75%. Sensitivity was lowest in the study by Randolph

Table 3 Voice symptoms as screening test for preoperative vocal cord palsy (sensitivity and specificity calculated from those studies with available data)

Studies	Prevalence of preoperative VCP (%)		Sensitivity, % [95% CI]*	Specificity, % [95% CI]	P**
	Patients with voice symptoms	Patients without voice symptoms			
Lee *et al*. (22)	8/19 (42.11)	3/445 (0.67)	73 [39-94]	98 [96-99]	<0.0001
Lang *et al*. (16)	3/33 (9.09)	4/269 (1.49)	43 [10-82]	90 [86-93]	0.03
Shin *et al*. (25)	7/24 (29.17)	0/174 (0)	100 [59-100]	91 [86-95]	<0.0001
Schlosser *et al*. (15)	7/94 (7.45)	6/601 (0.99)	54 [25-81]	87 [85-90]	<0.0001
Randolph *et al*.† (9)	5/6 (83.33)	10/15 (66.67)	33 [11-61]	83 [36-99]	0.76
Farrag *et al*. (29)	15/48 (31.25)	7/292 (2.40)	68 [45-86]	90 [86-93]	<0.0001
Yeung *et al*. (14)	0/18 (0)	1/142 (0.70)	0 [0-97%]	88 [82-93]	0.21

†, analyzed only patients with locally invasive cancer; *CI, confidence interval calculated using Wilson's method (35); **, comparison of prevalence of VCP between patients with and without voice symptoms applying Chi-square test or Fisher's exact test when appropriate; VCP, vocal cord palsy.

Table 4 Relative risk for preoperative vocal cord palsy in patients with diagnosis of cancer with respect to benign thyroid (calculated from those studies with available data)

Studies	Prevalence of preoperative VCP		Relative risk, % (95% CI)*	P**
	Patients with thyroid cancer	Patients with benign thyroid		
Franch-Arcas, 2014†	2/104 (1.92)	5/380 (1.32)	1.5 (0.3-7.4)	0.64
Xin *et al*. (21)	11/900 (1.22)	28/712 (3.93)	0.3 (0.2-0.6)	0.0006
Lee *et al*. (22)	4/278 (1.44)	7/186 (3.76)	0.4 (0.1-1.3)	0.13
Lang *et al*. (16)	5/101 (4.95)	2/201 (0.99)	5 (0.9-25.2)	0.06
Randolph *et al*. (9)	15/135 (11.11)	1/230 (0.43)	26 (3.4-191)	0.002
Steurer *et al*. (31)	11/164 (6.71)	3/399 (0.75)	8.9 (2.5-31.5)	0.0003
Row-Jones *et al*. (32)	7/87 (8.04)	22/2,321 (0.95)	8.5 (3.7-19.3)	<0.0001
Järhult *et al*. (13)	2/21 (9.52)	0/153 (0)	35.0 (1.7-705)	0.03
Holl-Allen *et al*. (34)	5/44 (11.36)	8/1,156 (0.69)	16.4 (5.6-48.2)	<0.0001

†, unpublished data from the author; *CI, confidence interval calculated using Katz's method (39); **, Chi-square test or Fisher's exact test when appropriate; VCP, vocal cord palsy.

et al.: 33% had symptoms and 66% were asymptomatic (9). Within the total group of 365 patients undergoing thyroidectomy, there were 16 cases of preoperative VCP and all but one were attributable to locally invasive thyroid cancer. Since in that study sensitivity was calculated only from the group of 21 patients with invasive cancer, the confidence interval for the sensitivity determination is very broad (11-61%). Accordingly, the sensitivity of 33% should not be universally extrapolated. As discussed above, a long-standing, slow-growing tumor may allow for contralateral compensation and thus obscure symptoms. The >85% specificity determined for most of the studies means that among patients without VCP >85% will also not have voice symptoms, but 15% will have voice symptoms.

We can therefore conclude that voice symptoms are not a good predictor of the presence of VCP. While they may contribute to a preoperative diagnosis or suspicion of VCP, their presence is by no means pathognomonic.

Thyroid cancer

Hoarseness and VCP in a patient with a thyroid nodule have long been considered as indicative of advanced thyroid cancer. In the study by Randolph *et al*. (9), the presence of preoperative VCP had an excellent predictive value for the detection of invasive thyroid cancer at surgery (sensitivity 76%, specificity 100%). However, as commented above, these figures must be interpreted with caution since all but one of the cases of VCP in that study were occurred in patients with invasive cancer.

Local invasion seems to be the main reason for the increased risk of VCP in patients with thyroid cancer. However, locally advanced cancer may not always be diagnosed preoperatively and the suspicion or diagnosis of thyroid cancer may be enough to justify performing a laryngoscopy as part of the preoperative workup. This is especially true for patients with tumors that are not anterior in their anatomical location—that is, at a distance from the course of the RLN—and where the presence of extrathyroidal invasion is difficult to confirm. If preoperative VCP is encountered, radiological and other diagnostic workups may be expanded accordingly and surgical planning will need to consider a more complex procedure. Furthermore, when found at surgery, a nerve invaded by tumor may be better managed if there is previous knowledge of its functional state. A functional nerve should be preserved providing that there is no residual gross disease (38).

Relative risk for preoperative vocal cord palsy in patients with diagnosis of cancer with respect to benign thyroid is shown in *Table 4*. In most of the studies, a diagnosis of cancer increased the risk of VCP. This finding likely derived from the inclusion of patients with local advancer cancer, although this was not clearly stated in the eight studies. Everything considered, all patients with suspected invasive cancer—and perhaps also all patients with suspected or diagnosed cancer—should undergo preoperative laryngoscopy.

Table 5 Relative risk for preoperative vocal cord palsy in patients with secondary surgery (previous neck surgery) with respect to patients with primary surgery (calculated from those studies with available data)

Studies	Prevalence of preoperative VCP (%)		Relative risk, % (95% CI)*	P**
	Patients with previous surgery	Patients with primary surgery		
Lee *et al*. (22)	6/68 (8.82)	5/396 (1.26)	6.9 (2.1-22.2)	0.004
Lang *et al*. (16)	6/29 (20.69)	1/273 (0.36)	56.4 (7.0-453.1)	<0.0001
Shin *et al*. (25)	3/40 (7.50)	4/158 (2.53)	2.96 (0.7-12.7)	0.14
Roh *et al*. (28)	2/21 (9.52)	12/298 (4.26)	2.3 (0.5-9.8)	0.23
Schlosser *et al*. (15)	6/65 (9.23)	7/630 (1.11)	8.3 (2.8-23.9)	<0.0001
Steurer et al. (31)	5/47 (10.64)	9/516 (1.74)	6.1 (2.1-17.4)	0.0001

*CI, confidence interval calculated using Katz's method (39); **, Chi-square test or Fisher's exact test when appropriate; VCP, vocal cord palsy.

Previous surgery and the increased risk of vocal cord paralysis

Surgical injury is the most frequent etiology of VCP. While thyroid surgery remains the single most frequent operation associated with VCP, surgical procedures involving an anterior approach to the cervical spine, carotid endarterectomy, cardiothoracic surgery, and skull base surgery, are examples of non-thyroid procedures that also have been associated with postoperative VCP. Advances in thyroid surgery and the increasing implementation of these other procedures have increased the relative incidence of the latter as the major cause of VCP with a surgical etiology. Events associated with endotracheal intubation are also worth considering.

The association of revision (secondary) surgery with preoperative VCP could be evaluated based on data obtained from six of the reviewed studies, most of which showed a strong relationship between previous neck surgery and preoperative VCP. The relative risk for preoperative vocal cord palsy in patients with previous neck surgery is shown in *Table 5*; the data demonstrate that all patients with previous surgery, including the above-mentioned non-thyroid surgical procedures, should be scheduled for preoperative laryngoscopy.

Recommendations on preoperative laryngoscopy from current guidelines

Several current guidelines regarding thyroid procedures, including those of the American Thyroid Association, American Association of Clinical Endocrinologists, European Thyroid Association, Spanish Association of Endocrinology and Nutrition, and The European Society for Medical Oncology, make no reference at all to laryngoscopy as part of the preoperative workup for thyroid nodules (12,40-42).

The positive recommendations provided by other guidelines are summarized in *Table 6*. Most of them agree regarding a routine policy for patients with thyroid cancer (37,38,43-47,49,52). The recent guidelines for anaplastic cancer from the American Thyroid Association also point out that preoperative laryngoscopy can be used to assess the opposite vocal cord, vocal cord mobility, endolaryngeal pathology, and potential disease extension into the subglottic or upper tracheal area (49). The European Consensus of 2006 recommends preoperative laryngoscopy only in patients with locally advanced cancer or symptoms (51). Two of the guidelines put forward a more general "recommended for all cases" policy statement, including cases of benign thyroid disease (8,50). The guideline on benign thyroid disease of the German Association of Endocrine Surgeons is somewhat ambiguous in that preoperative laryngoscopy "is recommended in general" but "is indispensable in patients with dysphonia or after previous surgery in the neck" (50).

The level of evidence of the recommendations from the examined guidelines (53) is low. Half of the recommendations are based on level 5 evidence (grade of recommendation D) and the rest on level 2b evidence (grade of recommendation B-C), and almost all of them referred to only two studies, those of Randolph *et al*. (9) and Farrag *et al*. (29).

Table 6 Summary of guidelines/consensus on preoperative laryngoscopy

Guideline: scope [Year]	Recommendation†	Referred literature	LE/GR‡
British Thyroid Association: thyroid cancer [2014] (43)	"Is recommended prior to surgery for diagnostic and audit purposes"	Chandrasekhar *et al*. (37)	2b/B-C
NCCN [2014] (44)	"Consider evaluation of vocal cord mobility in all cases"		5/D
AHNS: invasive differentiated thyroid cancer [2014] (38)	"Is recommended in the management of differentiated thyroid cancer"	Farrag *et al*. (29); Randolph *et al*. (9)	2b/B-C
AEC: thyroid surgery clinical pathway [2014] (45)	"If voice symptoms, previous neck surgery, IONM planned, thyroid cancer, or big benign goiters"		5/D
Japanese Society of Thyroid Surgeons: treatment of thyroid tumor [2013] (46)	Recommended "for the evaluation of invasion to the recurrent nerve"	Randolph *et al*. (9)	2b/B-C
German Association of Endocrine Surgeon: malignant thyroid tumors [2013] (47)	"Generally recommended. It is imperative after previous neck surgery and when the voice is abnormal"	Farrag *et al*. (29); Randolph *et al*. (9)	2b/B-C
American Academy of Otolaryngology-Head and Neck Surgery Foundation: clinical practice guideline for optimize voice outcomes [2013] (37)	"If voice impaired, thyroid cancer with suspected extrathyroidal extension or prior neck surgery"	Farrag *et al*. (29); Randolph *et al*. (9); Curley *et al*. (33); Curran *et al*. (48)	2b/B-C
American Thyroid Association Guidelines: anaplastic thyroid cancer [2012] (49)	"Every patient should undergo initial evaluation of the vocal cords"		5/D
International Neural Monitoring Study Group: Standards in electrophysiologic IONM [2011] (8)	"Preoperative glottic function information in all cases is essential for accurate monitoring"	Randolph *et al*. (9)	2b/B-C
German Association of Endocrine Surgeon: benign thyroid [2011] (50)	"Is recommended in general. Is indispensable in patients with dysphonia or after previous surgery in the neck"	Farrag *et al*. (29); Randolph *et al*. (9); Steurer *et al*. (31)	2b/B-C
European Consensus: differentiated thyroid carcinoma [2006] (51)	"In the presence of locally aggressive cancers with signs or symptoms of extrathyroidal invasion"		5/D
British Association of Endocrine Surgeons: endocrine diseases [2003] (52)	When "history of voice change, previous thyroid surgery or if thyroid malignancy"		5/D

†, quoted text from guidelines; ‡, classification from the Oxford Centre for Evidence-Based Medicine (53); NCCN, National Comprehensive Cancer Network: thyroid carcinoma; AHNS, American Head and Neck Society; AEC, Asociación Española de Cirujanos; IONM, intraoperative neural monitoring; LE, level of evidence; GR, grade of recommendation.

The more specific "Clinical Practice Guideline for Optimize Voice Outcome," from the American Academy of Otolaryngology-Head and Neck Surgery Foundation, recommends a selective policy when "voice impaired, thyroid cancer with suspected extrathyroidal extension or prior neck surgery" is present (37). It also notes that while preoperative laryngoscopy would be ideal in all patients undergoing thyroidectomy, the combined level of evidence is not high enough to expand the recommendation to all patients, including those with a normal voice and no prior neck surgery.

Is there a case for selective preoperative laryngoscopy?

Whether cases of VCP would remain undiagnosed if laryngoscopy was performed only in patients at high risk is unclear. With the adoption of a selective preoperative laryngoscopy approach, the risk of an undiagnosed VCP will never be equal to zero. Therefore, the important question is whether the magnitude of this risk may be considered as low as can be reasonably ascertained. Unfortunately, the data included in this review do not provide a definitive

answer to the dilemma. Indeed, only 8 out of the 20 studies contain information that is useful in this regard, as they provide combined data on the number of preoperative VCPs in patients without voice symptoms, thyroid cancer, or previous neck surgery (9,14-16,22,25,29,31).

Three of these eight studies recommend routine laryngoscopy:

(I) Shin *et al*. recommended routine laryngoscopy "because glottic function cannot be predicted by voice assessment" (25). However, in their analysis of 198 patients, including 7 with preoperative VCPs, none were asymptomatic. Thus, if a selective laryngoscopy approach had been adopted, not a single case of VCP would have been missed.

(II) In the study by Farrag *et al*., among 292 patients, there were 5 with asymptomatic VCP associated with slowly progressive benign disease (29). However, whether these five patients were the same five who underwent revision surgery, also mentioned in the study, could not be determined from the data.

(III) Randolph *et al*. also strongly recommended routine laryngoscopy (9). However, according to their data, excluding carcinoma, there was only 1 patient with VCP among the 344 patients evaluated and he or she seems to have been symptomatic (data were unclear in this regard). In this series a selective preoperative laryngoscopy approach would not have resulted in undiagnosed cases of preoperative VCP.

The remaining five studies concluded that a selective approach may also be appropriate:

(I) In the study by Lang *et al*. the prevalence of asymptomatic VCP in a previously non-operated group of patients was 1/245 (0.41%) (16);

(II) In the study by Lee *et al*. only 1 out of 389 asymptomatic and previously non-operated patients had a VCP (0.25%) (22);

(III) In the study by Schlosser *et al*., among the 420 patients with neither voice symptoms, nor revision surgery, nor thyroid cancer, only 1 patient had preoperative VCP (0.23%) (15);

(IV) In the 372 previously non-operated patients with benign thyroid disease evaluated by Steurer *et al*., there were 3 cases of preoperative VCP (0.8%) (31). Unfortunately it was unclear whether the three patients were asymptomatic;

(V) Finally, in the study by Yeung *et al*., the prevalence of VCP in asymptomatic patients was 1/142 (0.7%) (14).

A clear recommendation cannot be made based on the examined evidence. Whether a <0.5% risk of undiagnosed VCP is acceptable is a matter of debate.

If a policy of selective preoperative laryngoscopy is adopted, then voice symptoms should be assessed through a careful history. However, in the following clinical settings, direct fiber-optic laryngoscopy should certainly be performed (*Figure 1*):

(I) Past or present history of hoarseness or change in voice quality, as noted by either the patient or the surgeon;

(II) History of prior surgery in which the RLN or vagus nerves may have been at risk for injury: thyroid/parathyroid operations, anterior cervical spine, carotid endarterectomy, cervical esophagus, lateral neck, skull base, cardiothoracic procedures and history of any adverse event associated with endotracheal intubation;

(III) Past history of stroke or diabetic neuropathy;

(IV) Large retrosternal or compressive goiters;

(V) Suspicion of a locally advanced cancer or posteriorly situated malignancies. Optionally, all patients with thyroid cancer may be considered eligible for laryngoscopy.

Final remarks

Knowledge of the precise status of the vocal cords in all patients undergoing thyroid-related surgery is good practice for thyroid surgeons. The detection of a VCP preoperatively may modify the planned surgical technique, suggest invasive malignancy, or influence the management of an invaded nerve found at surgery. In addition, preoperative data provide an accurate baseline for postoperative laryngeal assessment. Only routine preoperative laryngoscopy may detect all VCPs. If preoperative laryngoscopy is performed only in patients at high risk (selective approach), a few VCPs (up to 0.5% of cases) will remain undetected. Whether the number of possible undetected palsies is as low as can be reasonably ascertained is a matter of debate.

Neither the necessary laryngoscopy equipment nor the skills required to perform the procedure may be universally available in endocrine surgery units. If the selective approach is adopted, then direct laryngoscopy is advised for all patients with present or past voice symptoms, a history of surgery in which the vagus and RLNs may have been at risk or any adverse events associated with endotracheal intubation, a past history of stroke or diabetic neuropathy,

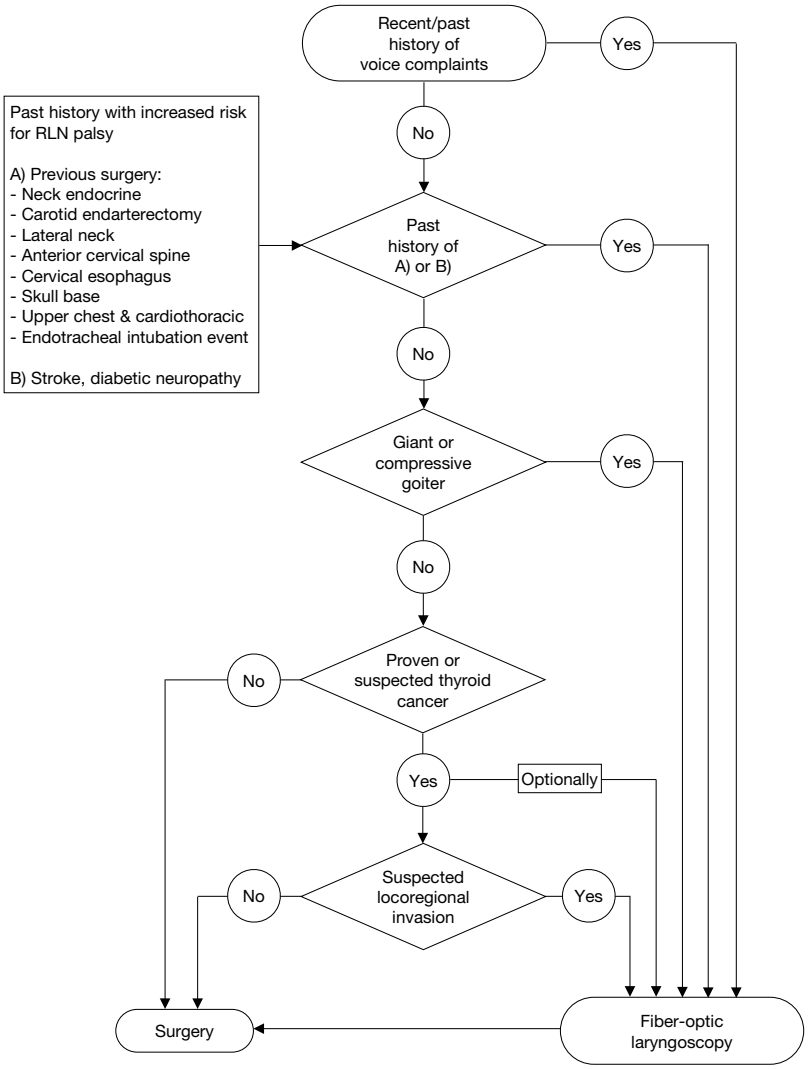

Figure 1 Suggested decision algorithm for preoperative selective laryngoscopy. RLN, recurrent laryngeal nerve.

large retrosternal or compressive goiters, and in patients with a diagnosis or suspicion of advanced thyroid cancer.

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References

1. Dralle H. Thyroid incidentaloma. Overdiagnosis and overtreatment of healthy persons with thyroid illness? Chirurg 2007;78:677-86.
2. Chen AY, Jemal A, Ward EM. Increasing incidence of differentiated thyroid cancer in the United States, 1988-2005. Cancer 2009;115:3801-7.
3. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. JAMA 2006;295:2164-7.
4. Hodin R, Clark O, Doherty G, et al. Voice issues and laryngoscopy in thyroid surgery patients. Surgery 2013;154:46-7.
5. Randolph GW. The importance of pre- and postoperative laryngeal examination for thyroid surgery. Thyroid 2010;20:453-8.
6. Sancho JJ, Pascual-Damieta M, Pereira JA, et al. Risk factors for transient vocal cord palsy after thyroidectomy.

Br J Surg 2008;95:961-7.
7. Bergenfelz A, Jansson S, Kristoffersson A, et al. Complications to thyroid surgery: results as reported in a database from a multicenter audit comprising 3,660 patients. Langenbecks Arch Surg 2008;393:667-73.
8. Randolph GW, Dralle H; International Intraoperative Monitoring Study Group, Abdullah H, et al. Electrophysiologic recurrent laryngeal nerve monitoring during thyroid and parathyroid surgery: international standards guideline statement. Laryngoscope 2011;121 Suppl 1:S1-16.
9. Randolph GW, Kamani D. The importance of preoperative laryngoscopy in patients undergoing thyroidectomy: voice, vocal cord function, and the preoperative detection of invasive thyroid malignancy. Surgery 2006;139:357-62.
10. American Association of Endocrine Surgeons (AAES). Fellowhip Programs. 2014. Available online: http://www.endocrinesurgery.org/fellowships/curriculum.html. Accessed November 22th 2014.
11. Cobin RH, Gharib H, Bergman DA, et al. AACE/AAES medical/surgical guidelines for clinical practice: management of thyroid carcinoma. American Association of Clinical Endocrinologists. American College of Endocrinology. Endocr Pract 2001;7:202-20, Erratum in: Endocr Pract 2008;14:802-3.
12. Gharib H, Papini E, Paschke R, et al. American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and EuropeanThyroid Association Medical Guidelines for Clinical Practice for the Diagnosis and Management of Thyroid Nodules. Endocr Pract 2010;16 Suppl 1:1-43.
13. Järhult J, Lindestad PA, Nordenström J, et al. Routine examination of the vocal cords before and after thyroid and parathyroid surgery. Br J Surg 1991;78:1116-7.
14. Yeung P, Erskine C, Mathews P, et al. Voice changes and thyroid surgery: is pre-operative indirect laryngoscopy necessary? Aust N Z J Surg 1999;69:632-4.
15. Schlosser K, Zeuner M, Wagner M, et al. Laryngoscopy in thyroid surgery--essential standard or unnecessary routine? Surgery 2007;142:858-64; discussion 864.
16. Lang BH, Chu KK, Tsang RK, et al. Evaluating the incidence, clinical significance and predictors for vocal cord palsy and incidental laryngopharyngeal conditions before elective thyroidectomy: is there a case for routine laryngoscopic examination? World J Surg 2014;38:385-91.
17. Myssiorek D. Recurrent laryngeal nerve paralysis: anatomy and etiology. Otolaryngol Clin North Am 2004;37:25-44.
18. Rosenthal LH, Benninger MS, Deeb RH. Vocal fold immobility: a longitudinal analysis of etiology over 20 years. Laryngoscope 2007;117:1864-70.
19. Schlosser K, Maschuw K, Hassan I, et al. Are diabetic patients at a greater risk to develop a vocal fold palsy during thyroid surgery than nondiabetic patients? Surgery 2008;143:352-8.
20. Lorenz K, Abuazab M, Sekulla C, et al. Results of intraoperative neuromonitoring in thyroid surgery and preoperative vocal cord paralysis. World J Surg 2014;38:582-91.
21. Xin J, Liu X, Sun H, et al. A laryngoscopy-based classification system for perioperative abnormal vocal cord movement in thyroid surgery. J Int Med Res 2014;42:1029-37.
22. Lee CY, Long KL, Eldridge RJ, et al. Preoperative laryngoscopy in thyroid surgery: Do patients' subjective voice complaints matter? Surgery 2014;156:1477-82; discussion 1482-3.
23. Wong KP, Lang BH, Ng SH, et al. A prospective, assessor-blind evaluation of surgeon-performed transcutaneous laryngeal ultrasonography in vocal cord examination before and after thyroidectomy. Surgery 2013;154:1158-64; discussion 1164-5.
24. Nam IC, Bae JS, Shim MR, et al. The importance of preoperative laryngeal examination before thyroidectomy and the usefulness of a voice questionnaire in screening. World J Surg 2012;36:303-9.
25. Shin JJ, Grillo HC, Mathisen D, et al. The surgical management of goiter: Part I. Preoperative evaluation. Laryngoscope 2011;121:60-7.
26. Wang CC, Wang CP, Tsai TL, et al. The basis of preoperative vocal fold paralysis in a series of patients undergoing thyroid surgery: the preponderance of benign thyroid disease. Thyroid 2011;21:867-72.
27. Goretzki PE, Schwarz K, Brinkmann J, et al. The impact of intraoperative neuromonitoring (IONM) on surgical strategy in bilateral thyroid diseases: is it worth the effort? World J Surg 2010;34:1274-84.
28. Roh JL, Yoon YH, Park CI. Recurrent laryngeal nerve paralysis in patients with papillary thyroid carcinomas: evaluation and management of resulting vocal dysfunction. Am J Surg 2009;197:459-65.
29. Farrag TY, Samlan RA, Lin FR, et al. The utility of evaluating true vocal fold motion before thyroid surgery. Laryngoscope 2006;116:235-8.
30. Chan WF, Lo CY, Lam KY, et al. Recurrent laryngeal nerve palsy in well-differentiated thyroid carcinoma: clinicopathologic features and outcome study. World J

Surg 2004;28:1093-8.
31. Steurer M, Passler C, Denk DM, et al. Advantages of recurrent laryngeal nerve identification in thyroidectomy and parathyroidectomy and the importance of preoperative and postoperative laryngoscopic examination in more than 1000 nerves at risk. Laryngoscope 2002;112:124-33.
32. Rowe-Jones JM, Rosswick RP, Leighton SE. Benign thyroid disease and vocal cord palsy. Ann R Coll Surg Engl 1993;75:241-4.
33. Curley JW, Timms MS. Incidence of abnormality in routine 'vocal cord checks'. J Laryngol Otol 1989;103:1057-8.
34. Holl-Allen RT. Laryngeal nerve paralysis and benign thyroid disease. Arch Otolaryngol 1967;85:335-7.
35. Newcombe RG, Altman DG. Proportions and their differences. In: Altman DG, Machin D, Bryant TN, et al. eds. Statistics with confidence. London: British Medical Journal; 2000:45-56.
36. Sittel C, Stennert E, Thumfart WF, et al. Prognostic value of laryngeal electromyography in vocal fold paralysis. Arch Otolaryngol Head Neck Surg 2001;127:155-60.
37. Chandrasekhar SS, Randolph GW, Seidman MD, et al. Clinical practice guideline: improving voice outcomes after thyroid surgery. Otolaryngol Head Neck Surg 2013;148:S1-37.
38. Shindo ML, Caruana SM, Kandil E, et al. Management of invasive well-differentiated thyroid cancer: an American Head and Neck Society consensus statement. AHNS consensus statement. Head Neck 2014;36:1379-90.
39. Morris JA, Gardner MJ. Epidemiological studies. In: Altman DG, Machin D, Bryant TN, et al. eds. Statistics with confidence. London: British Medical Journal; 2000;57-72.
40. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167-214.
41. Gómez Sáez JM. Taking of position in relationship to the protocol of the current treatment of thyroid nodules and differentiated thyroid cancer. Endocrinol Nutr 2010;57:370-5.
42. Pacini F, Castagna MG, Brilli L, et al. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23 Suppl 7:vii110-9.
43. Perros P, Boelaert K, Colley S, et al. Guidelines for the management of thyroid cancer. Clin Endocrinol (Oxf) 2014;81 Suppl 1:1-122.
44. NCCN. Thyroid Carcinoma. In: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). National Comprehensive Cancer Network, Inc. 2014. Available online: http://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf. Accessed November 22th 2014.
45. Colina-Alonso A, Flores-Pastor B, Gutiérrez-Rodríguez MT, et al. eds. Clinical Pathway for Thyroid Surgery. 2014 ed. Madrid: Asociación Española de Cirujanos; 2014.
46. Takami H, Ito Y, Noguchi H, et al. eds. Treatment of thyroid tumor. Japanese clinical guidelines. 2013 ed. Tokyo: Springer Japan; 2013.
47. Dralle H, Musholt TJ, Schabram J, et al. German Association of Endocrine Surgeons practice guideline for the surgical management of malignant thyroid tumors. Langenbecks Arch Surg 2013;398:347-75.
48. Curran AJ, Smyth D, Sheehan SJ, et al. Recurrent laryngeal nerve dysfunction following carotid endarterectomy. J R Coll Surg Edinb 1997;42:168-70.
49. Smallridge RC, Ain KB, Asa SL, et al. American Thyroid Association guidelines for management of patients with anaplastic thyroid cancer. Thyroid 2012;22:1104-39.
50. Musholt TJ, Clerici T, Dralle H, et al. German Association of Endocrine Surgeons practice guidelines for the surgical treatment of benign thyroid disease. Langenbecks Arch Surg 2011;396:639-49.
51. Pacini F, Schlumberger M, Dralle H, et al. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol 2006;154:787-803.
52. British Association of Endocrine Surgeons (BAES) Guidelines and Training Sub-Group. Guidelines for the surgical management of endocrine disease and training requirements for endocrine surgery. 2003. Available online: http://www.baets.org.uk/guidelines. Accessed November 22th 2014.
53. OCEBM Levels of Evidence Working Group. The Oxford 2011 Levels of Evidence. Oxford Centre for Evidence-Based Medicine. 2011. Available online: http://www.cebm.net/index.aspx?o=5653. Accessed December 19th 2014.

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Loss of signal in recurrent nerve neuromonitoring: causes and management

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Abstract: During recurrent laryngeal nerve (RLN) neuromonitoring in thyroid surgery, laryngeal electromyography (EMG) amplitude may be correlated with the number of muscle fibers participating in the polarization and these might be correlated with the function of RLN. If RLN is severely injured during the operation, most nerve fibers do not transmit nerve impulse and substantial decrease of EMG amplitude or loss of signal (LOS) will occur. True LOS at the end of an operation often indicates a postoperative fixed vocal cord, and the surgeon should consider the optimal contralateral surgery timing in patients with planned bilateral thyroid operation to avoid the disaster of bilateral vocal cord palsy. However, LOS recovery and false LOS may occur and may lead to an unnecessary 2nd operation. Therefore, a reliable modality for intraoperative LOS evaluation and management would afford the surgeon real-time information that could help guide surgical procedure and planning. The updated causes, algorithm, and management of LOS during RLN neuromonitoring are reviewed and summarized.

Keywords: Recurrent laryngeal nerve (RLN); intraoperative neuromonitoring (IONM); thyroid surgery; electromyography (EMG); loss of signal (LOS); vocal cord palsy

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Introduction

Routine identification of recurrent laryngeal nerve (RLN) has been recommended as the gold standard of care during thyroid surgery (1). Intraoperative neuromonitoring (IONM) has been widely accepted as an adjunct to help facilitate the identification and dissection of RLN, detect nerve injury, and elucidate its mechanism to improve surgical technique. In addition, it is also helpful to predict the outcome of vocal cord function during the operation (2-5). The RLN supplies the intrinsic muscles of the larynx. One nerve axon and all the muscle fibers innervated by it are called a motor unit. Effective muscle contraction usually requires the activation of numerous motor units at once. During IONM of RLN in thyroid surgery, measures of laryngeal electromyography (EMG) amplitude may be correlated with the number of muscle fibers participating in the polarization and these might be correlated with the function of RLN (3,6). If the EMG response is unchanged after the operation as compared with the initial EMG signal, it suggests normal intraoperative RLN function and may predict postoperative normal vocal cord function. If RLN is severely injured during the operation, most nerve fibers do not transmit nerve conduction and loss of the EMG signal (LOS) will occur when stimulating the RLN or vagus nerve. True LOS at the end of operation often indicates a postoperative

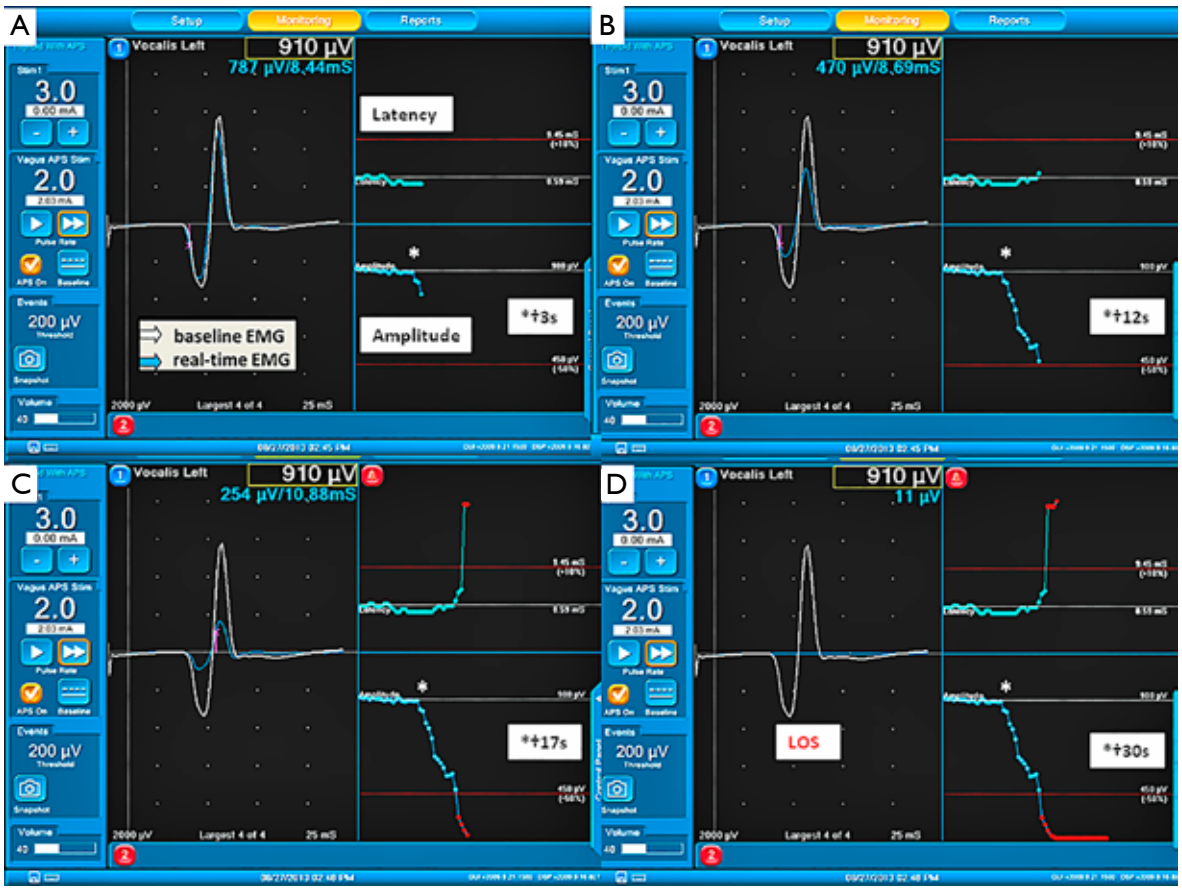

Figure 1 Example of EMG degrades to LOS from initial satisfactory baseline EMG after a left RLN traction injury during continuous IONM in thyroid surgery. The latency and amplitude waveforms were displayed separately, and an upper limit threshold for latency (+10%) and a lower limit threshold for amplitude (50%) were depicted as separate alarm lines. (A) That 3 s after the EMG signals started to show a progressive decrease in amplitude from the baseline EMG (star sign); (B) by 12 s after the start of EMG change, the EMG amplitude showed a nearly 50% decrease, but the EMG latency did not show a significant change; (C) by 17 s, the amplitude and latency crossed the limit threshold (-50% and +10%), and an alarm was displayed on the monitor screen (red bell sign) with acoustic alert; (D) from 20 to 30 s, the EMG waveform completely disappeared and the LOS occurred. EMG, electromyography; LOS, loss of signal; RLN, recurrent laryngeal nerve; IONM; intraoperative neuromonitoring.

fixed vocal cord, and a two-stage thyroidectomy has been recommended in patients with planned bilateral thyroid operation to avoid the disaster of bilateral vocal cord palsy in some studies (3,7). However, LOS may be false owing to several potential factors, such as monitor dysfunction, malposition of endotracheal tube (ETT) electrodes, misuse of neuromuscular blocking agents (NMBAs), etc., and may lead to unnecessary 2nd operation. A reliable modality for intraoperative LOS evaluation and management would afford the surgeon real-time information that could help guide surgical procedure and planning, especially in the patient with a planned bilateral thyroid operation.

Causes of LOS

Criteria

According to the current literature and international standards guideline statement (3), LOS is defined as EMG signal degrades to <100 µV from initial satisfactory EMG with suprathreshold level of stimulation (i.e., >1 or 2 mA) (*Figure 1*) on dry field.

True LOS

When the RLN is injured and the elicited EMG signal

<100 μV, it is called true LOS. Currently, RLN injury can be classified into two subtypes (3-5). Recent studies reported that over 70% (8-10) of injury is the type I or segmental injury that features a disrupted point or segment of nerve conduction on RLN, and this was often caused by clamping, traction, compression or thermal injury. Positive EMG signal at laryngeal entry point but negative signal at proximal point of exposed RLN or vagus nerve indicates a type I injury. We can detect the injured point by testing the RLN from laryngeal entry point to proximal area. For traction injury, the nerve is often stretched forward or compressed by the Berry's area, and most of the injured point can be mapped in the distal 1 cm of its course (9). For type I injured nerve, surgeons might also be able to potentially correct the lesion if there is a clip, suture, vessel or fibrotic band entrapping the nerve at this point and avoid permanent RLN injury.

The other subtype is the type II or global injury that features no disrupted point of nerve conduction on the whole exposed RLN but positive response from contralateral vagus nerve stimulation. The exact mechanism of type II injury is still not well understood, but overstretching during medial retraction of the thyroid lobe was thought to be the most possible cause and the nerve might be injured at a more distal intralaryngeal focus (5).

False LOS

Normal RLN function as evidenced by the presence of a laryngeal twitch, but no EMG signal is called false LOS. It features no injured point on the exposed RLN and no response from contralateral vagus nerve stimulation. False LOS may be caused by monitoring equipment dysfunction, EMG tube malposition, or misuse of NMBAs.

Monitoring equipment dysfunction

The recording electrodes, grounding electrode and associated connections at the interface-connector box and monitor might be dislodged or displaced and should be rechecked. The use of electrocauterization might have broken the fuse.

The stimulating probe can be checked on the muscle to identify its twitch, and the monitor can be reviewed for appropriate current return.

ETT malposition

Malpositioned ETT may imply either inadequate or excessive depth relative to the vocal cords (11,12). It can occur due to excessive traction on trachea, particularly in a large goiter operation. In our experience, translaryngeal stimulation is a simple and useful method to check ETT position:

(I) If artifact EMG signal is elicited with 1-2 mA on thyroid and tracheal cartilage, it suggests normal functioning of monitor equipment.

(II) If artifact EMG signal is elicited lower than the cricoid cartilage, it suggests downward displacement of the tube.

(III) If artifact EMG signal is elicited upper than the middle of the thyroid cartilage, it suggests upward displacement.

The corrective maneuver for malpositioned ETT can be done by the surgeon performing the vagal stimulation while the anesthesiologist readjusts the tube (3). Vagal stimulation should return the robust waveform when correct ETT placement has been established. We routinely use laryngo fiberscope examination to ensure the presence of laryngeal twitch and to adjust electrodes position, when false LOS is suspected (4).

Misuse of NMBAs

Repeated administration of any NMBA intraoperatively results in LOS. Therefore, the surgeon should take a few seconds to re-confirm this issue with the anesthetist when LOS occurs. If a NABA has been inadvertently administered, some waiting time (i.e., 20 to 30 minutes) may be needed to wear off the effect, or reversal agents may be given to allow for resumption of normal muscle twitch activity.

Algorithm of intraoperative LOS

In the scenario of intraoperative LOS, an efficient algorithm (*Figure 2*) can be followed for determining the causes of LOS:

LOS during RLN dissection

In the scenario of intraoperative LOS and laryngeal entry point of RLN has not yet been exposed, the authors suggest the first step is to perform the contralateral vagus nerve stimulation.

(I) Negative contralateral vagus nerve stimulation means the monitor is not functionally working, and surgeons should consider this is a false LOS episode and further exclude the common reasons caused by monitoring equipment dysfunction,

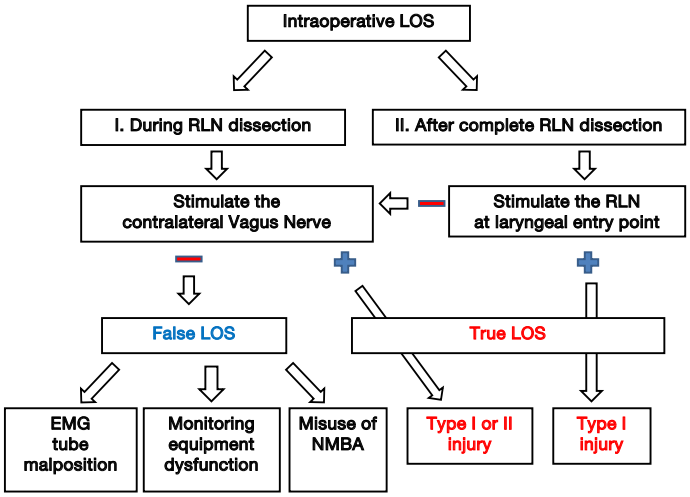

Figure 2 Algorithm of intraoperative LOS. LOS, loss of signal; RLN, recurrent laryngeal nerve; EMG, electromyography; NMBA, neuromuscular blocking agent.

EMG tube malposition, and misuse of NMBAs.

(II) Positive contralateral vagus nerve stimulation means the monitor is functionally working, and surgeons should consider this is a true LOS episode.

LOS after complete RLN dissection

If the intraoperative LOS occurs near the end or after complete RLN dissection and the laryngeal entry point has been exposed, the authors suggest the first step is to stimulate the RLN at laryngeal entry point.

(I) If there is a positive EMG signal at laryngeal entry point but negative signal at proximal point of exposed RLN or vagus nerve, the situation indicates a type I nerve injury. Surgeons can detect the injured point by testing the RLN from laryngeal entry point to proximal area.

(II) If negative ipsilateral EMG signal at laryngeal entry point but there is positive contralateral vagus nerve stimulation, this excludes monitor dysfunction and suggests a type II (Global) injury lesion.

Although the assessment of laryngeal twitch response by the surgeon is recommended as one of the first step for intraoperative LOS evaluation in the current guideline statement (3), the twitch response may vary among patients (race, sex and age) and the interpretation may vary among surgeons (training, and experience). Since the surgeons can easily perform the contralateral vagus nerve stimulation or RLN stimulation at laryngeal entry point to differentiate the false and true LOS (*Figure 2*), the authors suggest these procedures may be a more practical and objective initial steps than laryngeal twitch assessment when facing the intraoperative LOS.

Management of the true LOS

Map lesion and elucidate the causes of nerve injury

During thyroid operations, especially during the phase of lateral thyroid and RLN dissection, the RLN can be injured by the surgical maneuvers of transection, traction, clamping, mechanical trauma, or electro-cauterization. In the setting of true LOS, the surgeon should make an effort to identify the injured segment of nerve by serially testing the entire segment of exposed RLN from distal to proximal to see if a neurapraxic segment of LOS can be identified. The identification of such a segment then can allow the surgeons to elucidate the surgical pitfalls that caused the nerve injury and improve their surgical techniques (4,5).

Recheck the EMG at the end of operation

Three possible outcomes of intraoperative true LOS can be observed at the end of operation, including: (I) persistent LOS (no recovery); (II) partial signal recovery (*Figure 3*); and (III) complete signal recovery, and the outcome of cord mobility, can be either normal, weakened or fixed (5).

Previously, the capability of intraoperative recovery of LOS after RLN injury was under debate, but our recent experimental study has confirmed the phenomenon of

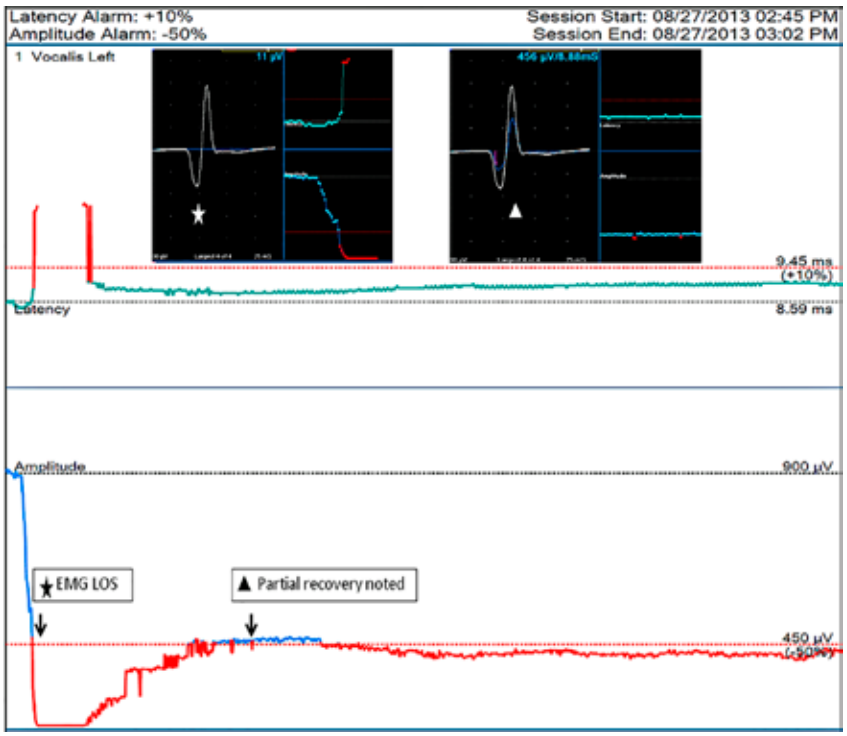

Figure 3 Example of intraoperative partial recovery of LOS after left RLN traction injury during continuous IONM. The EMG degrades to LOS after a left RLN traction (star sign), and the EMG show a progressive partial recovery to 50% of baseline amplitude after the 5 minute after traction stress was released (triangle sign). LOS, loss of signal; IONM, intraoperative neuromonitoring; EMG, electromyography; RLN, recurrent laryngeal nerve.

intraoperative recovery of severely weakened or lost EMG signals after acute RLN traction, and we found that the degree of recovery is related to the extent of the injury (13). Chiang *et al*. (5) reported 13 nerves with LOS caused by traction or constricting injuries; the EMG signal regained complete recovery in 3 nerves, partial recovery in 3 and no recovery in 7. The outcome of cord mobility was normal in all nerves with complete recovery and 2 nerves with partial recovery, weak in the remaining nerve with partial recovery, and fixed mobility in all nerves without signal recovery. Sitges-Serra *et al*. (14) also reported that 15 RLNs had re-entry signal among 16 nerves with intraoperative LOS (over 90%) and only 3 nerves developed temporary vocal palsy. Therefore, intraoperative LOS episode does not always indicate vocal cord paralysis after operation. Some LOS represent transient neuropraxia of short duration and the nerve may regain the signal before the end of operation (13). For preventing unnecessary 2nd operation, 20 minutes of waiting is necessary before making a decision to perform a staged thyroidectomy (14).

Consider optimal contralateral surgery timing

One of the worst complications in thyroid surgery is bilateral RLN paralysis, which can lead to transient or definitive tracheotomy. Sadowski *et al*. (15) reported the systematic use of IONM and the change in operative strategy will lead to an almost 0% rate of bilateral RLN palsy, at least in benign thyroid conditions. True LOS with no or only a subtle recovery at the end of operation indicates a high risk of at least a postoperative temporary vocal palsy, and therefore surgeon must consider whether a two-stage thyroidectomy is needed in patients with planned bilateral thyroid operation, even in cases of malignancies, to avoid the disaster of bilateral vocal cord palsy.

Follow-up of the post-operative laryngeal examination

Symptomatic assessment of vocal cord paralysis is notoriously inaccurate, as noted previously (16-19). Recognition of preoperative vocal cord paralysis is essential if the surgeon is to reduce the risk of contralateral injury

and bilateral cord paralysis (16). Therefore, during standardized IONM, all patients need to have preoperative and postoperative laryngeal examination, best assisted with video-recording, if the true rate of RLN injury is to be appreciated (4). This is especially important for patients experiencing intraoperative true LOS, where more regular postoperative laryngeal examination should be arranged to record and access the function status of vocal cord. When vocal dysfunction is identified, follow-up occurs every 2 weeks initially and every 4 weeks thereafter until recovery is achieved. Generally, dysfunction is considered permanent if it persists 6 months postoperatively.

Surgeons need to realize that false negative result of an intraoperative true LOS can happen if it is very transient and the nerve recovers before laryngeal examination is performed. Dionigi *et al*. (20) reported that the rate of RLN palsy is influenced by the "timing" of the postoperative laryngoscopy. They also suggest the proper timing of laryngeal inspection is at second day post-op (T2) and the reason of the slightly superior sensitivity of T2 compared to T1 (day 0 in the recovery room) may be associated to patient's poor compliance, self-adherence, and degree to which he/she correctly follows medical advice during the laryngeal examination early after extubation (T1).

Future perspective

In addition to 100 μV, which is currently used as the threshold value of LOS in most studies (3-5,7,14,21-24), other threshold values for prediction of nerve function impairment have been reported recently [i.e., 200 (25) or 280 μV (26)]. Genther *et al*. (25) concluded that laryngeal IONM can predict a favorable outcome of laryngeal mobility in cases in which the response is at least 200 μV. Under this value, the risk of immediate postoperative vocal palsy is about 72%. Another study by Pavier *et al*. (26) reported that the threshold value to assure postoperative laryngeal mobility is 280 μV; the risk of palsy under this value is about 50%. Therefore, some surgeons might choose to use a higher threshold value for LOS (i.e., from 200 to 300 μV). A higher threshold value for LOS might be helpful for early detection of adverse EMG change and for decreasing the artifact during dissection close to the trachea (Chiang and Wu, unpublished data).

In fact, EMG amplitudes during IONM may vary significantly within a patient and among patients. In patients with relatively higher (for example, amplitude >1,500 μV) or lower baseline signals (for example, amplitude <400 μV) than the reported normative data (mean amplitudes of initial vagus nerve or RLN stimulation around 500 to 1,200 μV) (8-10,24,27-30), the false positive or negative rates for prediction of laryngeal mobility outcome would be expected to be high when using the absolute threshold values (100, 200, or 280 μV) for LOS.

In the setting of continuous vagal IONM, surgeons can utilize the monitor software to set lower limit threshold by percentage (%) of amplitude reduction (50% for instance) to alarm the adverse EMG changes, so that they can correct certain maneuvers immediately to prevent irreversible nerve injury (13,21). Therefore, additional work in the future may also consider to use these relative threshold values (i.e., % of amplitude reduction from initial signal) as one of the criteria for the definition of LOS (80% or 90% amplitude reduction for instance) and compare their validity in the prediction of postoperative vocal cord function (Chiang and Wu, unpublished data).

Conclusions

The updated causes, algorithm, and management of LOS during RLN neuromonitoring are reviewed and summarized in this article. Because the threshold criteria of LOS has yet to be clearly and accurately defined, additional studies are needed to compare the validity of using different threshold values (i.e., 100 *vs*. 200-300 μV *vs*. % of amplitude reduction) as LOS definition for better prediction of vocal mobility outcome.

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References

1. Chiang FY, Wang LF, Huang YF, et al. Recurrent laryngeal nerve palsy after thyroidectomy with routine identification of the recurrent laryngeal nerve. Surgery 2005;137:342-7.
2. Randolph GW. eds. Surgery of the Thyroid and Parathyroid Glands. 2nd ed. Philadelphia, PA: Saunders, 2013.
3. Randolph GW, Dralle H; International Intraoperative Monitoring Study Group, Abdullah H, et al.

Electrophysiologic recurrent laryngeal nerve monitoring during thyroid and parathyroid surgery: international standards guideline statement. Laryngoscope 2011;121 Suppl 1:S1-16.
4. Chiang FY, Lee KW, Chen HC, et al. Standardization of intraoperative neuromonitoring of recurrent laryngeal nerve in thyroid operation. World J Surg 2010;34:223-9.
5. Chiang FY, Lu IC, Kuo WR, et al. The mechanism of recurrent laryngeal nerve injury during thyroid surgery--the application of intraoperative neuromonitoring. Surgery 2008;143:743-9.
6. Wu CW, Lu IC, Randolph GW, et al. Investigation of optimal intensity and safety of electrical nerve stimulation during intraoperative neuromonitoring of the recurrent laryngeal nerve: a prospective porcine model. Head Neck 2010;32:1295-301.
7. Melin M, Schwarz K, Lammers BJ, et al. IONM-guided goiter surgery leading to two-stage thyroidectomy--indication and results. Langenbecks Arch Surg 2013;398:411-8.
8. Dionigi G, Chiang FY, Rausei S, et al. Surgical anatomy and neurophysiology of the vagus nerve (VN) for standardised intraoperative neuromonitoring (IONM) of the inferior laryngeal nerve (ILN) during thyroidectomy. Langenbecks Arch Surg 2010;395:893-9.
9. Dionigi G, Alesina PF, Barczynski M, et al. Recurrent laryngeal nerve injury in video-assisted thyroidectomy: lessons learned from neuromonitoring. Surg Endosc 2012;26:2601-8.
10. Wu CW, Dionigi G, Chen HC, et al. Vagal nerve stimulation without dissecting the carotid sheath during intraoperative neuromonitoring of the recurrent laryngeal nerve in thyroid surgery. Head Neck 2013;35:1443-7.
11. Lu IC, Chu KS, Tsai CJ, et al. Optimal depth of NIM EMG endotracheal tube for intraoperative neuromonitoring of the recurrent laryngeal nerve during thyroidectomy. World J Surg 2008;32:1935-9.
12. Tsai CJ, Tseng KY, Wang FY, et al. Electromyographic endotracheal tube placement during thyroid surgery in neuromonitoring of recurrent laryngeal nerve. Kaohsiung J Med Sci 2011;27:96-101.
13. Wu CW, Dionigi G, Sun H, et al. Intraoperative neuromonitoring for the early detection and prevention of RLN traction injury in thyroid surgery: a porcine model. Surgery 2014;155:329-39.
14. Sitges-Serra A, Fontané J, Dueñas JP, et al. Prospective study on loss of signal on the first side during neuromonitoring of the recurrent laryngeal nerve in total thyroidectomy. Br J Surg 2013;100:662-6.
15. Sadowski SM, Soardo P, Leuchter I, et al. Systematic use of recurrent laryngeal nerve neuromonitoring changes the operative strategy in planned bilateral thyroidectomy. Thyroid 2013;23:329-33.
16. Randolph GW, Kamani D. The importance of preoperative laryngoscopy in patients undergoing thyroidectomy: voice, vocal cord function, and the preoperative detection of invasive thyroid malignancy. Surgery 2006;139:357-62.
17. Steurer M, Passler C, Denk DM, et al. Advantages of recurrent laryngeal nerve identification in thyroidectomy and parathyroidectomy and the importance of preoperative and postoperative laryngoscopic examination in more than 1000 nerves at risk. Laryngoscope 2002;112:124-33.
18. Rueger RG. Benign disease of the thyroid gland and vocal cord paralysis. Laryngoscope 1974;84:897-907.
19. Huppler EG, Schmidt HW, Devine KD, et al. Ultimate outcome of patients with vocal-cord paralysis of undetermined cause. Am Rev Tuberc 1956;73:52-60.
20. Dionigi G, Boni L, Rovera F, et al. Postoperative laryngoscopy in thyroid surgery: proper timing to detect recurrent laryngeal nerve injury. Langenbecks Arch Surg 2010;395:327-31.
21. Schneider R, Randolph GW, Sekulla C, et al. Continuous intraoperative vagus nerve stimulation for identification of imminent recurrent laryngeal nerve injury. Head Neck 2013;35:1591-8.
22. Jonas J. Continuous vagal nerve stimulation for recurrent laryngeal nerve protection in thyroid surgery. Eur Surg Res 2010;44:185-91.
23. Cernea CR, Brandão LG, Hojaij FC, et al. Negative and positive predictive values of nerve monitoring in thyroidectomy. Head Neck 2012;34:175-9.
24. Caragacianu D, Kamani D, Randolph GW. Intraoperative monitoring: normative range associated with normal postoperative glottic function. Laryngoscope 2013;123:3026-31.
25. Genther DJ, Kandil EH, Noureldine SI, et al. Correlation of final evoked potential amplitudes on intraoperative electromyography of the recurrent laryngeal nerve with immediate postoperative vocal fold function after thyroid and parathyroid surgery. JAMA Otolaryngol Head Neck Surg 2014;140:124-8.
26. Pavier Y, Saroul N, Pereira B, et al. Acute prediction of laryngeal outcome during thyroid surgery by electromyographic laryngeal monitoring. Head Neck 2014. [Epub ahead of print].
27. Lorenz K, Sekulla C, Schelle J, et al. What are normal

quantitative parameters of intraoperative neuromonitoring (IONM) in thyroid surgery? Langenbecks Arch Surg 2010;395:901-9.
28. Potenza AS, Phelan EA, Cernea CR, et al. Normative intra-operative electrophysiologic waveform analysis of superior laryngeal nerve external branch and recurrent laryngeal nerve in patients undergoing thyroid surgery. World J Surg 2013;37:2336-42.
29. Chiang FY, Lu IC, Tsai CJ, et al. Does extensive dissection of recurrent laryngeal nerve during thyroid operation increase the risk of nerve injury? Evidence from the application of intraoperative neuromonitoring. Am J Otolaryngol 2011;32:499-503.
30. Chu KS, Wu SH, Lu IC, et al. Feasibility of intraoperative neuromonitoring during thyroid surgery after administration of nondepolarizing neuromuscular blocking agents. World J Surg 2009;33:1408-13.

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Management of anaplastic thyroid cancer

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Abstract: Anaplastic thyroid cancer (ATC) is a deadly disease with a dismal prognosis. Molecular analyses of ATC tumors have yielded interesting results, which could help in understanding the underlying mechanisms of this aggressive disease process. Managing ATC can be challenging and includes rapid diagnosis, adequate staging, and interdisciplinary, multimodal treatments to optimize patient outcome. Treatments include surgical resection to gross negative margins when possible, as well as neo- or adjuvant treatment with chemotherapy or external beam radiation (XRT) for locoregional disease. New treatment strategies include evaluating the benefits of vascular disrupting agents and tyrosine kinase inhibitors for advanced ATC with driver mutations, which can be targeted. This review summarizes key concepts in managing ATC.

Keywords: Anaplastic thyroid cancer (ATC); surgery; diagnosis; prognosis; treatment

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Introduction

Anaplastic thyroid cancer (ATC) occurs in less than 2% of all thyroid cancer cases, affecting 1 to 2 individuals per million every year in the United States, and it is almost uniformly lethal. Patients are usually in their 6^{th} or 7^{th} decade of life at presentation, have an average median survival of 5 months, and less than 20% are alive 1 year after diagnosis (1,2). Due to the extremely aggressive behavior of ATC, the American Joint Committee on Cancer (AJCC) defines all of its stages as stage IV. Depending on the extension of the primary tumor, lymph node involvement, or presence of distant metastases (DM), ATC staging is divided into stage IVa, IVb, and IVc (*Table 1*). Although survival rates have not significantly improved in six decades, multimodality treatment, including surgery, radiation, chemotherapy, and targeted therapy, is considered the best strategy for improving outcome in patients diagnosed with ATC (3).

Pathogenesis

Different histopathologic growth patterns of ATC have been described, including spindle, pleomorphic, and squamoid morphologies. One of these patterns may predominate in a given tumor, or the tumor may show a mixed feature of two, or even all three, types. All three growth patterns have common distinctive features of dedifferentiated behavior, such as giant cells, numerous mitotic figures and atypical mitoses, extensive necrosis surrounded by inflammatory infiltrates and occasionally osteoclast-like giant cells, as well as, less commonly, the presence of neoplastic bone and cartilage (4-7). Although useful for diagnosis of ATC on histo- and cytopathology, histopathologic growth patterns do not appear to be associated with patient prognosis (8,9).

ATC is thought to originate in differentiated thyroid cancers of follicular cell origin, as a result of dedifferentiation. Up to 80% of ATC occurs in the setting of a long-standing goiter, possibly in the background of an undiagnosed, well-differentiated thyroid cancer (8). Dedifferentiation is associated with gains and deletions in multiple chromosomal regions and involves a complex process involving multiple events, including cell cycle derangement and signal transduction pathway disturbances (10-12).

Several mutations have been described in ATCs (*Table 2*). Some, such as those in the *BRAF* and *RAS* oncogenes, are

Table 1 Staging of anaplastic thyroid cancer

Classification	Tumor	Lymph nodes	Metastases
Stage IVa	T4a[†]	Any N	M0
Stage IVb	T4b[‡]	Any N	M0
Stage IVc	Any T	Any N	M1

[†]T4a, tumor does not extend beyond the thyroid capsule; [‡]T4b, tumor extends beyond the thyroid capsule (http://www.cancer.org/cancer/thyroidcancer/detailedguide/thyroid-cancer-staging).

Table 2 Commonly mutated genes and differentially expressed microRNAs in ATC (13)

Gene mutation	Frequency of mutation in ATC (%)	microRNA	Expression
Axin	82	222	Upregulated
TP53	55	221	Upregulated
B-Catenin	38	146b	Upregulated
BRAF	26	106a,b	Upregulated
RAS	22	17-92	Upregulated
PIK3CA	17	618	Downregulated
PTEN	12	138	Downregulated
APC	9	125b	Downregulated
		30d	Downregulated
		26a	Downregulated

ATC, anaplastic thyroid cancer.

also commonly found in differentiated thyroid cancers, implying that these mutations may be early events in cancer formation (14-17). *PIK3CA* and *PTEN* gene mutations also occur in both differentiated thyroid cancer and ATC (14,16,17). Mutant *PIK3CA* and aberrant activation of the PI3K/Akt pathway were found in greater than 50% of ATCs. These abnormalities are believed to play an important role in thyroid cancer progression, as they have been suggested to promote progression of adenomas to follicular thyroid cancer and ATC based on a frequency of mutation/activation of this pathway that is relatively higher in cancer than in benign tumors (18,19).

The *TP53* tumor suppressor gene mutation, on the other hand, is found almost exclusively in ATCs and likely represents a late event in dedifferentiation (20,21). This hypothesis is supported by experiments achieving redifferentiation of ATC tissue and restoration of cellular response to physiologic stimuli after re-expression of wild-type p53 (22). Decreased *E-Cadherin* and *B-Catenin*

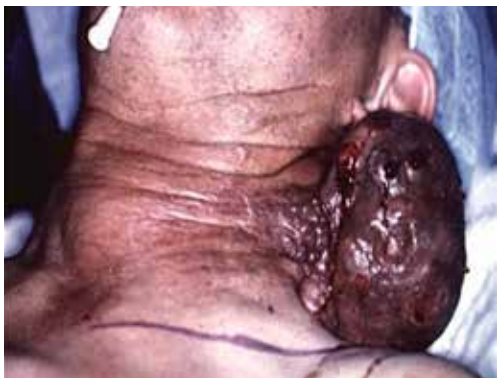

Figure 1 Patient with ATC who presented with a large fungating neck mass. ATC, anaplastic thyroid cancer.

expression has also been found in poorly differentiated thyroid cancer and ATC. Loss of both adhesion molecules is associated with progressive loss of tumor differentiation and epithelial-to-mesenchymal transition, and low membrane *B-Catenin* expression and *CTNNB1* exon3 mutation have been associated with poor prognosis in ATC (18,23,24). Additional dysregulated genetic events, such as microRNA and epigenetic alterations, may also contribute to ATC pathogenesis (2,25,26) (*Table 2*). Currently, most clinical management guidelines, such as those of the American Thyroid Association and the European Thyroid Association, do not recommend the use of molecular studies for diagnosis or management of ATC, as there is insufficient evidence of their clinical utility (9).

Clinical presentation and diagnosis

Most patients with ATC present with a rapidly enlarging neck mass (*Figure 1*) and locoregional symptoms, such as dyspnea, dysphagia, and neck pain. Other symptoms of ATC can be related to invasion in any neck structure, including the recurrent laryngeal nerve (RLN) (causing hoarseness), parasympathetic chain (causing Horner's syndrome), or even carotid arteries (causing stroke, hematoma).

Approximately 40% of patients with ATC initially present with cervical lymphadenopathy, and up to 43% of patients have DM, most commonly to the lung, followed by bone and brain metastases (1).

The most important management consideration in patients with ATC is a rapid and accurate assessment of the disease burden, since tumor doubling time can be very short (i.e., days), therefore acutely compromising the airway in these patients and in some cases, rendering the

Figure 2 CT of the neck in a patient with a large ATC displacing the trachea laterally (A, black arrow) and showing a hypermetabolic focus on a PET scan (B, white arrow). ATC, anaplastic thyroid cancer.

tumor unresectable. Airway assessment and management should always have the highest priority and include a direct laryngoscopy and bronchoscopy if tracheal invasion is suspected.

As with any thyroid mass, a fine needle aspiration (FNA) should be performed first. This often secures the diagnosis (27). If the FNA is nondiagnostic, a core needle or open biopsy should be undertaken (9). The differential diagnosis for ATC includes poorly differentiated thyroid cancer, large cell lymphomas, medullary thyroid carcinoma, direct extension of a laryngeal carcinoma, primary squamous cell carcinoma of the thyroid, and metastatic melanoma (6,9).

Laboratory evaluation in patients with ATC should include complete blood count, basic metabolic profile, liver function, coagulation factors, and thyroid function tests (9). Thyrotoxicosis, hypocalcemia, and leukocytosis have all been described in patients with ATC. Additionally, since ATC occurs most commonly in patients who are elderly and some of these patients suffer from dysphagia and weight loss, a thorough nutritional assessment, including measuring albumin and/or pre-albumin levels, should be performed preoperatively.

Cross-sectional imaging such as CT and MRI of the neck and chest should be obtained prior to surgery to assess the extent of the tumor and degree of invasion of adjacent structures (*Figure 2*). Such information is critical for operative planning and/or to determine whether neoadjuvant therapy is indicated. Radiologic studies should not delay urgent therapeutic intervention and should be scheduled expeditiously. High-resolution ultrasound is a convenient, rapid, and easy imaging test for assessing tumor extension, involvement of central or lateral nodes, and invasion into adjacent structures (9). In patients with symptoms suggestive of tumor involvement, esophagogastroduodenoscopy (EGD) and/or bronchoscopy can assess esophageal or tracheal involvement, respectively.

Although, as with any other cancer, a complete staging should be performed before treatment, this process should not delay primary management of ATC (e.g., biopsy to diagnose DM). CT imaging of the head, chest, abdomen, and pelvis are helpful in ruling out DM. ^{18}FDG PET CT has recently gained favor for ATC staging since it appears to be more accurate at detecting DM than routine total body CT (28). Additionally, high FDG uptake values on PET have been correlated with poor survival in ATC (28). Additional tests, such as serum markers, should be used if another primary tumor is suspected. Finally, a biopsy of metastases, with or without immunohistochemistry, can confirm the diagnosis of metastatic ATC (9).

Surgical treatment

There are two cardinal rules for the management and surgical planning of patients with ATC: (I) assessment of airway; and (II) expeditious treatment ("Time is of the essence").

Maintaining and securing a patent airway in patients with ATC can be challenging. Routine tracheostomy is not recommended, does not improve quality of life or prolong life, and is best avoided unless there is impending airway compromise (29). Recommendations for tracheostomy include: (I) acute airway distress; (II) unresectable tumors that would not benefit from debulking; or (III) mild dyspnea unresponsive to corticosteroids. A tracheostomy should be

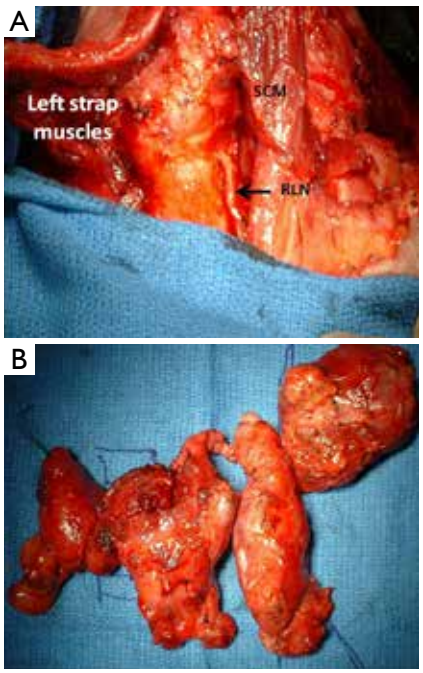

Figure 3 Resection bed (A) after removal of local advanced ATC; (B) specimen of en-bloc resection of locally advanced ATC involving left internal jugular vein and lymph nodes metastases to the left central (level 6) and lateral (level 2, 3, and 4) neck and posterior triangle (level 5). ATC, anaplastic thyroid cancer; SCM, sternocleidomastoideus muscle; RLN, recurrent laryngeal nerve.

done in the operating room and by an experienced surgeon since large tumor mass and bleeding can obscure visibility. Tracheal stents can be useful for airway stabilization in the mid-trachea, but are rarely helpful in the subglottic area. The option of palliation without tracheostomy should be given to patients with unresectable ATC because tumor plugging, erosion, and bleeding can result from tracheostomy placement in these patients, significantly impairing their quality of life.

Surgical intervention should be determined based on preoperative staging. A good rule of thumb is that all patients with stage IVa or stage IVb, in which grossly negative margins (R1) can be obtained, should have a resection since complete resection is associated with prolonged disease-free and overall survival (1,30,31) (*Figure 3*). In the 2-15% of patients with ATC who present with stage IVa (intrathyroidal tumor), a total thyroidectomy with a therapeutic central and lateral neck node dissection is recommended. This recommendation also applies to stage IVb tumors, although neoadjuvant preoperative radiotherapy (XRT) can sometimes be considered in order to downstage locally unresectable disease and subsequently enable complete gross resection. However, here again, airway preservation should always have the highest priority.

Gross resection, and not debulking, should be the main goal in patients with ATC, but the extent of resection should be carefully weighed against the potentially devastating morbidity of certain procedures. Planned limited resection of the trachea or larynx may be performed with minimal morbidity; however, laryngectomy or esophagectomy are associated with high morbidity rates and are usually not undertaken in the setting of such an aggressive cancer with short survival times. It is also not reasonable to perform extended resections if a gross tumor is anticipated to be left behind in the neck or superior mediastinum.

In the special, and very rare, circumstance in which a microscopic focus of ATC is found incidentally within a differentiated thyroid cancer after thyroidectomy, the appropriate extent of thyroidectomy is unclear as there is no outcome data to support a specific surgical strategy. Although certain centers advocate a more conservative approach when an incidental focus of ATC is found, many advocate performing a completion thyroidectomy (32). In such clinical scenarios, it is reasonable to adapt an approach that is best for the differentiated thyroid cancer (i.e., the non-ATC component of the malignancy). The benefit of adjuvant radiotherapy with or without chemotherapy has not clearly been proven in this setting, and the ATA guidelines recommend close observation with frequent anatomic imaging (9).

Palliative resection of the primary tumor in stage IVc patients should be considered if possible, to avoid future, or treat current, airway compromise or esophageal obstruction; such an approach has the potential to prolong survival and enhance quality of life (33).

Complications of ATC resections include hemorrhage, chylous fistulae, vocal cord paralysis, surgical site infection, dysphagia, salivary fistulae, and hypoparathyroidism.

Systemic and external beam radiation (XRT) treatment

In patients with ATC, the benefit of systemic chemotherapy and XRT is unclear but may be considered in three clinical settings: (I) as neoadjuvant therapy for locoregional ATC to downstage the tumor; (II) as adjuvant therapy after complete ATC resection or for low-volume locoregional and distant residual disease; and (III) as palliative therapy.

There is no standard chemotherapy regimen for ATC, and, in the setting of unresectable or symptomatic disease, systemic chemotherapy is best employed in a clinical trial, as no agent(s) has provided a survival advantage significant enough to warrant its use outside of a clinical trial.

Adjuvant therapy in the form of XRT or chemotherapy should be started as soon as the patient recovers from surgery, usually within 2 or 3 weeks after surgery (9). Some, but not all, retrospective studies suggest that multimodal therapy with a combination of surgery (R0 or R1) and definitive XRT (with or without concurrent chemotherapy) achieves better survival rates (1,9). Even patients who have R2 resections or unresected disease and have good performance status should be offered radiation because this may result in better local disease control.

In patients with nonmetastatic ATC and good performance status, cytotoxic chemotherapy should be added to XRT. In the past, doxorubicin has been used most often; however, more recent drugs, such as cisplatin or paclitaxel, have been used as radiosensitizing agents, and studies of these drugs have reported better 1-year survival rates, as compared to historical controls (34-37).

In cases of advanced metastatic disease (stage IVc) related to ATC, no cytotoxic or targeted systemic therapy has definitively been shown to have curative potential or to prolong survival rates. Therefore, the patient's disease status, performance status, and his or her wishes must be considered before choosing the best approach, as most therapies have risks and side effects (dysphagia, odynophagia, and chemotherapy-induced neutropenia). Determining whether the patient has symptomatic or life-threatening focal disease (calling for treatment with "palliative" XRT) or more diffuse systemic disease progression (calling for systemic therapy) helps in determining the appropriate therapeutic approach. Doxorubicin is the only FDA-approved drug for systemic therapy that may be used to treat ATC, and, while it has achieved modest effects against advanced ATC, it is often used in combination with other modalities (38).

A US national cancer registry study shows a longer median survival rate with combined therapies: for stage IVa ATC, the median survival is 11.2 months using a combination of all three modalities (surgery, XRT, and chemotherapy) *vs.* 9.3 months if surgery and radiation were performed without chemotherapy. For stage IVc ATC, the median survival is 4.9 *vs.* 3.5 months, respectively (39).

As no systemic therapy has been shown to improve the survival rate or quality of life in patients with advanced ATC, new clinical trials with targeted therapies are needed, and patients should be enrolled in them as soon as possible. In a randomized study, fosbretabulin, a vascular disrupting agent, showed some benefits when added to paclitaxel and carboplatin (40). A recent phase II trial in 20 patients with advanced disease who were treated with daily sorafenib, a tyrosine kinase inhibitor, showed overall median progression-free survival of 1.9 months, with a median and a 1-year survival rate of 3.9 months and 20%, respectively (41). In one patient with a BRAF V600E-mutated ATC, the use of vemurafenib resulted in nearly complete tumor regression (42). Further, whole-exome sequencing in pretreated, responsive and then resistant tumor tissue to everolimus showed mTOR pathway activation in ATC as a target for therapy in clinical trials (43).

In the case of advanced ATC with DM, there is no standard systemic therapy recommended. Metastases are common to the lung and liver, which, in most cases, present with numerous lesions. In such cases, depending on patient functional status and tolerance, treatment with focal radiotherapy or radiofrequency ablation may be considered for palliation.

Surveillance and follow up

Patients with ATC who have had a complete resection without persistent disease should undergo aggressive surveillance with cross-sectional imaging every 1-3 months for the first year, and every 4-6 months thereafter. FDG PET should be considered as a useful tool to monitor recurrence or to assess the success of treatment with adjuvant therapies. Thyroglobulin measurements and radioactive iodine scanning are not useful in ATC (9).

Prognosis

Several studies have examined the factors affecting prognosis in patients with ATC (*Table 3*). These prognostic factors, including patient age, tumor size, and clinical stage, should be considered when evaluating patients for treatment (9). A vast majority of patients will ultimately die from their disease and a thorough discussion regarding prognosis should be held with patients, so they understand the impact of their disease on their quality of life, as well as the potential benefit of participating in experimental clinical trials. Additionally, empathy to comfort and pain issues in the final moments of a patient's life are of utmost importance. A discussion regarding "do not resuscitate" (DNR) or "allow natural death" (AND) orders should be

Table 3 Prognostic factors associated with decreased or increased mortality in ATC

First author	Year	Patient number	Mean 1-year survival (%)	Mortality
Decreased mortality				
Kihara (44)	2004	19	21	Complete resection
Kebebew (1)	2005	516	19	Age <60, no ETE, combined surgery + XRT
Kim (45)	2007	121	16	Age <60, tumor <7 cm, lower extent of disease
Increased mortality				
Sugitani (46)	2001	47	16	Acute symptoms, WBC >10 k, tumor >5 cm, DM
Akaishi (47)	2011	100	21	Age >70, WBC >10 k, ETE+, DM
Sugitani (32)	2012	677	15	Age >70, acute symptoms, WBC >10 k, tumor >5 cm, T4b, DM

ATC, anaplastic thyroid cancer; ETE, extrathyroidal extension; XRT, external beam radiation; WBC, white blood cell count; DM, distant metastases.

implemented by the treating clinician. An AND order may have the advantage of less ambiguity in emergency situation requiring potential life extending measures such as intubation.

Conclusions

ATC is a deadly disease with dismal long-term survival rates. Treatment strategy should be based on recommendations from a multidisciplinary team including surgeons, medical oncologists, endocrinologists and radiation oncologists. Best management practices include rapid assessment of disease burden, including potential airway compromise, adequate staging, and operative therapy with the goal of gross complete resection combined with chemo- and/or radiotherapy. Although there have been advances in understanding the molecular pathogenesis of this aggressive cancer over the last two decades, more work needs to be done to identify suitable targets for successful tumor-directed therapy.

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References

1. Kebebew E, Greenspan FS, Clark OH, et al. Anaplastic thyroid carcinoma. Treatment outcome and prognostic factors. Cancer 2005;103:1330-5.
2. Smallridge RC, Copland JA. Anaplastic thyroid carcinoma: pathogenesis and emerging therapies. Clin Oncol (R Coll Radiol) 2010;22:486-97.
3. Kebebew E. Anaplastic thyroid cancer: rare, fatal, and neglected. Surgery 2012;152:1088-9.
4. Bronner MP, LiVolsi VA. Spindle cell squamous carcinoma of the thyroid: an unusual anaplastic tumor associated with tall cell papillary cancer. Mod Pathol 1991;4:637-43.
5. Gaffey MJ, Lack EE, Christ ML, et al. Anaplastic thyroid carcinoma with osteoclast-like giant cells. A clinicopathologic, immunohistochemical, and ultrastructural study. Am J Surg Pathol 1991;15:160-8.
6. Ordóñez NG, El-Naggar AK, Hickey RC, et al. Anaplastic thyroid carcinoma. Immunocytochemical study of 32 cases. Am J Clin Pathol 1991;96:15-24.
7. Yoshida A, Kamma H, Asaga T, et al. Proliferative activity in thyroid tumors. Cancer 1992;69:2548-52.
8. O'Neill JP, Shaha AR. Anaplastic thyroid cancer. Oral Oncol 2013;49:702-6.
9. Smallridge RC, Ain KB, Asa SL, et al. American Thyroid Association guidelines for management of patients with anaplastic thyroid cancer. Thyroid 2012;22:1104-39.
10. Hunt JL, Tometsko M, LiVolsi VA, et al. Molecular evidence of anaplastic transformation in coexisting well-differentiated and anaplastic carcinomas of the thyroid. Am J Surg Pathol 2003;27:1559-64.
11. Kadota M, Tamaki Y, Sekimoto M, et al. Loss of heterozygosity on chromosome 16p and 18q in anaplastic thyroid carcinoma. Oncol Rep 2003;10:35-8.
12. Kitamura Y, Shimizu K, Tanaka S, et al. Allelotyping of anaplastic thyroid carcinoma: frequent allelic losses on 1q, 9p, 11, 17, 19p, and 22q. Genes Chromosomes Cancer

2000;27:244-51.
13. Smallridge RC, Marlow LA, Copland JA. Anaplastic thyroid cancer: molecular pathogenesis and emerging therapies. Endocr Relat Cancer 2009;16:17-44.
14. Charles RP, Silva J, Iezza G, et al. Activating BRAF and PIK3CA mutations cooperate to promote anaplastic thyroid carcinogenesis. Mol Cancer Res 2014;12:979-86.
15. Sugg SL, Ezzat S, Zheng L, et al. Oncogene profile of papillary thyroid carcinoma. Surgery 1999;125:46-52.
16. Pita JM, Figueiredo IF, Moura MM, et al. Cell cycle deregulation and TP53 and RAS mutations are major events in poorly differentiated and undifferentiated thyroid carcinomas. J Clin Endocrinol Metab 2014;99:E497-507.
17. Santarpia L, El-Naggar AK, Cote GJ, et al. Phosphatidylinositol 3-kinase/akt and ras/raf-mitogen-activated protein kinase pathway mutations in anaplastic thyroid cancer. J Clin Endocrinol Metab 2008;93:278-84.
18. García-Rostán G, Costa AM, Pereira-Castro I, et al. Mutation of the PIK3CA gene in anaplastic thyroid cancer. Cancer Res 2005;65:10199-207.
19. Hou P, Liu D, Shan Y, et al. Genetic alterations and their relationship in the phosphatidylinositol 3-kinase/Akt pathway in thyroid cancer. Clin Cancer Res 2007;13:1161-70.
20. Kondo T, Nakazawa T, Murata SI, et al. Expression of CD73 and its ecto-5'-nucleotidase activity are elevated in papillary thyroid carcinomas. Histopathology 2006;48:612-4.
21. Nikiforova MN, Kimura ET, Gandhi M, et al. BRAF mutations in thyroid tumors are restricted to papillary carcinomas and anaplastic or poorly differentiated carcinomas arising from papillary carcinomas. J Clin Endocrinol Metab 2003;88:5399-404.
22. Moretti F, Nanni S, Farsetti A, et al. Effects of exogenous p53 transduction in thyroid tumor cells with different p53 status. J Clin Endocrinol Metab 2000;85:302-8.
23. Garcia-Rostan G, Camp RL, Herrero A, et al. Beta-catenin dysregulation in thyroid neoplasms: down-regulation, aberrant nuclear expression, and CTNNB1 exon 3 mutations are markers for aggressive tumor phenotypes and poor prognosis. Am J Pathol 2001;158:987-96.
24. Wiseman SM, Masoudi H, Niblock P, et al. Derangement of the E-cadherin/catenin complex is involved in transformation of differentiated to anaplastic thyroid carcinoma. Am J Surg 2006;191:581-7.
25. Reddi HV, Driscoll CB, Madde P, et al. Redifferentiation and induction of tumor suppressors miR-122 and miR-375 by the PAX8/PPARγ fusion protein inhibits anaplastic thyroid cancer: a novel therapeutic strategy. Cancer Gene Ther 2013;20:267-75.
26. Zhang Z, Liu ZB, Ren WM, et al. The miR-200 family regulates the epithelial-mesenchymal transition induced by EGF/EGFR in anaplastic thyroid cancer cells. Int J Mol Med 2012;30:856-62.
27. Bauman ME, Tao LC. Cytopathology of papillary carcinoma of the thyroid with anaplastic transformation. A case report. Acta Cytol 1995;39:525-9.
28. Poisson T, Deandreis D, Leboulleux S, et al. 18F-fluorodeoxyglucose positron emission tomography and computed tomography in anaplastic thyroid cancer. Eur J Nucl Med Mol Imaging 2010;37:2277-85.
29. Hölting T, Meybier H, Buhr H. Problems of tracheotomy in locally invasive anaplastic thyroid cancer. Langenbecks Arch Chir 1989;374:72-6.
30. McIver B, Hay ID, Giuffrida DF, et al. Anaplastic thyroid carcinoma: a 50-year experience at a single institution. Surgery 2001;130:1028-34.
31. Passler C, Scheuba C, Prager G, et al. Anaplastic (undifferentiated) thyroid carcinoma (ATC). A retrospective analysis. Langenbecks Arch Surg 1999;384:284-93.
32. Sugitani I, Miyauchi A, Sugino K, et al. Prognostic factors and treatment outcomes for anaplastic thyroid carcinoma: ATC Research Consortium of Japan cohort study of 677 patients. World J Surg 2012;36:1247-54.
33. Nilsson O, Lindeberg J, Zedenius J, et al. Anaplastic giant cell carcinoma of the thyroid gland: treatment and survival over a 25-year period. World J Surg 1998;22:725-30.
34. Swaak-Kragten AT, de Wilt JH, Schmitz PI, et al. Multimodality treatment for anaplastic thyroid carcinoma--treatment outcome in 75 patients. Radiother Oncol 2009;92:100-4.
35. Bhatia A, Rao A, Ang KK, et al. Anaplastic thyroid cancer: Clinical outcomes with conformal radiotherapy. Head Neck 2010;32:829-36.
36. De Crevoisier R, Baudin E, Bachelot A, et al. Combined treatment of anaplastic thyroid carcinoma with surgery, chemotherapy, and hyperfractionated accelerated external radiotherapy. Int J Radiat Oncol Biol Phys 2004;60:1137-43.
37. Sosa JA, Balkissoon J, Lu SP, et al. Thyroidectomy followed by fosbretabulin (CA4P) combination regimen appears to suggest improvement in patient survival in anaplastic thyroid cancer. Surgery 2012;152:1078-87.
38. Tennvall J, Lundell G, Wahlberg P, et al. Anaplastic thyroid carcinoma: three protocols combining doxorubicin,

hyperfractionated radiotherapy and surgery. Br J Cancer 2002;86:1848-53.
39. Haymart MR, Banerjee M, Yin H, et al. Marginal treatment benefit in anaplastic thyroid cancer. Cancer 2013;119:3133-9.
40. Sosa JA, Elisei R, Jarzab B, et al. Randomized safety and efficacy study of fosbretabulin with paclitaxel/carboplatin against anaplastic thyroid carcinoma. Thyroid 2014;24:232-40.
41. Savvides P, Nagaiah G, Lavertu P, et al. Phase II trial of sorafenib in patients with advanced anaplastic carcinoma of the thyroid. Thyroid 2013;23:600-4.
42. Rosove MH, Peddi PF, Glaspy JA. BRAF V600E inhibition in anaplastic thyroid cancer. N Engl J Med 2013;368:684-5.
43. Wagle N, Grabiner BC, Van Allen EM, et al. Response and acquired resistance to everolimus in anaplastic thyroid cancer. N Engl J Med 2014;371:1426-33.
44. Kihara M, Miyauchi A, Yamauchi A, et al. Prognostic factors of anaplastic thyroid carcinoma. Surg Today 2004;34:394-8.
45. Kim TY, Kim KW, Jung TS, et al. Prognostic factors for Korean patients with anaplastic thyroid carcinoma. Head Neck 2007;29:765-72.
46. Sugitani I, Kasai N, Fujimoto Y, et al. Prognostic factors and therapeutic strategy for anaplastic carcinoma of the thyroid. World J Surg 2001;25:617-22.
47. Akaishi J, Sugino K, Kitagawa W, et al. Prognostic factors and treatment outcomes of 100 cases of anaplastic thyroid carcinoma. Thyroid 2011;21:1183-9.

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Recurrence of papillary thyroid cancer after optimized surgery

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Abstract: Recurrence of papillary thyroid cancer (PTC) after optimized surgery requires a full understanding of the disease, especially as it has changed in the last 15 years, what comprises optimized surgery, and the different types and implications of disease relapse that can be encountered. PTC has evolved to tumors that are much smaller than previously seen, largely due to various high quality imaging studies obtained for different reasons, but serendipitously identifying thyroid nodules that prove to be papillary thyroid microcarcinomas (PTMC). With rare exception, these cancers are cured by conservative surgery without additional therapy, and seldom result in recurrent disease. PTC is highly curable in 85% of cases because of its rather innocent biologic behavior. Therefore, the shift in emphasis from disease survival to recurrence is appropriate. As a result of three technologic advances—high-resolution ultrasound (US), recombinant TSH, and highly sensitive thyroglobulin (Tg)—disease relapse can be discovered when it is subclinical. Endocrinologists who largely control administration of radioactive iodine have used it to ablate barely detectable or even biochemically apparent disease, hoping to reduce recurrence and perhaps improve survival. Surgeons, in response to this new intense postoperative surveillance that has uncovered very small volume disease, have responded by utilizing US preoperatively to image this disease, and incorporated varying degrees of lymphadenectomy into their initial treatment algorithm. Bilateral thyroid resection—either total or near-total thyroidectomy—remains the standard for PTC >1 cm, although recent data has re-emphasized the value of unilateral lobectomy in treating even some PTC measuring 1-4 cm. Therapeutic lymphadenectomy has universal approval, but when lymph nodes in the central neck are not worrisome to the surgeon's intraoperative assessment, although that judgment in incorrect up to 50%, whether they should be excised has reached a central point of controversy. Disease relapse can occur individually or in combination of three different forms: lymph node metastasis (LNM), true soft tissue local recurrence, and distant disease. The latter two are worrisome for potentially life-threatening consequences whereas nodal metastases are often persistent from the initial operation, and mostly comprise a biologic nuisance rather than virulent disease. A moderate surgical approach of bilateral thyroid resection, with usual central neck nodal clearance, and lateral internal jugular lymphadenectomy for node-positive disease can be performed safely, and with about a 5% recurrence rate.

Keywords: Papillary thyroid cancer (PTC); recurrence; surgery; lymph nodes

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Introduction

Even though this eight-word title is seemingly simple and straightforward, the three major topics—papillary thyroid cancer (PTC), optimized surgery, and recurrence—are actually complex and sometimes controversial. In contrast to most malignancies, where the focus and endpoint is survival, the endpoint here is recurrence, which I think is entirely appropriate. To comprehend fully this overall subject requires appreciation of the multitude of factors of each topic, recognizing that virtually no controlled trials have been conducted.

PTC—context of the disease

In the United States an explosive rise in the frequency of diagnosing PTC had been seen, resulting in a nearly 800% increase over the prior 35 years, according to SEER registry data (1). Similar increases have been verified in Europe and Japan.

Papillary thyroid microcarcinoma (PTMC)

Nearly 50% of the increase proved to be PTC of 1 cm or smaller, and 87% were ≤2 cm. However, thyroid cancer mortality has remained flat, implying that these small cancers would not likely have progressed to be life-threatening. This dramatic rise in subclinical disease has been attributed largely to more frequent and widespread use of imaging of the head and neck for unrelated investigations, with the unanticipated discovery of these incidental cancers. The largest increase had been found in patients of 45 years and older, to the point that the most frequent diagnosis of PTC currently in the United States is a "papillary thyroid microcarcinoma" (PTMC) of ≤1 cm in a patient of 45 years or older (2). One of the conclusions of this study by Hughes *et al.* was that "the minimal clinical significance of microcarcinomas may mean that treatment of these tumors will provide minimal to no benefit in terms of survival, recurrence, or risk of progression to locally advanced disease in individual patients or the population as a whole". Actually, the frequency of small PTC has been known for years, derived from autopsy studies ranging from 5.6% to 35.6% (3). So common were these PTMC that the authors concluded they could "be regarded as a normal finding". Moreover, because these tumors seemed to remain small or even to regress in the vast majority of cases, these authors suggested that "in practice, detection of (PTMC) without regional metastases should not lead to any treatment." A similar autopsy study of over 1,000 cases found 6.2% PTMC, and determined that "no surgical or other therapeutic consequence should be followed whenever such a small carcinomas is found incidentally in a gland removed for reasons other than tumor" (4).

The innocent biologic behavior of these PTMC when identified clinically is amply verified by a bold and unique study by Ito (5,6), effectively demonstrating the natural history of these tumors. Whereas 1,055 PTMC patients were operated, a selected group of 340 patients were observed without surgery with a mean of 74 months follow-up. Only 2 patients of all these patients had distant metastasis at diagnosis, and only 2 (0.14%) patients died of cancer, 79 and 94 months after initial operation. With a threshold of 3 mm for meaningful enlargement of the PTMC in the observation group, 5- and 10-year enlargement occurred in only 6.7% and 16%, respectively. Eventually, 1/3 of the observed patients underwent thyroidectomy with no subsequent recurrences, indicating that even with signs of disease progression in an observed patient, surgical treatment remains highly successful and "not too late".

Several large series have been published regarding PTMC. Hay (7) investigated 900 patients with PTMC from Mayo Clinic from 1945-2004, with a mean follow-up of 17.2 years. Despite tumors being multifocal in 23%, associated with lymph node metastases (LNM) in 31%, 3 (0.3%) with distant metastases at diagnosis, the 20- and 40-year tumor recurrence rates were only 6% and 8%, respectively. None of the 892 patients with initial complete resection developed metastatic spread during 20 postoperative years. Chow (8) reported the cause-specific survival, locoregional metastasis failure-free survival, and distant metastasis failure-free survival rates at 10 years to be 100%, 92%, and 97%. Of 281 PTMC patients treated at Gustave-Roussy Institute, only 3.9% had locoregional recurrence, and a single patient had lung metastasis (9). Finally, a meta-analysis substantiated these large series with review of 9,313 patients (10), only 35 cases (0.37%) had distant metastases at diagnosis, and cancer-specific death occurred in only 0.34% (32 of 9,379 patients).

To summarize regarding PTMC, even though the label of cancer is applied to these small tumors, with rare exception, they are biologically innocent. Even though spread to lymph nodes at surgical resection occurs in about 30% (7,8), these metastasis are usually quite small and recurrence is seldom seen. It would seem only rational that in the near future, the interventional resources utilized to treat PTMC will be scaled back to fit the almost inert biologic behavior of these tumors.

PTC—biology of disease

Next, to consider PTC excluding tumors of 1 cm or smaller, over the prior three decades prognostic scoring systems have been developed that reliably predict the risk of disease-related mortality. MACIS (11) (metastasis, age, completeness of surgery, gross local invasion, and tumor size) has emerged as the best and most widely accepted system directed specifically for PTC. Universally used and accepted, however, is the TNM system which has specific criteria for most malignancies. Separate risk groups can be identified based on a combination of clinical and pathology criteria, consistently demonstrating that about 85% of patients with PTC have a <5% risk of disease-specific death over at least 20 years (11,12). The factors within the TNM and MACIS systems for predicting mortality rely on markers of more virulent biology (tumor size, invasiveness, distant spread, even age correlates with more virulent disease as does the ability of the surgeon to remove completely the disease). It is well to remember Blake Cady's keen insight into tumor biology and the interplay with surgical intervention. To paraphrase, "Biology is King; patient selection is Queen. Technical details of surgical procedures are the Princes and Princesses of the realm who frequently try to overthrow the powerful forces of the King and Queen, usually to no long-term avail…technical wizardry cannot overcome biological restraints." (13). One of the unique characteristics of PTC is the relative lack of influence on mortality of LNM. This has been consistently verified in multiple prognostic scoring systems, derived from multivariate analysis. Only when the lymph nodes are large and invasive of surrounding soft tissue with extranodal spread—a biologic characteristic mirroring the aggressiveness of the primary tumor—do the lymph nodes signify worse prognosis (14,15). In fact, prior to about 2003, LNM attracted only modest attention. To add routine radical surgery for lymph node disease, in the face of the widely held opinion that LNM did not reduce survival, was further discouraged as it was associated with alarming results. Mazzaferri reported that extensive lymph node dissections were associated with hypoparathyroidism in 20% and an overall complication rate of 44%; yet recurrences were not prevented with a recurrence rate of 2% per year, and a 20% complication rate with further reoperation (16).

Disease relapse testing—fear

With the turn of the new millennium, it seemed that the goal of endocrinologists was to eradicate all detectable and potentially all molecular evidence of PTC disease. Intertwined in the development of this attitude were two new extraordinarily sensitive measures to detect miniscule disease: high-resolution ultrasound (US), and stimulated thyroglobulin (Tg). US could identify potentially abnormal LNM of only a few millimeters, and verify disease presence with the addition of US-directed fine needle aspiration. Studies on the use of Tg determined that a stimulated (rh-TSH) Tg of only 2 ng/mL should prompt further investigation (even though seldom could structural disease be found even with US until the Tg was ≥4 ng/mL). Armed with this information, the use of ^{131}I for therapeutic ablation of this trace disease became standard of care. The economic burden of these practices produced an overall probability of medical bankruptcy of 5%, and a risk almost 3.5 time higher than controls—a rate exceeded only by lung cancer (17). Moreover, thyroid cancer had the highest bankruptcy rate of all cancers at 1 year after the diagnosis.

Fear of dire consequences from LNMs was generated when contradictory evidence emerged. A population-based, case-control study of over 5,000 patients in Sweden with PTC found that LNM were associated with a 2.5-fold increased mortality (18). In another study, LNM were associated with a 4-fold increase in local recurrence, and a 2.5-fold increase in cause-specific mortality (19). Serum Tg level, in addition to its role as a very sensitive marker of disease, was reported to be predictive of disease-free remission and death (20). Mazzaferri offered the perspective that up to 25% of patients with PTC of 1.5 cm or smaller will have persistent or recurrent disease, whereas the combination of total thyroidectomy and radioactive iodine (RAI) has the potential to reduce this risk to zero (21). Kloos and Mazzaferri further warned, "Although mortality rates for DTC are low, tumor recurrence rates are high and may portend death from thyroid cancer." (22).

Shift of emphasis: disease-specific mortality to relapse

Reassuringly, however, in a meta-analysis of 23 studies regarding the use of RAI for PTC, the 10-year disease-specific mortality remained extremely low at about 1.7% (23). With the new fixation of concern on lymph node relapse, the new ability to uncover even tiny amounts of disease during the course of compulsive postoperative disease surveillance, consequent liberal use of RAI to ablate this modest disease, the fear on the part of physicians and patients alike that even miniscule amounts of cancer was extremely worrisome and required intervention, surgeons felt the obvious impetus

to minimize any potential disease relapse at the time of surgery. Disease relapse occurs in three important forms: distant disease, "true" local recurrence (soft tissue disease not within lymph nodes), and lymph nodes. While the first two are evidence of biologically aggressive disease that may eventually be life-threatening, they are distinctly uncommon in most consecutive series of PTC—consistent with the known very low disease-specific mortality of PTC. However, about 90% of PTC disease relapse is LNM. These LNM are the usual culprits identified during postoperative surveillance, and, therefore, have been the focus of considerable study and debate over the prior 15 years.

Lymph node metastasis (LNM)

LNM occur early and often in PTC, initially located in compartment VI (C-VI; central neck compartment bordered laterally by the carotid arteries, superiorly by the hyoid bone, and inferiorly at or just below the sternal notch). They are often small, escaping the detection by the surgeon in up to 50% (24). Noguchi authored what is now a classic study involving systematic node dissection in 57 patients (25). The key findings were (I) LNM were present in 90% of patients, 57% of which were <3 mm; (II) the LNM occurred initially in C-VI followed soon by spread to compartments III and IV (low and mid internal jugular lymph nodes from the base of the neck at and slightly below the clavicle extending superiorly to the level of the hyoid bone); and (III) LNM were misjudged in 80% to be negative by the surgeon. Rather stunning, however, was a subsequent study by the same group involving 300 patients who were operated without systematic lymph node dissection, but without reported recurrences (26). Similar studies have confirmed that while LNMs may be present in 60% of patients operated even with PTMCs, if systematic node dissection is not performed, recurrence may be rare, even less than 1% in one study (27). Carried to the extreme, Qubain (28) studied 80 patients who underwent nodal dissection with all nodes being negative for metastasis by H & E staining. The overall rate of positive lymph nodes by cytokeratin immunohistochemistry was 53%, with >90% positive nodes in the central compartment. Nevertheless, all patients were alive at the time of follow-up, implying that the node positivity was not life-threatening. More recent efforts to characterize LNM principally by size has been undertaken by Randolph (29), and, consistent with breast cancer research, to constitute a clinical threat, the metastasis must be at least 0.2 mm in size (the size threshold thought to be necessary for neovascularity, not just individual tumor cells surviving by diffusion of nutrients). However, the actual size and virulence thresholds for LNM of PTC to relapse clinically remain to be fully elucidated.

Because the burden of disease within lymph nodes associated with PTC that is of clinical significance is not fully understood, and no randomized clinical trials are available nor likely to be performed to answer this question, debate over this topic has taken center stage among endocrine surgeons. Macroscopic LNM are unanimously accepted as indication for node dissection, but node clearance, especially in C-VI when intraoperatively evident LNMs are not apparent, is controversial.

Optimized surgery for PTC

Surgery for PTC can be divided into two components: thyroidectomy, and lymphadenectomy. Based on the preponderance of data from large, relevant retrospective studies, the American Thyroid Association (ATA) has enumerated a treatment strategy with (30):

(I) Several reasonable overall goals:
  (i) Remove the tumor and metastatic nodes as well as locally involved structures;
  (ii) Minimize morbidity;
  (iii) Allow staging that facilitates further management and follow-up;
  (iv) Minimize disease recurrence, both local and distant.

(II) Specific to surgical goals, excerpts from Recommendation 15 state:
  (i) "To remove the primary tumor, disease that has extended beyond the thyroid capsule and involved cervical lymph nodes. Completeness of surgical resection is an important determinant of outcome, while residual metastatic lymph nodes represent the most common site of disease persistence/recurrence."
  (ii) "To minimize the risk of disease recurrence and metastatic spread. Adequate surgery is the most important treatment variable influencing prognosis…"

(III) The specific tactics to achieve the goals are also enumerated:
  (i) For PTC >1 cm, total or near-total thyroidectomy is indicated. Lobectomy is sufficient for <1 cm PTC if low risk, unifocal, intrathyroid, with no metastatic lymph nodes

Table 1 Frequency of PTC recurrence according to ATA recurrence risk classification (biochemical and structural)

Risk classification frequency by % of patient group	Structural disease, %	Elevated Tg, %	Total recurrence, %
Low, 25%	3	11	14
Intermediate, 50%	21	22	43
High, 25%	68	18	86

PTC, papillary thyroid cancer; ATA, American Thyroid Association; Tg, thyroglobulin.

or prior radiation;

(ii) Therapeutic clearance of C-VI or lateral neck LNM is indicated;

(iii) Prophylactic clearance of C-VI may be performed;

(iv) No C-VI dissection may be appropriate for small, T1-2 PTC.

An important corollary to the above guidelines is that "these recommendations should be interpreted in light of available surgical expertise".

Controversies—extent of thyroidectomy

Extending over at least three decades was the debate over the extent of the thyroidectomy. Publication of a sentinel study in 2007 by Bilimoria (31) based on the NCDB database showed that recurrence was slightly but statistically higher (9.8% *vs.* 7.7%) and survival was slightly lower (97.1% *vs.* 98.4%) in lobectomy patients *vs.* bilateral resection. However, lobectomy had been shown to be equivalent to near-total (NTTx) or total thyroidectomy (TTx) in survival in T1-2 N0 patients in publications from Memorial Sloan Kettering Cancer Center (32) and our institution (33). The controversy has been re-kindled by two recent publications for PTC even as large as 4 cm (34,35). The Japanese study reviewed over 1,000 patients who underwent lobectomy for tumors up to 4 cm in size, with follow-up of 17.6 years (without addition of RAI), in the absence of clinically positive lymph nodes or extrathyroidal extension, no patient under 45 years of age died. The American study re-analyzed 61,775 patients from the NCDB, and overall survival was similar in patients undergoing total thyroidectomy versus lobectomy for tumors 1-4 cm in size. Because the overwhelmingly large number of patients treated with bilateral resection, the general consensus today that bilateral resection is preferred, and the complexity of using RAI or Tg follow-up in lobectomy patients, it is reasonable to accept bilateral resection—either NTTx or TTx—as the optimal extent of thyroidectomy for PTC >1 cm.

Extent of lymphadenectomy

As alluded to previously, the increasing extent of lymphadenectomy was at least initially driven by the frequency of relapse of LNM coincident with the introduction of and rapid acceptance of new technologies for detecting this disease: high-resolution US, recombinant TSH, and Tg. With the ability to detect postoperatively, tiny, subclinical disease, surgeons naturally responded with more aggressive methods to detect and remove these nodes. It rapidly became clear that US was far more sensitive for detecting even macroscopic lymph nodes than clinical examination, so preoperative US became routine (36,37).

Whereas a number of studies suggested a very low relapse rate even in the absence of more thorough lymphadenectomy, a major study from Memorial Sloan Kettering by Tuttle (38) elucidated a more realistic picture of the behavior of PTC. Studying 588 patients who had undergone total thyroidectomy, appropriate lymph node dissection and routine RAI, they utilized the ATA Risk of Recurrence Classification to estimate the chance of recurrence of these patients according to their pathology and subsequent radioactive scans (*Table 1*).

- Low risk: no local or distant metastasis; no local invasion or aggressive histology; R0 surgical resection; no ^{131}I outside of the thyroid bed;
- Intermediate risk: microinvasion, ^{131}I or LNM present outside the thyroid bed; aggressive histology or vascular invasion could be present;
- High risk: macroinvasion, incomplete resection—gross residual, or distant metastases were present.

Almost 25% of the low and intermediate groups developed structural disease recurrence, and >50% had either biochemical or structural recurrence despite excellent surgical and RAI treatments. Yet following additional treatments, at the time of final follow-up with a median of 7 years, 67% were free of disease, persistence/recurrence was present in 28% (only 1-2% being true local recurrence—soft tissue disease), and only 5% had died of

disease, of whom 26 of 28 initially had stage IV disease. This study confirms that, despite high quality local treatments structural recurrence in PTC occurs in 25% and that frequency is doubled if biochemical criteria for recurrence are included. However, in the absence of distant disease at the time of diagnosis, PTC is rarely lethal (39,40).

Value and rationale for C-VI lymph node dissection

With the current practice of intense postoperative surveillance searching for even miniscule disease, the efforts to achieve thorough lymph node dissection are worth serious consideration. Because therapeutic lymph node dissection is virtually unanimously supported, the focus of debate has revolved around what is termed "prophylactic" dissection—removing nodes even when not grossly abnormal in the judgment of the surgeon. Also, until recently, few in Western countries have supported lateral jugular lymph node dissection (compartments variably including II-V). Therefore, C-VI "prophylactic" node dissection has attracted considerable attention and investigation. The reasons to undertake routine C-VI lymph node dissection include:

(I) Preoperative US in the initial cervical exploration is nearly blind to the detection of LNM in C-VI (in contradistinction to lateral neck LNM) (36,37);
(II) Surgeons cannot reliably differentiate innocent from LNM in many cases;
(III) LNMs occur in up to 50% of patients operated on for PTC (41);
(IV) Missed LNM are typically found along the recurrent laryngeal nerve (RLN) in the trachea-esophageal groove, a potentially dangerous location if reoperation becomes necessary;
(V) Dissection would logically lead to reductions in relapse and consequently reoperation;
(VI) C-VI dissection can be accomplished safely, although this is a major statement of contention;
(VII) Disease staging could be changed for patients over 45 years, from stage I to stage III, with potential for additional treatment implications;
(VIII) RAI is unreliably effective in "cleaning up" residual macroscopic LNM.

In support of above statements, Sywak from a highly respected surgical group in Sydney, Australia reviewed 447 clinically node-negative PTC patients, with 391 having undergone only TTx, whereas the remaining 56 underwent TTx plus ipsilateral central neck lymph node dissection (CLND) (42). The CLND group had a statistically lower Tg than those with TTx only. An undetectable Tg was achieved by 72% with CLND as opposed to only 43% with TTx alone. Worth added consideration is the fact that at least biochemically, fewer than half of the TTx patients were actually cured in expert surgical hands. Three additional, recently published powerful studies support CLND, with sufficient numbers of patients to reach statistical differences. All followed a similar study design: comparison of TTx plus CLND *vs.* TTx only; the PTCs were >1 cm; retrospective analysis; and all patients were clinically node negative. A multi-institutional study of 606 patients showed recurrence-free survival to be statistically greater when CLND was added (*Figure 1*) (43). Stimulated Tg was also lower as was evidence of any recurrence. Similarly, disease-specific survival was superior in the CLND group in a second study of 640 patients (*Figure 2*) (44). And finally, in a third study by Hartl (45), the rate of C-VI reoperation and Tg were lower with CLND as was overall reintervention. A meta-analysis of prophylactic CLND confirmed a 35% lower recurrence with CLND, but at a cost of 26% higher rate of temporary hypocalcemia (46).

Surgical approaches—variations

As noted previously, the most widely accepted approach to PTC, size >1 cm, is bilateral thyroidectomy, either NTTx or Tx. So the differences in overall surgical management are focused on the central and lateral compartment lymph nodes. Essentially all agree that preoperative US is crucial, and clinically positive lymph nodes should be dissected in a compartment-oriented (rather than "node-picking") approach. Those surgeons who support a more conservative approach to C-VI CLND raise significant concern about risk to the RLN and at least temporary hypoparathyroidism. Additionally, they cite studies that DFS, OS and even actual LNM relapse are quite uncommon in the absence of elective or prophylactic CLND. They also find support from prominent endocrinologists who have stated, "As long as postoperative RAI is planned, dissection of nonpalpable lymph nodes is probably not essential." (47).

A moderate approach, favored by surgeons at Mayo Clinic, is to add routine C-VI CLND, and add lateral jugular node dissection (typically C-III and C-IV with possible addition of C-II as indicated) if US or palpable positive nodes identified.

More aggressive approaches have been advocated not only including routine C-VI dissection, but routine C-III and

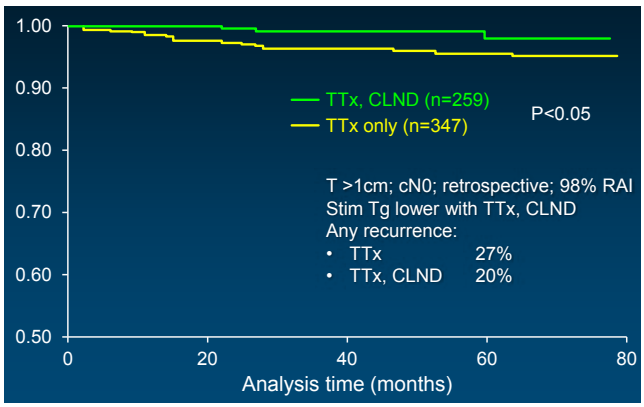

Figure 1 Compartment VI recurrence-free survival; multi-institutional study (N=606). CLND, central neck lymph node dissection; RAI, radioactive iodine ablation; Tg, thyroglobulin; TTx, total thyroidectomy. Reprinted with permission (43).

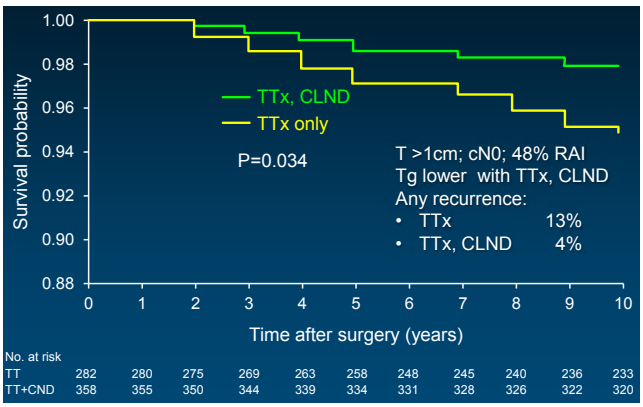

Figure 2 Disease-specific survival (N=640). CLND, central neck lymph node dissection; RAI, radioactive iodine ablation; Tg, thyroglobulin; TTx, total thyroidectomy. Reprinted with permission (44).

C-IV ± C-II-V on the side of the tumor (48). With a yield of 42% positive nodes in the lateral dissection, they have been criticized for the inadequacy of the preoperative US and the morbidity of lateral neck dissection particularly in the node-negative patients. Even more aggressive, not only routine C-VI dissection, but routine bilateral lateral jugular node dissection (C-III-IV ± II) has been reported (49).

Disease recurrence

Definition of terms

Relapse of PTC can occur in three forms: distant metastasis, "true" local recurrence, and disease within lymph nodes (LNM). It is estimated that 90% of disease relapse in PTC is LNM, and because of the usual indolent nature of the disease, and because relapse is typically identified within the first 3-4 years (50), this most likely represents disease persistence with possible enlargement rather than true recurrence. Although LNM and local recurrence are often lumped together, they represent very different entities both biologically and with respect to surgical re-excision. LNMs most typically are well-defined and most often—in the absence of significant extranodal spread—can be excised precisely without need for either resection or damage to surrounding structures. In contrast, true local recurrence (newly formed disease found within soft tissue, often densely attached or invading these structures) makes surgical resection more difficult and potentially involving sacrifice of important structures such as RLN, tracheal cartilage, etc. This is a reflection of more virulent disease that mirrors the initial aggressive thyroid cancer. Distinguishing LNM from local recurrence may be extremely difficult preoperatively, and sometime even intraoperatively when lymph nodes have been totally replaced with disease that also had gross extranodal disease. Modern day surveillance usually discovers residual disease much earlier than in prior decades, and the implications of contemporary disease discovery is vastly different than in times past. Many years ago, disease recurrence became evident by new symptoms such as hoarseness or new enlarging mass. It was this type of disease that Gagel was referring to when he stated that 40-50% of patients who die of thyroid carcinoma do so because of recurrent disease in the central compartment of the neck, and a high percentage of patients with recurrence in the thyroid bed (as high as 50%) will die of their carcinoma (51). It is well to recall the study by Tuttle (38) of 588 patient, only 5% had died of disease of whom 26 of 28 initially had stage IV disease.

Our reoperative experience with PTC at Mayo Clinic (52) included 410 patients who were operated from 1999-2008. This encompassed a widely heterogeneous group of patients, ranging over 9 decades in age, nearly 75% having been given an average of 200 mCi of RAI, and having undergone multiple previous neck operations to a maximum of seven involving both the central and the lateral neck. These patients all had structural disease, identifiable by either palpation and/or imaging. We were gratified that nearly three-quarters of our patients at last follow-up had

no structural evidence of disease. Strikingly, however, 25% of the reoperative patients had either died of disease (11%) or were alive with structurally persistent disease (14%). This is a highly selected group containing a disproportionate number of very high-risk patients, not reflective of the usual population of PTC patients initially coming to surgical intervention.

Recurrence of PTC after optimized surgery

Having considered in detail the disease PTC, aspects of optimized surgery for this disease, and different forms and implications of disease recurrence, a coherent management plan can be synthesized.

- For the dramatic rise in diagnosis of small PTMCs, restraint in the surgical approach should be the rule rather than the exception. Lobectomy only, unless there is disease on the contralateral side, should be amply sufficient. The addition of unilateral lymph node dissection is optional, but should not threaten the RLN. With this approach, hypoparathyroidism is positively avoided. Use of RAI is not justified. Ultimately, progress could be made in this country to avoid operation altogether except for cases with threatening characteristics.
- In the current climate of nearly routine use of RAI, compulsive use of postoperative surveillance, and aggressive intervention for even subclinical disease, total thyroidectomy for PTC >1 cm still must remain standard of care. The future should narrow the need for bilateral resection as moderation in the compulsion for both diagnosis and intervention for subclinical PTC disease is embraced. More aggressive surgical measures will remain important for biologically aggressive disease.
- As has occurred with other malignancies, notably breast cancer, recognition that not every molecule of disease needs to be ablated to allow long-term, disease-free survival. As molecular thumbprinting of PTC matures, directed therapy will be developed as opposed to the blanket RAI adjuvant therapy currently employed. Clinically important disease will be targeted, and indolent, biologically inert microscopic disease will be tolerated—both at the time of initial diagnosis and surgery, and postoperatively. This process is still in its infancy, but suspicious lymph nodes found by US postoperatively that are <8-10 mm are being intentionally observed rather than subjected to US-FNA. Once a diagnosis of "cancer" is pronounced, the patient understandably is worried, wants some form of intervention and clearance of disease.
- Initial CLND for C-VI remains appropriately controversial. Mandated surgical clearance of indeterminate or innocent C-VI nodes that might threaten normal parathyroid function or the integrity of the RLN is unacceptable. However, to clear the C-VI nodes and reliably maintain blood supply and function of the superior parathyroid glands is almost always possible in capable surgical hands. Because it is presently impossible to predict which apparently innocent but actually metastatically involved C-VI lymph nodes will prove to be worrisome enough to at least be biopsied, proved positive, and ultimately lead to additional intervention, it seems that CLND is justified when it can be performed safely. A risk-stratified approach recommended by the European Society of Endocrine Surgeons seems very reasonable (53).
- Prophylactic lateral jugular lymph node dissection has to this point been unacceptable in the United States as the sensitivity and reliability of preoperative US, when carefully performed by experienced sonographers, has been a quite acceptable alternative.

As evidence in support of this approach, the results are presented of the Mayo Clinic moderate surgical approach (41) including preoperative US for detection and mapping of LNM NTTx or TTx; routine C-VI CLND, and lateral internal jugular lymph node dissection when indicated by either positive nodes detected by palpation or US. From 1999-2006, 420 patients were treated with this comprehensive approach, and excluded only the few patients who were found intraoperatively to be unresectable. Tumors were multicentric in 40%, averaged 1.7 cm in size, were bilateral in 30%, demonstrated extrathyroidal extension in 17%, were associated with C-VI LNM in 51% and lateral LNMs in 20%, and had MACIS low-risk prognostic scores in 84%. RAI was used in 40% of patients. Relapse of LNM occurred in previously operated fields in 5% of patients; 3% had true local recurrence or distant metastasis, with complications limited to 1.2% hypoparathyroidism and only a single patient suffered unintentional RLN paralysis. Only a single patient had died as a direct result of PTC at last follow-up.

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References

1. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. JAMA 2006;295:2164-7.
2. Hughes DT, Haymart MR, Miller BS, et al. The most commonly occurring papillary thyroid cancer in the United States is now a microcarcinoma in a patient older than 45 years. Thyroid 2011;21:231-6.
3. Harach HR, Franssila KO, Wasenius VM. Occult papillary carcinoma of the thyroid. A "normal" finding in Finland. A systematic autopsy study. Cancer 1985;56:531-8.
4. Lang W, Borrusch H, Bauer L. Occult carcinomas of the thyroid. Evaluation of 1,020 sequential autopsies. Am J Clin Pathol 1988;90:72-6.
5. Ito Y, Uruno T, Nakano K, et al. An observation trial without surgical treatment in patients with papillary microcarcinoma of the thyroid. Thyroid 2003;13:381-7.
6. Ito Y, Miyauchi A, Inoue H, et al. An observational trial for papillary thyroid microcarcinoma in Japanese patients. World J Surg 2010;34:28-35.
7. Hay ID, Hutchinson ME, Gonzalez-Losada T, et al. Papillary thyroid microcarcinoma: a study of 900 cases observed in a 60-year period. Surgery 2008;144:980-7; discussion 987-8.
8. Chow SM, Law SC, Chan JK, et al. Papillary microcarcinoma of the thyroid-Prognostic significance of lymph node metastasis and multifocality. Cancer 2003;98:31-40.
9. Baudin E, Travagli JP, Ropers J, et al. Microcarcinoma of the thyroid gland: the Gustave-Roussy Institute experience. Cancer 1998;83:553-9.
10. Roti E, degli Uberti EC, Bondanelli M, et al. Thyroid papillary microcarcinoma: a descriptive and meta-analysis study. Eur J Endocrinol 2008;159:659-73.
11. Hay ID, Bergstralh EJ, Goellner JR, et al. Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. Surgery 1993;114:1050-7; discussion 1057-8.
12. Cady B, Rossi R. An expanded view of risk-group definition in differentiated thyroid carcinoma. Surgery 1988;104:947-53.
13. Cady B. Basic principles in surgical oncologyu. Presidential Address. Arch Surgery 1978;132:338-46.
14. Hay ID, Bergstralh EJ, Grant CS, et al. Impact of primary surgery on outcome in 300 patients with pathologic tumor-node-metastasis stage III papillary thyroid carcinoma treated at one institution from 1940 through 1989. Surgery 1999;126:1173-81; discussion 1181-2.
15. Voutilainen PE, Multanen MM, Leppäniemi AK, et al. Prognosis after lymph node recurrence in papillary thyroid carcinoma depends on age. Thyroid 2001;11:953-7.
16. Mazzaferri EL, Young RL, Oertel JE, et al. Papillary thyroid carcinoma: the impact of therapy in 576 patients. Medicine (Baltimore) 1977;56:171-96.
17. Ramsey S, Blough D, Kirchhoff A, et al. Washington State cancer patients found to be at greater risk for bankruptcy than people without a cancer diagnosis. Health Aff (Millwood) 2013;32:1143-52.
18. Lundgren E, Ljunghall S, Akerström G, et al. Case-control study on symptoms and signs of "asymptomatic" primary hyperparathyroidism. Surgery 1998;124:980-5; discussion 985-6.
19. Loh KC, Greenspan FS, Gee L, et al. Pathological tumor-node-metastasis (pTNM) staging for papillary and follicular thyroid carcinomas: a retrospective analysis of 700 patients. J Clin Endocrinol Metab 1997;82:3553-62.
20. Heemstra KA, Liu YY, Stokkel M, et al. Serum thyroglobulin concentrations predict disease-free remission and death in differentiated thyroid carcinoma. Clin Endocrinol (Oxf) 2007;66:58-64.
21. Mazzaferri EL. Management of low-risk differentiated thyroid cancer. Endocr Pract 2007;13:498-512.
22. Kloos RT, Mazzaferri EL. A single recombinant human thyrotropin-stimulated serum thyroglobulin measurement predicts differentiated thyroid carcinoma metastases three to five years later. J Clin Endocrinol Metab 2005;90:5047-57.
23. Sawka AM, Thephamongkhol K, Brouwers M, et al. Clinical review 170: A systematic review and metaanalysis of the effectiveness of radioactive iodine remnant ablation for well-differentiated thyroid cancer. J Clin Endocrinol Metab 2004;89:3668-76.
24. Machens A, Hinze R, Thomusch O, et al. Pattern of nodal metastasis for primary and reoperative thyroid cancer. World J Surg 2002;26:22-8.
25. Noguchi S, Noguchi A, Murakami N. Papillary carcinoma of the thyroid. I. Developing pattern of metastasis. Cancer 1970;26:1053-60.
26. Noguchi S, Murakami N. The value of lymph-node dissection in patients with differentiated thyroid cancer.

Surg Clin North Am 1987;67:251-61.
27. Wada N, Duh QY, Sugino K, et al. Lymph node metastasis from 259 papillary thyroid microcarcinomas: frequency, pattern of occurrence and recurrence, and optimal strategy for neck dissection. Ann Surg 2003;237:399-407.
28. Qubain SW, Nakano S, Baba M, et al. Distribution of lymph node micrometastasis in pN0 well-differentiated thyroid carcinoma. Surgery 2002;131:249-56.
29. Randolph GW, Duh QY, Heller KS, et al. The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension. Thyroid 2012;22:1144-52.
30. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167-214.
31. Bilimoria KY, Bentrem DJ, Ko CY, et al. Extent of surgery affects survival for papillary thyroid cancer. Ann Surg 2007;246:375-81; discussion 381-4.
32. Nixon IJ, Ganly I, Patel SG, et al. Thyroid lobectomy for treatment of well differentiated intrathyroid malignancy. Surgery 2012;151:571-9.
33. Hay ID, Grant CS, Taylor WF, et al. Ipsilateral lobectomy versus bilateral lobar resection in papillary thyroid carcinoma: a retrospective analysis of surgical outcome using a novel prognostic scoring system. Surgery 1987;102:1088-95.
34. Matsuzu K, Sugino K, Masudo K, et al. Thyroid lobectomy for papillary thyroid cancer: long-term follow-up study of 1,088 cases. World J Surg 2014;38:68-79.
35. Adam MA, Pura J, Gu L, et al. Extent of surgery for papillary thyroid cancer is not associated with survival: an analysis of 61,775 patients. Ann Surg 2014;260:601-5; discussion 605-7.
36. Kouvaraki MA, Shapiro SE, Fornage BD, et al. Role of preoperative ultrasonography in the surgical management of patients with thyroid cancer. Surgery 2003;134:946-54; discussion 954-5.
37. Stulak JM, Grant CS, Farley DR, et al. Value of preoperative ultrasonography in the surgical management of initial and reoperative papillary thyroid cancer. Arch Surg 2006;141:489-94; discussion 494-6.
38. Tuttle RM, Tala H, Shah J, et al. Estimating risk of recurrence in differentiated thyroid cancer after total thyroidectomy and radioactive iodine remnant ablation: using response to therapy variables to modify the initial risk estimates predicted by the new American Thyroid Association staging system. Thyroid 2010;20:1341-9.
39. Young S, Harari A, Smooke-Praw S, et al. Effect of reoperation on outcomes in papillary thyroid cancer. Surgery 2013;154:1354-61; discussion 1361-2.
40. Nixon IJ, Wang LY, Palmer FL, et al. The impact of nodal status on outcome in older patients with papillary thyroid cancer. Surgery 2014;156:137-46.
41. Grant CS, Stulak JM, Thompson GB, et al. Risks and adequacy of an optimized surgical approach to the primary surgical management of papillary thyroid carcinoma treated during 1999-2006. World J Surg 2010;34:1239-46.
42. Sywak M, Cornford L, Roach P, et al. Routine ipsilateral level VI lymphadenectomy reduces postoperative thyroglobulin levels in papillary thyroid cancer. Surgery 2006;140:1000-5; discussion 1005-7.
43. Popadich A, Levin O, Lee JC, et al. A multicenter cohort study of total thyroidectomy and routine central lymph node dissection for cN0 papillary thyroid cancer. Surgery 2011;150:1048-57.
44. Barczyński M, Konturek A, Stopa M, et al. Prophylactic central neck dissection for papillary thyroid cancer. Br J Surg 2013;100:410-8.
45. Hartl DM, Mamelle E, Borget I, et al. Influence of prophylactic neck dissection on rate of retreatment for papillary thyroid carcinoma. World J Surg 2013;37:1951-8.
46. Lang BH, Ng SH, Lau LL, et al. A systematic review and meta-analysis of prophylactic central neck dissection on short-term locoregional recurrence in papillary thyroid carcinoma after total thyroidectomy. Thyroid 2013;23:1087-98.
47. Pearce EN, Braverman LE. Papillary thyroid microcarcinoma outcomes and implications for treatment. J Clin Endocrinol Metab 2004;89:3710-2.
48. Bonnet S, Hartl D, Leboulleux S, et al. Prophylactic lymph node dissection for papillary thyroid cancer less than 2 cm: implications for radioiodine treatment. J Clin Endocrinol Metab 2009;94:1162-7.
49. Ducoudray R, Trésallet C, Godiris-Petit G, et al. Prophylactic lymph node dissection in papillary thyroid carcinoma: is there a place for lateral neck dissection? World J Surg 2013;37:1584-91.
50. Durante C, Montesano T, Torlontano M, et al. Papillary thyroid cancer: time course of recurrences during postsurgery surveillance. J Clin Endocrinol Metab

2013;98:636-42.
51. Gagel RF, Goepfert H, Callender DL. Changing concepts in the pathogenesis and management of thyroid carcinoma. CA Cancer J Clin 1996;46:261-83.
52. Onkendi EO, McKenzie TJ, Richards ML, et al. Reoperative experience with papillary thyroid cancer. World J Surg, 2014;38:645-52.
53. Sancho JJ, Lennard TW, Paunovic I, et al. Prophylactic central neck disection in papillary thyroid cancer: a consensus report of the European Society of Endocrine Surgeons (ESES). Langenbecks Arch Surg 2014;399:155-63.

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Defining the syndromes of parathyroid failure after total thyroidectomy

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Abstract: Acute and chronic parathyroid insufficiency syndromes are the most common complication after total thyroidectomy. Permanent hypoparathyroidism imposes an important medical burden on patient lifestyle due to the need for lifetime medication, regular visits and significant long-term costs. Its true prevalence has been underestimated due to lack of clear definitions, inadequate follow-up and conflicts of interest when reporting individual patient series. The aim of this review is to propose precise definitions for the different syndromes associated to parathyroid failure based on the follow-up and management of patients developing hypocalcemia (<8 mg/dL at 24 hours) after first-time total thyroidectomy for cancer or goiter at our unit. Short and long-term post-thyroidectomy parathyroid failure presents as three different metabolic syndromes: (I) postoperative hypocalcemia is defined as a s-Ca <8 mg/dL (<2 mmol/L) within 24 hours after surgery requiring calcium/vit D replacement therapy at the time of hospital discharge; (II) protracted hypoparathyroidism as a subnormal iPTH concentration (<13 pg/mL) and/or need for calcium/vit D replacement at 4-6 weeks; and (III) permanent hypoparathyroidism as a subnormal iPTH concentration (<13 pg/mL) and/or need for calcium/vit D replacement 1 year after total thyroidectomy. Each of these syndromes has its own pattern of recovery and should be approached with different therapeutic strategies.

Keywords: Definitions; hypocalcemia; hypoparathyroidism; parathyroid splinting; total thyroidectomy

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Postoperative hypocalcemia is the most common complication after total thyroidectomy (1-4) and impacts negatively of patient's quality of life due to the need for lifetime medication, regular visits and significant long-term costs. A recent study carried out a survey of 374 patients with permanent hypoparathyroidism (>80% post-thyroidectomy). Of those polled, 75% experienced more than 10 symptoms despite appropriate treatment, nearly 80% had visited emergency department and or required hospital stay and 85% reported disabilities to perform household activities (5).

The impact of postoperative parathyroid failure

The estimated prevalence of postoperative hypocalcemia and permanent hypoparathyroidism according to a recent review and meta-analysis (6) varies from 19% to 38% and from 0% and 3% respectively. Its true prevalence, however, is probably underestimated for reasons shown in *Table 1*.

National registries and large multicenter studies have shown that the rates of permanent hypoparathyroidism are much higher than those reported from single institutions, its prevalence ranging from 6% to 12% (*Table 2*). The Fourth National Audit of the British Association of Endocrine and Thyroid Surgeons (11) reported a 12.1% rate of permanent hypoparathyroidism after total thyroidectomy, while the Scandinavian Quality Register for Thyroid and Parathyroid Surgery (13) records a 6.4%. A multicenter German study showed a prevalence of 9% (8), quite similar

Table 1 Reasons for the underestimation of the prevalence hypocalcemia and hypoparathyroidism

Lack of clear definitions
Conflicts of interest
Variety of laboratory ranges for normocalcemia and reference values
Timing of blood sampling in the postoperative period
Wide range in thyroid procedures included in the analysis
Different case mix
Small series
Missing data in national audits
Different policies for calcium and vitamin D supplements
Short/incomplete follow-up
Follow-up not performed by the surgical team but by referring physicians

Table 2 Prevalence and definitions of hypocalcemia and permanent hypoparathyroidism in national registries and large multicenter studies

Study	Year	No. of procedures	Postoperative hypocalcemia prevalence	Definition	Value	Timing of blood sampling	Permanent hypoparathyroidism prevalence	Definition	Time at diagnosis
Hundahl *et al*. (7) (The ACS Commission on Cancer)	2000	1,926 TT	Not available	Unspecified	Unspecified	Not available	12.4%	Unspecified	Not available
Thomusch *et al*. (8)	2003	5,846 BT	24%	In ward calcium/vit D treatment	Unspecified	Not available	9%	Undetectable PTH vitamin D or calcium supplementation	6 months after surgery
Swedish register (9)	2008	1,648 BT	9.9%	Ca and/or vit D supplementation at discharge	Unspecified	Day 1	4.4%	Vit D and/ or calcium supplementation	6 months after surgery
Swedish register (10) (Graves' disease)	2012	956 TT	13.6%	Ca and/or vit D supplementation at discharge			4.3%	Vit D supplementation	6 months after surgery
BAETS Fourth National Audit Report (11)	2012	3,788 TT	27.4%	Serum calcium	<2.1 mmol/L	Day 1	12.1%	Calcium/vit D supplementation	6 months after surgery
Duclos *et al*. (12)	2012	2,669 TT	Not available	Serum calcium	< 2 mmol/L	48 h	2.6%	Calcium/vit D supplementation	6 months after surgery

TT, total thyroidectomy; BT, bilateral thyroidectomy.

to that observed in thyroid cancer patients in the USA (7). Furthermore, in some of these registries, the true rate of permanent hypoparathyroidism may be underestimated due to failure to follow-up all patients. For example, in the 2012 BAETS registry (11), 25% of patients do not have long term data on calcium and vitamin D replacement.

As can be seen in *Table 2*, there are substantial differences in the definitions of hypoparathyroidism and, especially postoperative hypocalcemia. Approximately, half of the reported studies define postoperative hypocalcemia as the need for calcium or vitamin D supplements whereas the rest define it according to low s-Ca concentrations, usually within 24 hours after surgery. The majority of these studies define permanent hypoparathyroidism as the need for calcium and or vitamin D supplements at 6 months after surgery. In addition, some of these analyses include conservative bilateral procedures and not only total thyroidectomies (8-12).

Some authors (14-16) have highlighted the lack of standardised definitions for postoperative hypocalcemia and hypoparathyroidism after total thyroidectomy. A review of 19 publications (14) showed that 26% of the studies failed to provide appropriate definitions for hypocalcemia, transient and permanent hypoparathyroidism. When provided, there was inconsistency in the biochemical definition of hypocalcemia (cut-off points ranging from 1.8 to 2.12 mmol/L). Mehanna *et al.* (16) applied different definitions reported in the literature to their cohort of thyroidectomy patients and demonstrated how the rate of hypocalcemia ranged from 0% to 46% depending on the definition used.

Not only do surgeons underestimate the prevalence of postoperative parathyroid failure, but also the impact of long-term hypoparathyroidism on patients' well-being (5,17). Besides recurrent symptoms of hypocalcemia, patients with permanent hypoparathyroidism are at risk of developing renal failure, basal ganglia calcifications, neuropsychiatric derangements and infections (18,19).

Etiology and pathophysiology of iatrogenic hypoparathyroidism

The general consensus is that the main cause of hypocalcemia is an acute parathyroid insufficiency due to a reduction of the functioning parathyroid parenchyma (1,20). Impaired PTH secretion leads to postoperative hypocalcemia by inhibiting bone resorption and reducing 1,25-dihydroxyvitamin D synthesis in the kidney resulting in a reduced intestinal absorption of calcium (21).

An early postoperative decrease in serum iPTH concentrations associated with a s-Ca <8 mg/dL has been shown in several studies (22-24), and is consistent with the hypothesis that acute parathyroid insufficiency often occurs after total thyroidectomy. Barczyński *et al.* demonstrated a significantly lower iPTH serum concentrations and a higher drop of iPTH at skin closure and 4 hours after total thyroidectomy in patients developing hypocalcemia compared to normocalcemic patients (22). They concluded that iPTH levels <10 pg/mL at 4 hours after total thyroidectomy had the best precision to predict hypocalcemia (s-Ca <8 mg/dL) 24 hours after surgery, a positive predictive value of 90%. Grodski *et al.*'s review (23) found that post-thyroidectomy PTH levels accurately predict hypocalcemia, which is unlikely to occur if iPTH levels are normal, and can be used cautiously to discharge patients on the first postoperative day (24).

The reduction of the functioning parathyroid tissue is secondary to an intraoperative damage to the parathyroid glands caused by a combination of factors such as mechanical or thermal trauma, gland devascularization, obstruction of venous outflow, inadvertent parathyroid excision, and parathyroid autotransplantation. Fewer parathyroid glands identified during total thyroidectomy may result in gland injury and accidental parathyroidectomy (8,9). Few parathyroid glands kept in situ due to incidental parathyroidectomy (1,25-29) or autotransplantation (9,10,20,30,31) has been repeatedly reported to be a crucial factor leading to acute parathyroid insufficiency. This, however, has not been properly substantiated by biochemical tests until recently (32).

Other factors that may contribute to the development of post-thyroidectomy hypocalcemia include hemodilution, urinary calcium excretion facilitated by surgical stress, calcitonin release due to thyroid manipulation, vitamin D deficiency and hungry bone syndrome (14). Studies on PTH postoperative kinetics, however, cast little doubt about the major role of parathyroid failure in the pathogenesis of postoperative hypocalcemia.

Definitions of parathyroid failure syndromes at the Hospital del Mar

Postoperative hypocalcemia

There is consensus that the diagnosis and treatment of postoperative hypocalcemia must precede the development of symptoms and that PTH and/or s-Ca should be monitored after total thyroidectomy in order to start treatment before

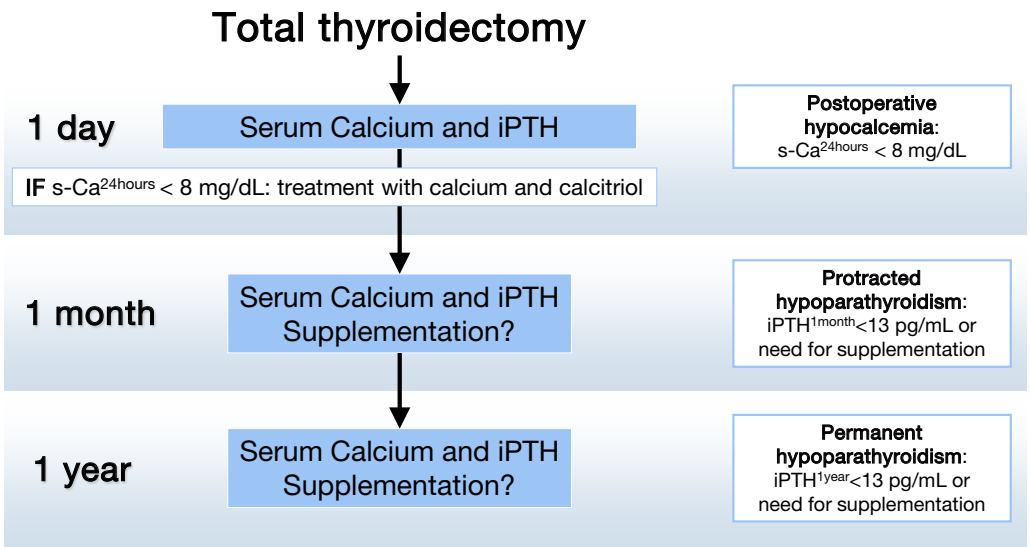

Figure 1 Time points for classification of patients developing hypocalcemia after total thyroidectomy at the Hospital del Mar.

symptoms occur. Alternatively, some groups have proposed to give calcium and vitamin D supplements to all patients (preventive therapeutic strategy) and do not care much about biochemical parameters (33). In some registries, calcium and vitamin D replacement are used as surrogate variables for postoperative hypocalcemia (8-10).

The cut-off value and timing of blood sampling used to define postoperative hypocalcemia differs. Most authors (1,22,26,27,34) agree on the biochemical diagnosis hypocalcaemia as a total s-Ca concentrations <8 mg/dL or 2 mmol/L. Total s-Ca is cheap and easy to interpret and is preferable to ionized calcium concentrations which are highly dependent on blood sampling, transport and pH. A cut-off of 8 mg/dL (2 mmol/L) corrects for recumbency and mild hemodilution, and only exceptionally are symptoms of hypocalcemia observed above this value. Other authors (20,35) define hypocalcemia as a s-Ca <1.8 or 1.9 mmol/L but this risks to underestimate the diagnosis of hypocalcemia since patients may develop symptoms when s-Ca drops below 2 mmol/L. Finally, raising the cut-off up to 2.1 mmol/L (36) may lead to an overestimation of hypocalcaemia rates and overtreatment.

Timing of s-Ca measurement after thyroidectomy is critical because it has an impact on the prevalence of hypocalcemia rates: the closer the blood sampling is performed to surgery the lower the rates of hypocalcemia will be. On the other hand, if s-Ca is determined too late, patients may develop clinical symptoms before treatment is commenced.

For these reasons, we adhere to the more widespread proposal that postoperative hypocalcemia be defined as a s-Ca <8 mg/dL (2 mmol/L) 24 hours after total thyroidectomy (26) and that oral treatment with calcium and calcitriol be started if s-Ca drops below this value. This selective therapeutic strategy allows for patients to be discharged home early on the next day and minimizes overtreatment of the normocalcemic patients.

In addition, we recommend that a second blood test including iPTH be obtained the morning following surgery. This postoperative iPTH concentration is used as a reference value to check parathyroid function recovery during patient follow up. If PTH is low or undetectable, calcium and calcitriol supplements are continued when the patient is seen the next week in the outpatient clinic. All patients with postoperative hypocalcemia are followed in our unit with regular checks of s-Ca and iPTH until recovery or a final diagnosis of permanent hypoparathyroidism (26) is made (*Figure 1*).

Protracted hypoparathyroidism

Parathyroid function recovery can be expected in at least two thirds of patients with postoperative hypocalcemia within 1 month of thyroidectomy. Those who need treatment beyond this time period suffer from protracted hypoparathyroidism. Promberger *et al.* (37) proposed the concept of protracted hypoparathyroidism for those patients requiring replacement therapy 2 weeks after thyroidectomy. This period of time, however, may be a little too short to

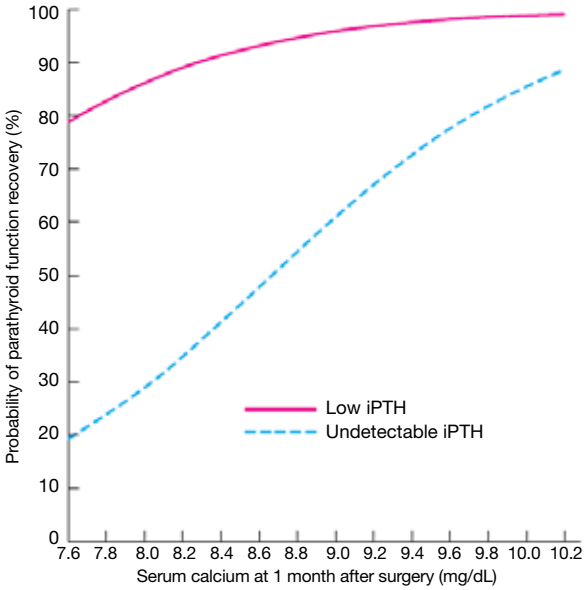

Figure 2 Probability of recovery of parathyroid function in patients with protracted hypoparathyroidism according to s-Ca and iPTH concentrations 1 month after total thyroidectomy. With permission from (26).

diagnose early parathyroid function recovery. Other authors assessed the hypoparathyroidism rates around 1 month after surgery. Hallgrimsson *et al*. (10), reported a 9.1% of protracted hypoparathyroidism assessing the need for vitamin D supplements at 6 weeks after surgery. Bergenfelz *et al*. (9) reported continuation of calcium, vitamin D or both in 7.8%, 2.6% and 7.3% of patients, respectively, 6 weeks after bilateral (not always total) thyroidectomy. In agreement with these two teams, we propose the following definition of protracted hypoparathyroidism: a subnormal iPTH concentration (<13 pg/mL) and/or need for calcium replacement with or without calcitriol at 4-6 weeks after thyroidectomy (26).

A proper definition of protracted hypoparathyroidism has clinical relevance as a predicting tool when informing patients. If the patient is hypoparathyroid 1 month after surgery, the probability of recovering the parathyroid function during the next 12 months is 75%. In addition, the chances of parathyroid function recovery after 1 month are better if iPTH is detectable (4-14 pg/mL) that when it is undetectable (26) (*Figure 2*).

Permanent hypoparathyroidism

Permanent hypoparathyroidism is defined as the need for replacement therapy 6 months (21) or 1 year after thyroidectomy (1,26). We propose to use the 1-year deadline since according to our data about 20% of patients who recover from protracted hypoparathyroidism do so after 6 months. Subnormal iPTH concentration (<13 pg/mL) is the rule in these cases. A closer look at permanent hypoparathyroidism allows for a subclassification of this syndrome into three conditions:

(I) Aparathyroidism (undetectable PTH, high phosphate);
(II) Hypoparathyroidism (detectable but subnormal iPTH concentrations, normal phosphate);
(III) Relative parathyroid insufficiency (normal iPTH levels but insufficient to maintain s-Ca within normal limits).

Broadly speaking, aparathyroidism always requires vitamin D supplementation, hypoparathyroidism can often be managed with calcium salts alone, and relative parathyroid insufficiency is seen in patients with associated conditions (treatment with biphosphonates, malabsorption, bowel resection, gastric bypass) impairing calcium absorption or resorption in whom there is an insufficient parathyroid functional reserve to respond to hypocalcemia. Interestingly, a study showed that the secretory response of parathyroid glands is impaired in some patients' long term after with total thyroidectomy despite PTH levels are within normal limits (38). After a hypocalcemic stimulus with sodium bicarbonate infusion, PTH levels increased in total thyroidectomy patients but to a lesser degree compared with non-thyroidectomized patients.

The best vitamin D substitute for treatment of permanent hypoparathyroidism is controversial. We favor calcifediol because is cheap, non-nephrotoxic and can be usually started as one ampoule (10,000 UI, 266 mg) twice a week. Once diagnosed and stabilized, patients with permanent hypoparathyroidism should be controlled twice a year. s-Ca, P, iPTH levels, 25-hydroxyvitamin D and 1,25-hydroxyvitamin D (particularly if calcitriol is being administered) are determined to adjust replacement therapy and prevent hypo- and hypercalcemia.

Risk factors for postoperative parathyroid failure

Postoperative hypocalcemia

A recent meta-analysis (6) isolated as predictive factors for transient hypocalcemia biochemical parameters such as preoperative calcium levels, perioperative PTH and

25-hydroxyvitamin D levels and postoperative magnesium. Additionally, surgical factors found to be predictive were reoperation for recurrent goiter or for bleeding. Graves' disease (8,39) and thyroid cancer (30) have been reported to be associated with higher rates of post-thyroidectomy hypocalcemia. Reported patient-related factors to hypocalcemia are younger age and female gender (8,39,40).

Lower perioperative levels or a larger decline in serum calcium (34,40,41), lower intraoperative or postoperative PTH levels (31,41,42), and also larger decline in intraoperative (22,41) and postoperative PTH (43-45) appear as biochemical factors associated with postoperative hypocalcemia as well as low preoperative vitamin D (34,46), low postoperative magnesium (47), high preoperative alkaline phosphatase and bone turnover markers (34,40) which is consistent with hungry bone syndrome.

With regard to surgical factors, increased risk of transient hypocalcaemia is mainly associated with the extent of surgery, central compartment node dissection (3,9,26,27), redo operations, reoperation for bleeding and wound infection (9,10). Some authors found that a lower hospital volume and therein, less experimented endocrine surgery team leads to an increase in hypocalcemia rates (10). Regarding surgical technique, few parathyroid glands maintained in situ due to inadvertent parathyroid excision (25-28) and/or autotransplantation (9,10,20,26,27,30,31,37) emerge as a major post-thyroidectomy hypocalcaemia risk factor. Gland injury and accidental parathyroid excision may be facilitated by failure to identify properly the parathyroid glands during total thyroidectomy (8,9). Hence, we usually look for parathyroid glands in their orthotopic position. Nevertheless, some authors have suggested that parathyroid gland identification has no influence on postoperative hypocalcemia (10,44) whereas others have considered it as a risk factor for hypocalcemia (31,48,49).

Protracted hypoparathyroidism

Protracted hypoparathyroidism is associated with weight of the resected thyroid gland, lymph node dissection, reoperation for bleeding, wound infection, esternotomy, few parathyroid glands identified and autotransplantation.

Multivariate analysis of our own data (32) revealed that protracted hypoparathyroidism was strongly associated with the number of parathyroid glands remaining *in situ*: 4-(excised + autografted). At this stage, the demographic and clinical variables as well as the extension of surgery were much less relevant. The prevalence of protracted hypoparathyroidism doubled in patients who received autotransplantation. There was a linear influence of the number of parathyroid glands remaining in situ on protracted hypoparathyroidism rates (32).

Permanent hypoparathyroidism

Despite attempts to predict permanent hypoparathyroidism on the basis of biochemical parameters at the time of hospital discharge the fact is that no single postoperative variable can be used to accurately predict it (50,51). A s-Ca level <1.88 mmol/L at 24 hours after surgery, identification of fewer parathyroid glands during the surgery (1,8) reoperation for bleeding (10), Graves' disease and heavier thyroid specimens (52) have been identified as independent predictors (6). Parathyroid function recovery, however, is a dynamic event and cannot be predicted early after thyroidectomy. Our data (32) indicate that the best predictors of iPTH recovery in patients with protracted hypoparathyroidism are the number of parathyroid glands remaining *in situ* and the s-Ca concentration at one month after surgery (see below).

Whether parathyroid autotransplantation prevents permanent hypoparathyroidism is a very controversial issue. All authors admit that autotransplantation results in higher rates of postoperative hypocalcemia but some have proposed that in the long-term it prevents permanent hypoparathyroidism (4,53-57). Several studies, however, have found a strong association between autotransplantation and permanent hypoparathyroidism (1,20,26,30).

In our hands, parathyroid autotransplantation in the SCM muscle using the fragmented tissue technique proposed by Olson *et al*. (4) resulted in a threefold increase of permanent hypoparathyroidism: 3% in non-transplanted *vs*. 9% in transplanted patients. Interestingly, in patients with three glands remaining *in situ*, the rate of permanent hypoparathyroidism was the same whether the fourth gland was autotransplanted or was found in the specimen in the pathology lab.

Likelihood of recovery of parathyroid function

Postoperative hypocalcaemia is usually (>60-70%) a transient phenomenon and calcium supplements can be stopped within 1 month after surgery. If calcium and calcitriol supplements are still required after 1 month, the chance to develop permanent hypoparathyroidism is 25%. Clinical and surgical variables (age, gender, extension

of surgery, diagnosis) do lose predictive significance and calcium and calcitriol dosage at hospital discharge, high s-Ca and low but detectable iPTH levels one month after surgery become the most relevant predictive variables (26). Higher s-Ca concentrations associated with higher calcium and calcitriol dosages at the time of hospital discharge have a positive effect on parathyroid function recovery. We have described this phenomenon as "parathyroid splinting", meaning that the injured and ischemic parathyroid glands are allowed to rest in a normal-high s-Ca environment (*Figure 2*). Parathyroid splinting has a synergistic effect with the number of parathyroid glands remaining *in situ* to facilitate recovery of the parathyroid function (32).

Conclusions

The approach to post-thyroidectomy hypoparathyroidism may be facilitated by the understanding of the three different metabolic syndromes of parathyroid failure. Selective calcium/vit D replacement therapy of postoperative hypocalcemia at the time of hospital discharge is recommended. A detectable iPTH, all parathyroid glands remaining *in situ* and high levels of serum calcium one month after surgery increase the likelihood of recovery from protracted hypoparathyroidism. Permanent hypoparathyroidism can be managed according to iPTH levels. Aparathyroidism with undetectable iPTH requires vitamin D supplementation whereas hypoparathyroidism (detectable but subnormal iPTH) can often be managed with calcium salts alone. Associated conditions such as malabsorption, gastric bypass or treatment with biphosphonates may cause a relative parathyroid insufficiency.

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References

1. Pattou F, Combemale F, Fabre S, et al. Hypocalcemia following thyroid surgery: incidence and prediction of outcome. World J Surg 1998;22:718-24.
2. Bhattacharyya N, Fried MP. Assessment of the morbidity and complications of total thyroidectomy. Arch Otolaryngol Head Neck Surg 2002;128:389-92.
3. Abboud B, Sargi Z, Akkam M, et al. Risk factors for postthyroidectomy hypocalcemia. J Am Coll Surg 2002;195:456-61.
4. Olson JA Jr, DeBenedetti MK, Baumann DS, et al. Parathyroid autotransplantation during thyroidectomy. Results of long-term follow-up. Ann Surg 1996;223:472-8; discussion 478-80.
5. Hadker N, Egan J, Sanders J, et al. Understanding the burden of illness associated with hypoparathyroidism reported among patients in the paradox study. Endocr Pract 2014;20:671-9.
6. Edafe O, Antakia R, Laskar N, et al. Systematic review and meta-analysis of predictors of post-thyroidectomy hypocalcaemia. Br J Surg 2014;101:307-20.
7. Hundahl SA, Cady B, Cunningham MP, et al. Initial results from a prospective cohort study of 5583 cases of thyroid carcinoma treated in the united states during 1996. U.S. and German Thyroid Cancer Study Group. An American College of Surgeons Commission on Cancer Patient Care Evaluation study. Cancer 2000;89:202-17.
8. Thomusch O, Machens A, Sekulla C, et al. The impact of surgical technique on postoperative hypoparathyroidism in bilateral thyroid surgery: a multivariate analysis of 5846 consecutive patients. Surgery 2003;133:180-5.
9. Bergenfelz A, Jansson S, Kristoffersson A, et al. Complications to thyroid surgery: results as reported in a database from a multicenter audit comprising 3,660 patients. Langenbecks Arch Surg 2008;393:667-73.
10. Hallgrimsson P, Nordenström E, Almquist M, et al. Risk factors for medically treated hypocalcemia after surgery for Graves' disease: a Swedish multicenter study of 1,157 patients. World J Surg 2012;36:1933-42.
11. Available online: http://www.baets.org.uk/
12. Duclos A, Peix JL, Colin C, et al. Influence of experience on performance of individual surgeons in thyroid surgery: prospective cross sectional multicentre study. BMJ 2012;344:d8041.
13. Available online: http://www.thyroid-parathyroidsurgery.com
14. Wu J, Harrison B. Hypocalcemia after Thyroidectomy: The Need for Improved Definitions. World J End Surg 2010; 2:17-20.
15. Balasubramanian SP. Iatrogenic/post-surgical hypoparathyroidism: where do we go from here? Endocrine 2014;47:357-9.
16. Mehanna HM, Jain A, Randeva H, et al. Postoperative hypocalcemia--the difference a definition makes. Head Neck 2010;32:279-83.
17. Cho NL, Moalem J, Chen L, et al. Surgeons and patients disagree on the potential consequences from hypoparathyroidism. Endocr Pract 2014;20:427-46.

18. Mitchell DM, Regan S, Cooley MR, et al. Long-term follow-up of patients with hypoparathyroidism. J Clin Endocrinol Metab 2012;97:4507-14.
19. Underbjerg L, Sikjaer T, Mosekilde L, et al. Postsurgical hypoparathyroidism--risk of fractures, psychiatric diseases, cancer, cataract, and infections. J Bone Miner Res 2014;29:2504-10.
20. Asari R, Passler C, Kaczirek K, et al. Hypoparathyroidism after total thyroidectomy: a prospective study. Arch Surg 2008;143:132-7; discussion 138.
21. Shoback D. Clinical practice. Hypoparathyroidism. N Engl J Med 2008;359:391-403.
22. Barczyński M, Cichoń S, Konturek A. Which criterion of intraoperative iPTH assay is the most accurate in prediction of true serum calcium levels after thyroid surgery? Langenbecks Arch Surg 2007;392:693-8.
23. Grodski S, Serpell J. Evidence for the role of perioperative PTH measurement after total thyroidectomy as a predictor of hypocalcemia. World J Surg 2008;32:1367-73.
24. Payne RJ, Hier MP, Tamilia M, et al. Postoperative parathyroid hormone level as a predictor of post-thyroidectomy hypocalcemia. J Otolaryngol 2003;32:362-7.
25. Glinoer D, Andry G, Chantrain G, et al. Clinical aspects of early and late hypocalcaemia afterthyroid surgery. Eur J Surg Oncol 2000;26:571-7.
26. Sitges-Serra A, Ruiz S, Girvent M, et al. Outcome of protracted hypoparathyroidism after total thyroidectomy. Br J Surg 2010;97:1687-95.
27. Pereira JA, Jimeno J, Miquel J, et al. Nodal yield, morbidity, and recurrence after central neck dissection for papillary thyroid carcinoma. Surgery 2005;138:1095-100.
28. McLeod IK, Arciero C, Noordzij JP, et al. The use of rapid parathyroid hormone assay in predicting postoperative hypocalcemia after total or completion thyroidectomy. Thyroid 2006;16:259-65.
29. Paek SH, Lee YM, Min SY, et al. Risk factors of hypoparathyroidism following total thyroidectomy for thyroid cancer. World J Surg 2013;37:94-101.
30. Roh JL, Park JY, Park CI. Total thyroidectomy plus neck dissection in differentiated papillary thyroid carcinoma patients: pattern of nodal metastasis, morbidity, recurrence, and postoperative levels of serum parathyroid hormone. Ann Surg 2007;245:604-10.
31. Lang BH, Yih PC, Ng KK. A prospective evaluation of quick intraoperative parathyroid hormone assay at the time of skin closure in predicting clinically relevant hypocalcemia after thyroidectomy. World J Surg 2012;36:1300-6.
32. Lorente-Poch L, Sancho JJ, Ruiz S, et al. Importance of in situ preservation of parathyroid glands during total thyroidectomy. Br J Surg 2015. [Epub ahead of print].
33. Wang TS, Cheung K, Roman SA, et al. To supplement or not to supplement: a cost-utility analysis of calcium and vitamin D repletion in patients after thyroidectomy. Ann Surg Oncol 2011;18:1293-9.
34. Erbil Y, Barbaros U, Temel B, et al. The impact of age, vitamin D(3) level, and incidental parathyroidectomy on postoperative hypocalcemia after total or near total thyroidectomy. Am J Surg 2009;197:439-46.
35. Wiseman JE, Mossanen M, Ituarte PH, et al. An algorithm informed by the parathyroid hormone level reduces hypocalcemic complications of thyroidectomy. World J Surg 2010;34:532-7.
36. Wilhelm SM, McHenry CR. Total thyroidectomy is superior to subtotal thyroidectomy for management of Graves' disease in the United States. World J Surg 2010;34:1261-4.
37. Promberger R, Ott J, Kober F, et al. Intra- and postoperative parathyroid hormone-kinetics do not advocate for autotransplantation of discolored parathyroid glands during thyroidectomy. Thyroid 2010;20:1371-5.
38. Anastasiou OE, Yavropoulou MP, Papavramidis TS, et al. Secretory capacity of the parathyroid glands after total thyroidectomy in normocalcemic subjects. J Clin Endocrinol Metab 2012;97:2341-6.
39. Pesce CE, Shiue Z, Tsai HL, et al. Postoperative hypocalcemia after thyroidectomy for Graves' disease. Thyroid 2010;20:1279-83.
40. Erbil Y, Bozbora A, Ozbey N, et al. Predictive value of age and serum parathormone and vitamin d3 levels for postoperative hypocalcemia after total thyroidectomy for nontoxic multinodular goiter. Arch Surg 2007;142:1182-7.
41. Walsh SR, Kumar B, Coveney EC. Serum calcium slope predicts hypocalcaemia following thyroid surgery. Int J Surg 2007;5:41-4.
42. Cavicchi O, Piccin O, Caliceti U, et al. Transient hypoparathyroidism following thyroidectomy: a prospective study and multivariate analysis of 604 consecutive patients. Otolaryngol Head Neck Surg 2007;137:654-8.
43. Chapman DB, French CC, Leng X, et al. Parathyroid hormone early percent change: an individualized approach to predict postthyroidectomy hypocalcemia. Am J Otolaryngol 2012;33:216-20.
44. Vanderlei FA, Vieira JG, Hojaij FC, et al. Parathyroid

hormone: an early predictor of symptomatic hypocalcemia after total thyroidectomy. Arq Bras Endocrinol Metabol 2012;56:168-72.
45. Lecerf P, Orry D, Perrodeau E, et al. Parathyroid hormone decline 4 hours after total thyroidectomy accurately predicts hypocalcemia. Surgery 2012;152:863-8.
46. Kirkby-Bott J, Markogiannakis H, Skandarajah A, et al. Preoperative vitamin D deficiency predicts postoperative hypocalcemia after total thyroidectomy. World J Surg 2011;35:324-30.
47. Wilson RB, Erskine C, Crowe PJ. Hypomagnesemia and hypocalcemia after thyroidectomy: prospective study. World J Surg 2000;24:722-6.
48. Pfleiderer AG, Ahmad N, Draper MR, et al. The timing of calcium measurements in helping to predict temporary and permanent hypocalcaemia in patients having completion and total thyroidectomies. Ann R Coll Surg Engl 2009;91:140-6.
49. Sheahan P, Mehanna R, Basheeth N, et al. Is systematic identification of all four parathyroid glands necessary during total thyroidectomy?: a prospective study. Laryngoscope 2013;123:2324-8.
50. Almquist M, Hallgrimsson P, Nordenström E, et al. Prediction of permanent hypoparathyroidism after total thyroidectomy. World J Surg 2014;38:2613-20.
51. Julián MT, Balibrea JM, Granada ML, et al. Intact parathyroid hormone measurement at 24 hours after thyroid surgery as predictor of parathyroid function at long term. Am J Surg 2013;206:783-9.
52. Thomusch O, Machens A, Sekulla C, et al. Multivariate analysis of risk factors for postoperative complications in benign goiter surgery: prospective multicenter study in Germany. World J Surg 2000;24:1335-41.
53. Gourgiotis S, Moustafellos P, Dimopoulos N, et al. Inadvertent parathyroidectomy during thyroid surgery: the incidence of a complication of thyroidectomy. Langenbecks Arch Surg 2006;391:557-60.
54. Ondik MP, McGinn J, Ruggiero F, et al. Unintentional parathyroidectomy and hypoparathyroidism in secondary central compartment surgery for thyroid cancer. Head Neck 2010;32:462-6.
55. Sakorafas GH, Stafyla V, Bramis C, et al. Incidental parathyroidectomy during thyroid surgery: an underappreciated complication of thyroidectomy. World J Surg 2005;29:1539-43.
56. Almquist M, Hallgrimsson P, Nordenström E, et al. Prediction of permanent hypoparathyroidism after total thyroidectomy. World J Surg 2014;38:2613-20.
57. Lo CY, Tam SC. Parathyroid autotransplantation during thyroidectomy: documentation of graft function. Arch Surg 2001;136:1381-5.

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Recovery of laryngeal function after intraoperative injury to the recurrent laryngeal nerve

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Abstract: Loss of function in the recurrent laryngeal nerve (RLN) during thyroid/parathyroid surgery, despite a macroscopically intact nerve, is a challenge which highlights the sensitivity and complexity of laryngeal innervation. Furthermore, the uncertain prognosis stresses a lack of capability to diagnose the reason behind the impaired function. There is a great deal of literature considering risk factors, surgical technique and mechanisms outside the nerve affecting the incidence of RLN paresis during surgery. To be able to prognosticate recovery in cases of laryngeal dysfunction and voice changes after thyroid surgery, the surgeon would first need to define the presence, location, and type of laryngeal nerve injury. There is little data describing the events within the nerve and the neurobiological reasons for the impaired function related to potential recovery and prognosis. In addition, very little data has been presented in order to clarify any differences between the transient and permanent injury of the RLN. This review aims, from an anatomical and neurobiological perspective, to provide an update on the current understandings of surgically-induced injury to the laryngeal nerves.

Keywords: Regeneration; thyroid surgery; nerve injury; vocal fold paresis; laryngeal EMG

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Recurrent laryngeal nerve (RLN) injury and voice alteration after thyroid surgery

Thyroid and parathyroid surgery is associated with a risk of traumatic injury to the superior and inferior RLN. Injury to the RLN results in acute paralysis of the vocal fold on the affected side, which leads to dysphonia, dysphagia, and aspiration problems. The clinical signs may vary, however, depending on the position of the paralyzed vocal fold relative to the midline and the degree of glottic insufficiency. A significant number of patients may even present as asymptomatic, and vocal fold mobility needs to be examined before and after surgery to detect an iatrogenic injury to the RLN (1-4). The reported risk for RLN injury after thyroid/parathyroid surgery varies from center to center. In the literature, injury rates of up to 38% can be found (5). It is difficult to compare these numbers, since the rate of detected RLN injury is dependent on how close to surgery the laryngoscopic examination is performed. In a large, retrospective study of patients that underwent total thyroidectomy due to malignant disease, the risk of postoperative vocal fold paresis was found to be 9.5% (6), of which 22% became permanent with resulting demand for secondary surgical intervention of the paralyzed vocal fold.

Subjective voice deficits are common after thyroid surgery (7). Subjective and objective voice alterations (8,9) are common after total thyroidectomy and most of them are independent of injury to the RLN or the superior laryngeal nerve (SLN) (10-12). These voice changes are believed to be caused by temporary disturbances in the laryngeal mechanical framework or extralaryngeal scarring, and they usually resolve to subclinical levels within weeks or months after the operation (9,13,14). Dividing the sternothyroid muscle has been shown not to affect voice outcome in a significant way (15). Even though the RLN is the most important provider of laryngeal motor innervation, injury

to the external branch of the SLN is also believed to cause significant voice changes, such as reduction in the fundamental frequency range, reduction in the highest obtainable fundamental frequency and vibratory phase asymmetry in the vocal folds (16-19). The external branch of the SLN has therefore gained increased attention among thyroid surgeons, and it is recommended that it should be preserved as well as the RLN during thyroid surgery (20).

In most cases of postoperative vocal fold paresis, the RLN is macroscopically intact and the injury is located within the peripheral nerve. To be able to prognosticate recovery, the surgeon would need to define the presence, location, and type of the nerve injury. However, very little data has been presented aimed at clarifying the differences between the transient and permanent injury of the RLN. This review aims to provide, from an anatomical and neurobiological perspective, an update on the current understanding of surgically-induced injury to the laryngeal nerves.

The laryngeal nerves

The larynx is innervated by two branches of the vagus nerve, the RLN, and the SLN. Both nerves carry motor, sensory, and autonomic (parasympathetic) fibers to the larynx (21). The lower motor neurons of the special efferent system controlling the intrinsic laryngeal muscles are located in the nucleus ambiguus in the lower brainstem, in a fairly well-studied somatotopical arrangement (22-30). The sensory neurons are located in the nodose ganglion and the parasympathetic cell bodies are located in the dorsal motor nucleus of the vagus in the brainstem. The mechanically complex laryngeal functions (airway protection reflexes, phonation, swallowing) require a rich and detailed neural control, projected through the RLN and SLN.

The RLN can be regarded as the most important motor nerve supply to the larynx, as it innervates 4 out of 5 intrinsic laryngeal muscles. It also has projections to the esophagus and trachea (23). The RLN divides into an anterior and posterior branch. The branching point is located either inside the larynx, or, as in roughly one third of cases, before the nerve entering point (31). The posterior branch projects superiorly to form the anastomosis of Galen with the internal branch of the SLN—this branch is probably sensory in nature (32). The anterior branch carries motor fibers (33,34) to the posterior thyroarytenoid muscle, lateral cricoarytenoid muscle and, finally, to the thyroarytenoid muscle (35-37). Within the larynx, the RLN and SLN break up into a plexus-like branching system (38), with several connections between the RLN and SLN (37). The exact functions of these small nerve branches are not fully known, but it has been demonstrated in animal experimental models that the intrinsic laryngeal muscles receive dual innervation from both the RLN and SLN (39,40).

The SLN originates from the inferior vagal ganglion at the C2 level in the neck (41). It divides into a larger, internal branch which enters the larynx through the thyrohyoid membrane (carrying sensory fibers down to the level of the glottis) and a smaller, external, branch which passes deep to the superior thyroid artery to innervate the cricothyroid muscle responsible for vocal fold lengthening and tension, important for high voice pitch (42). The external branch of the SLN continues through the cricothyroid muscle to reach the anterior glottis and the thyroarytenoid muscle. This branch, called “the human communicating nerve” (43), or “the cricothyroid connection branch” (44) thus represents an additional motor supply to the intrinsic laryngeal muscles other than the RLN, which may be important following RLN injury and reinnervation. This anatomy enables intraoperative monitoring of the external branch of the SLN through routine surface electrodes in the intubation tube (45), although the exact laryngological function of this nerve branch is not known (17).

Neurapraxia versus axonotmesis

From a clinical perspective, it is important to make the distinction between nerve conduction block , “neurapraxia”, and the more severe “axonotmesis”, which means presence of axonal injury (*Figure 1*). These classifications were first made by Seddon in 1942 (46) and later modified by Sunderland in 1951 (47). Surgically-induced nerve injuries seldom include complete transection of the nerve, but rather intraneural damage inside a macroscopically intact nerve due to pressure, crush or heating from adjacent use of cautery. Neurapraxia is the mildest form of injury, affecting the surrounding Schwann cells, but respecting the integrity of the axon (*Figure 1A*). The result is a conduction block lasting typically about 6-8 weeks followed by a complete return of function, when the Schwann cells have been repaired (48). This seems to be the case also for RLN injury (49). Following axonotmesis, there is a varying degree of axonal injury (*Figure 1B*), which could lead to neuronal death or dysfunctional reinnervation of the target cells. Axonotmesis, therefore, is associated with a poorer and more unpredictable

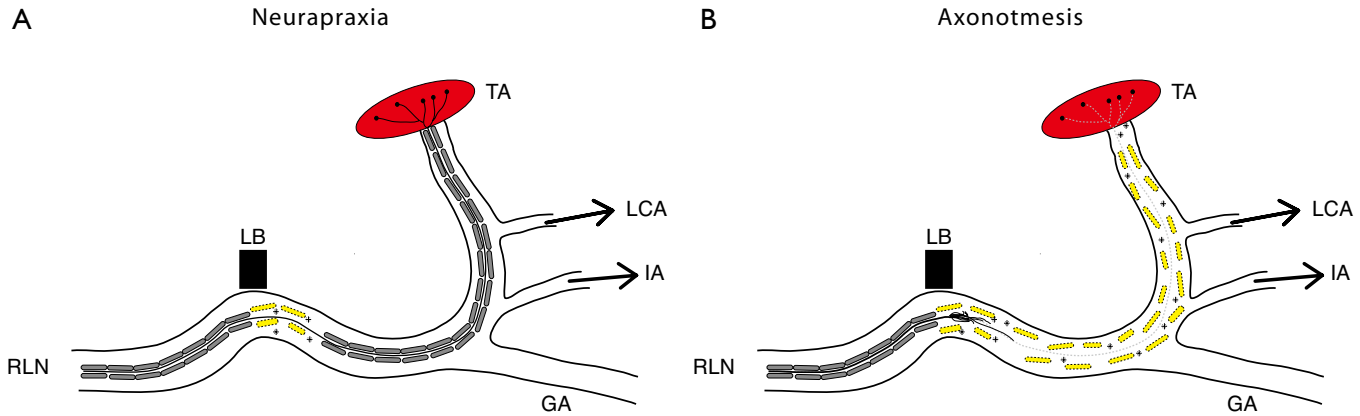

Figure 1 Schematic drawing of the RLN with intralaryngeal branches to IA, LCA and TA. The axon is surrounded by Schwann cells responsible for electrical propagation. Neurapraxia (A) with intact axonal integrity, facing spontaneous recovery. Axonotmesis (B) with disruption of axon and ongoing regeneration. RLN, recurrent laryngeal nerve; IA, interarytenoid muscle; LCA, lateral cricoarytenoid muscle; TA, thyroarytenoid muscle; LB, ligament of Berry; GA, anastomosis of Galen.

outcome for functional restitution.

Neurobiology behind impaired function

The motor neuron terminates at the neuromuscular junction, the motor end plate. The neuron is the secondary neuron and is part of the peripheral nervous system (PNS), as opposed to the primary motor neuron [central nervous system (CNS)], which runs from the cortex to terminate on the secondary neurons. The myelin around the axons in the CNS comes from oligodendrocytes. The CNS myelin contains several factors which are inhibitory to axonal growth and regeneration, which is one of the major problems after CNS injury, such as stroke or spinal cord injury (50). In the PNS, on the other hand, the myelin around the axons is derived from the Schwann cell. This milieu is attractive for axonal growth, which is why the peripheral nerve injury is usually associated with regeneration after axonal disruption (51-55). Following a peripheral nerve injury, which involves peripheral axon disruption, the distal part (which is disconnected from the neuron) will be neurophysiologically active until it degenerates (56) [Wallerian degeneration (57)] which, under normal conditions, will take approximately one week. Thus, a complete injury to the RLN which separates the nerve into two different parts, will give a negative signal using intraoperative nerve monitoring (IONM) and the distal part a positive signal in the thyroarytenoid muscle for several days. Re-exploring the distal end of the RLN at our institution for nerve re-construction confirms the positive signal for up to five days after complete injury after thyroid surgery (unpublished observation). After axonal injury within the macroscopically intact RLN, the distal axon also degenerates and, to achieve any functional recovery, the axon has to regenerate. In the literature, there has been considerable speculation concerning the reasons for the poor (or absent) functional recovery seen after injury to the RLN despite the fact that the nerve looks macroscopically intact during surgery. One factor associated with the insufficient recovery is a potential misguidance of RLN axons during regeneration, leading to non-functional reinnervation of laryngeal muscles. There are, however, studies that show that the degree of accurate innervation is very high after crush injury to the peripheral nerve (90%) (58) since the axon is guided by intact mechanical factors of the intact endoneural tubes (59). This may reduce the impact of the misguidance as a negative factor in the injured intact RLN.

The axotomy induces a retrograde injury signal to the neuron in the brainstem which is attacked by microglia and also surrounded by a profound astroglial reaction (60-62). The neuron downregulates its production of transmitter substances and turns the gene transcription to regeneration and re-innervation. The neuron is exposed to stress and is dependent on a continuous inflow of growth factors from the periphery (54). Motor neurons are more likely to die in response to peripheral axotomy the closer the axotomy is to the neuronal soma in the brainstem or spinal cord. The

more of the peripheral nerve which is in contact with the neuron soma, the more trophic support of growth factors is delivered to the neuron. The addition of growth factors radically improves the prognosis for the axotomized neuron (63-66). In addition, there are many experiments to support that distal peripheral nerve injury is associated with no or limited nerve cell death, including injury to the RLN (67).

The distal axotomy in the intact RLN also causes a synaptic displacement from the secondary motor neuron in the nucleus ambiguus, which then loses contact with higher cortical centers (68). These synapses from cortical neurons re-appear on the secondary motor neurons as the neurons manage to regenerate and re-establish contact with the target organ (muscle). The proceeding adaptation to the new neural circuits is referred to as plasticity of the nervous system. Thus, the macroscopically intact but injured RLN will recover spontaneously if there is only a conduction block caused by an impairment of electrical propagation due to Schwann cell affection. If there is a component of axonal injury within the nerve, the axon will not only have to re-innervate the laryngeal muscles, but the neuron in the brainstem will need a re-connection with cortical neurons by re-establishment of their synapses onto the secondary neuron in the brainstem.

Intraoperative nerve monitoring (IONM)

IONM of the RLN is performed by stimulating the peripheral nerve directly with an electrical current, with subsequent recording of muscle depolarization of the thyroarytenoid muscle. When a peripheral nerve is directly stimulated at supramaximal intensity, the result is depolarization of all axons and activation of all motor units projecting through the nerve, which leads to acetylcholine-mediated depolarization of muscle fibers. The intramuscular shift in electrical potential (voltage) can be recorded as a compound muscle action potential (CMAP), representing the sum of all motor unit activity. During IONM, the presence and the amplitude of the CMAP is utilized as an indirect measurement of motor nerve function during the surgery. Originally, RLN monitoring was made through needle electrodes inserted into the intrinsic laryngeal muscles. In modern clinical routine, thyroarytenoid depolarization is recorded through surface electrodes on the ventilation tube (69).

Manipulation of the surgical field may affect the RLN by traction, heating, entrapment or squeezing (crush injury), which leads to absence or reduced amplitude of the recorded CMAP following vagal stimulation. The neurobiological explanation for reduced CMAP amplitude is simply that a lower number of axons are transmitting the electrical signal, which means less depolarization of the monitored muscle. Provided that the vagal stimulation is performed in the same way [consistent with continuous monitoring (70)], the site of injury could be anywhere along the nerve, distal to the site of stimulation. When the signal is lost during surgery, it is not possible to use IONM to diagnose the type of nerve injury (axonotmesis or neurapraxia), it only tells us that there is a discontinuity of the electrical propagation within the nerve.

In order to categorize and group injuries to the RLN using IONM, one reported way is to define the injury to the RLN and loss of signal (LOS) from the vagal nerve as segmental (type 1) or global (type 2) (69,71). Looking at the basic neurobiology of the nerve, a LOS could originate from an injury anywhere from the stimulus (vagal nerve) to the neuromuscular endplate, including the muscle. The distal part of the nerve is excitable for several days after injury even after nerve transection injury (48), which makes it possible for the surgeon to pin-point the exact location of the nerve injury, by using the stimulation probe along the course of the peripheral nerve. A neurobiological explanation for the "global" (type 2) RLN injury could be that the location of the nerve injury is located distal to the nerve entry point under the inferior constrictor muscle, not affecting the whole neuron (i.e., a milder form of injury). From this perspective, type 1 and 2 injuries describe if the RLN conduction block is proximal or distal to the RLN/cricothyroid border (*Figure 2*).

Laryngeal EMG

Postoperative electrodiagnostic methods can be used to determine the presence and type of nerve injury, as well as to characterize the ongoing or completed reinnervation processes. Laryngeal electromyography (LEMG) was first introduced more than sixty years ago, and has evolved (72) into a valuable tool for laryngologists in diagnosing neurolaryngological disorders. It has been pointed out that LEMG is primarily a qualitative method (73) (presence of denervation potentials, degree of motor unit recruitment), which makes it a subjective test depending on the examiner and the technical settings. But LEMG has nevertheless been shown to have high positive predictive value in predicting the long-term outcome of patients with a poor prognosis (74-77) and it is used widely to predict

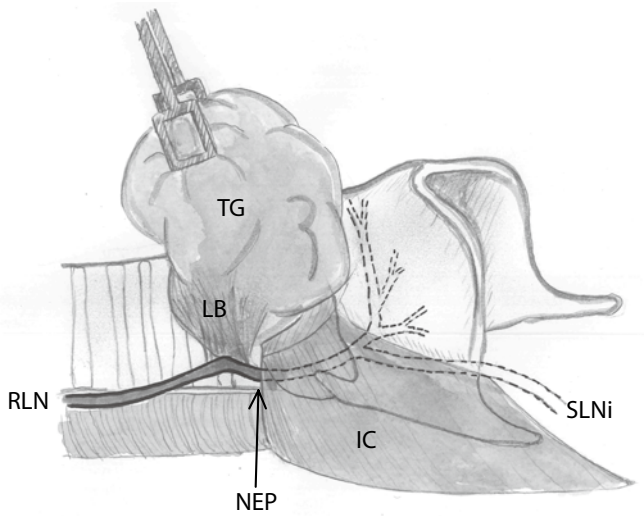

Figure 2 The RLN and the NEP under the IC. NEP may serve as an anatomical landmark in the classification of loss of vagal signal during thyroid surgery, e.g., lesion proximal to NEP (when there is a defined injury segment) or lesion distal to NEP (silent nerve to the NEP). RLN, recurrent laryngeal nerve; NEP, nerve entry point; IC, inferior constrictor muscle; TG, thyroid gland; SLNi, superior laryngeal nerve internal branch; GA, anastomosis of Galen; LB, ligament of Berry.

recovery regardless of the etiology behind the vocal fold paresis. Patients with pathological electromyographic findings at least two months after the paresis are most likely to need laryngeal framework surgery (76). In the case of postoperative vocal fold paresis after thyroid/parathyroid surgery, the prognostic information obtained from LEMG can be helpful to identify those cases where future interventions are necessary, which could mean surgical or pharmacological reinnervation therapies, or vocal fold medialization procedures. For patients with only a conduction block (neurapraxia) of the RLN, vocal fold movement is most likely to return. When using LEMG to obtain this information after thyroid surgery, it is important to take into consideration the timing of the examination. Denervation activity (indicating axonotmesis and poor prognosis) typically appears at three weeks after the RLN injury (48), and lasts until reinnervation is complete. Reinnervation of the intrinsic laryngeal muscles can be expected to take place rather promptly, given the high regenerative capacity of the RLN (78), together with collateral reinnervation by adjacent, intact nerve fibers (40). The optimal time window for postoperative LEMG seems to be 2-4 weeks after the nerve injury (49). Interpretation and analysis of electrophysiological data requires the expertise of a trained neurologist or clinical neurophysiologist, while insertion of the needle electrodes into the appropriate intrinsic laryngeal muscles is best performed by an ENT specialist. LEMG thus requires the cooperation and coordination of different clinical resources. A consensus paper for LEMG guidelines in the areas of indications, technical considerations, implementations and data interpretation was published by Volk *et al.* (79) in 2012.

Regeneration promotion

A mixed injury of demyelination (neurapraxia) and axonotmesis within the macroscopically intact RLN has a worse prognosis than demyelination alone, because of the need for regeneration and reinnervation of the target. Reinnervation of the intrinsic laryngeal muscles following axonotmesis is considered problematic (80), due to misguided, unorderly regeneration and perhaps also collateral reinnervation originating from adjacent, intact nerve fibers (40). Pathological reinnervation leads to a change in the somatotopic map, not in line with normal vocal fold function. Theoretically, it would be beneficial for the functional restitution to pace up and enhance regeneration/reinnervation by the RLN.

In vitro, it has been shown that the pace of the regenerating axon is regulated at the tip (growth cone), the motion of which is highly dependent on a delicate regulation of calcium ions (81,82). It was demonstrated that altering the intracellular concentration of calcium ions had a strict correlation to the ability of the growth cone to sprout (82). The regulation of intracellular calcium is also closely linked to the actions of the voltage-gated calcium channels present in the cellular membrane (82). *In vivo*, it has been confirmed that the transient quick calcium currents across the membrane of the growth cone occur with a certain frequency. If the calcium transient calcium currents are to some extent inhibited the pace of axonal elongation increases, and vice versa (83-85). In fact, blocking of the rapid calcium flow current across the membrane would increase the total time for axonal elongation, a principle further evaluated in experimental models. Nimodipine, a voltage-gated calcium flow antagonist to the L-type channels has been evaluated in rodent models, and is a pharmacologically good choice because it penetrates the blood brain barrier better than most other calcium flow antagonists (86). After systemic administration of

nimodipine, an improved regeneration and functional recovery has experimentally been achieved after injury to the sciatic (87), facial (88-90), hypoglossal (91) and RLNs (92). In the patient, nimodipine has been evaluated after recurrent laryngeal (49,93-95) and facial nerve injury (96-100), with promising functional outcomes. Taken together, there is substantial evidence that the administration of nimodipine after axonal injury to a peripheral nerve probably improves the functional outcome.

Even though there is emerging data that treatment with nimodipine may also be translated to the patient in some situations, the level of evidence for a using nimodipine for intraoperative RLN injury is still modest. Only a fraction of the patients with postoperative RLN paresis would benefit from a regeneration-promoting treatment (i.e., cases with axonotmesis). It is important, therefore, to search for further knowledge concerning diagnosis and prognosis after RLN injury after thyroid surgery.

Conclusions

Laryngeal dysfunction and voice problems are common after thyroid surgery, but only a fraction of these cases turn out to be chronic. Chronic laryngeal dysfunction is most commonly caused by axonal injury to the RLN or SLN. The clinical progress of symptoms and the eventual functional recovery of the target organ follow the general principles of peripheral nerve injury, even though the larynx can be regarded a special case in being functionally and neuroanatomically complex, with high demands for accurate neural supply. Today, it is possible for the clinician to utilize the information obtained from electrodiagnostic methods (IONM and postoperative LEMG), to characterize the nerve injury and predict the temporal course and functional result of the healing process. It is important to do so in order to be prepared for additional interventions, such as voice therapy, medialization surgery or regeneration/reinnervation therapies.

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References

1. Collazo-Clavell ML, Gharib H, Maragos NE. Relationship between vocal cord paralysis and benign thyroid disease. Head Neck 1995;17:24-30.
2. Farrag TY, Samlan RA, Lin FR, et al. The utility of evaluating true vocal fold motion before thyroid surgery. Laryngoscope 2006;116:235-8.
3. Randolph GW, Kamani D. The importance of preoperative laryngoscopy in patients undergoing thyroidectomy: voice, vocal cord function, and the preoperative detection of invasive thyroid malignancy. Surgery 2006;139:357-62.
4. Shaha AR. Routine laryngoscopy in thyroid surgery: A valuable adjunct. Surgery 2007;142:865-6.
5. Jeannon JP, Orabi AA, Bruch GA, et al. Diagnosis of recurrent laryngeal nerve palsy after thyroidectomy: a systematic review. Int J Clin Pract 2009;63:624-9.
6. Francis DO, Pearce EC, Ni S, et al. Epidemiology of vocal fold paralyses after total thyroidectomy for well-differentiated thyroid cancer in a Medicare population. Otolaryngol Head Neck Surg 2014;150:548-57.
7. Kuhn MA, Bloom G, Myssiorek D. Patient perspectives on dysphonia after thyroidectomy for thyroid cancer. J Voice 2013;27:111-4.
8. Vicente DA, Solomon NP, Avital I, et al. Voice outcomes after total thyroidectomy, partial thyroidectomy, or non-neck surgery using a prospective multifactorial assessment. J Am Coll Surg 2014;219:152-63.
9. Page C, Zaatar R, Biet A, et al. Subjective voice assessment after thyroid surgery: a prospective study of 395 patients. Indian J Med Sci 2007;61:448-54.
10. Hong KH, Kim YK. Phonatory characteristics of patients undergoing thyroidectomy without laryngeal nerve injury. Otolaryngol Head Neck Surg 1997;117:399-404.
11. Akyildiz S, Ogut F, Akyildiz M, et al. A multivariate analysis of objective voice changes after thyroidectomy without laryngeal nerve injury. Arch Otolaryngol Head Neck Surg 2008;134:596-602.
12. Debruyne F, Ostyn F, Delaere P, et al. Acoustic analysis of the speaking voice after thyroidectomy. J Voice 1997;11:479-82.
13. Maeda T, Saito M, Otsuki N, et al. Voice quality after surgical treatment for thyroid cancer. Thyroid 2013;23:847-53.
14. Minni A, Ruoppolo G, Barbaro M, et al. Long-term (12 to 18 months) functional voice assessment to detect voice alterations after thyroidectomy. Eur Rev Med Pharmacol Sci 2014;18:1704-8.
15. Henry LR, Solomon NP, Howard R, et al. The functional impact on voice of sternothyroid muscle division during thyroidectomy. Ann Surg Oncol 2008;15:2027-33.
16. Mendelsohn AH, Sung MW, Berke GS, et al. Strobokymographic and videostroboscopic analysis of

vocal fold motion in unilateral superior laryngeal nerve paralysis. Ann Otol Rhinol Laryngol 2007;116:85-91.
17. Orestes MI, Chhetri DK. Superior laryngeal nerve injury: effects, clinical findings, prognosis, and management options. Curr Opin Otolaryngol Head Neck Surg 2014;22:439-43.
18. Roy N, Barton ME, Smith ME, et al. An in vivo model of external superior laryngeal nerve paralysis: laryngoscopic findings. Laryngoscope 2009;119:1017-32.
19. Roy N, Smith ME, Dromey C, et al. Exploring the phonatory effects of external superior laryngeal nerve paralysis: an in vivo model. Laryngoscope 2009;119:816-26.
20. Chandrasekhar SS, Randolph GW, Seidman MD, et al. Clinical practice guideline: improving voice outcomes after thyroid surgery. Otolaryngol Head Neck Surg 2013;148:S1-37.
21. Gacek RR, Lyon MJ. Fiber components of the recurrent laryngeal nerve in the cat. Ann Otol Rhinol Laryngol 1976;85:460-71.
22. Berkowitz RG, Sun QJ, Chalmers J, et al. Identification of posterior cricoarytenoid motoneurons in the rat. Ann Otol Rhinol Laryngol 1999;108:1033-41.
23. Bieger D, Hopkins DA. Viscerotopic representation of the upper alimentary tract in the medulla oblongata in the rat: the nucleus ambiguus. J Comp Neurol 1987;262:546-62.
24. Gacek RR. Localization of laryngeal motor neurons in the kitten. Laryngoscope 1975;85:1841-61.
25. Gacek RR, Malmgren LT. Laryngeal motor innervation-central. In: Blitzer A, Brin MF, Sasaki CT, et al. eds. Neurologic disorders of the larynx. New York: Thieme, 1992:29-35.
26. Hinrichsen CF, Ryan AT. Localization of laryngeal motoneurons in the rat: morphologic evidence for dual innervation? Exp Neurol 1981;74:341-55.
27. Kobler JB, Datta S, Goyal RK, et al. Innervation of the larynx, pharynx, and upper esophageal sphincter of the rat. J Comp Neurol 1994;349:129-47.
28. Lobera B, Pásaro R, González-Barón S, et al. A morphological study of ambiguus nucleus motoneurons innervating the laryngeal muscles in the rat and cat. Neurosci Lett 1981;23:125-30.
29. Patrickson JW, Smith TE, Zhou SS. Motor neurons of the laryngeal nerves. Anat Rec 1991;230:551-6.
30. Portillo F, Pásaro R. Location of motoneurons supplying the intrinsic laryngeal muscles of rats. Horseradish peroxidase and fluorescence double-labeling study. Brain Behav Evol 1988;32:220-5.
31. Fontenot TE, Randolph GW, Friedlander PL, et al. Gender, race, and electrophysiologic characteristics of the branched recurrent laryngeal nerve. Laryngoscope 2014;124:2433-7.
32. Sandillon H. eds. Le role de l'anse de Galien Unités d'Enseignement et de Recherche des Siences Médicales. Bordeaux: Université de Bordeaux II, 1984.
33. Kandil E, Abdelghani S, Friedlander P, et al. Motor and sensory branching of the recurrent laryngeal nerve in thyroid surgery. Surgery 2011;150:1222-7.
34. Serpell JW, Yeung MJ, Grodski S. The motor fibers of the recurrent laryngeal nerve are located in the anterior extralaryngeal branch. Ann Surg 2009;249:648-52.
35. Maranillo E, León X, Ibañez M, et al. Variability of the nerve supply patterns of the human posterior cricoarytenoid muscle. Laryngoscope 2003;113:602-6.
36. Maranillo E, Leon X, Orus C, et al. Variability in nerve patterns of the adductor muscle group supplied by the recurrent laryngeal nerve. Laryngoscope 2005;115:358-62.
37. Sañudo JR, Maranillo E, León X, et al. An anatomical study of anastomoses between the laryngeal nerves. Laryngoscope 1999;109:983-7.
38. Dilworth TF. The Nerves of the Human Larynx. J Anat 1921;56:48-52.
39. Björck G, Margolin G, Måbäck GM, et al. New animal model for assessment of functional laryngeal motor innervation. Ann Otol Rhinol Laryngol 2012;121:695-9.
40. Hydman J, Mattsson P. Collateral reinnervation by the superior laryngeal nerve after recurrent laryngeal nerve injury. Muscle Nerve 2008;38:1280-9.
41. Monfared A, Kim D, Jaikumar S, et al. Microsurgical anatomy of the superior and recurrent laryngeal nerves. Neurosurgery 2001;49:925-32; discussion 932-3.
42. Shaw GY, Searl JP, Hoover LA. Diagnosis and treatment of unilateral cricothyroid muscle paralysis with a modified Isshiki type 4 thyroplasty. Otolaryngol Head Neck Surg 1995;113:679-88.
43. Wu BL, Sanders I, Mu L, et al. The human communicating nerve. An extension of the external superior laryngeal nerve that innervates the vocal cord. Arch Otolaryngol Head Neck Surg 1994;120:1321-8.
44. Maranillo E, León X, Quer M, et al. Is the external laryngeal nerve an exclusively motor nerve? The cricothyroid connection branch. Laryngoscope 2003;113:525-9.
45. Barczyński M, Randolph GW, Cernea CR, et al. External branch of the superior laryngeal nerve monitoring during thyroid and parathyroid surgery: International Neural

Monitoring Study Group standards guideline statement. Laryngoscope 2013;123 Suppl 4:S1-14.
46. Seddon HJ. A Classification of Nerve Injuries. Br Med J 1942;2:237-9.
47. Sunderland S. A classification of peripheral nerve injuries producing loss of function. Brain 1951;74:491-516.
48. Kimura J. eds. Electrodiagnosis in Diseases of Nerve and Muscle: Principles and Practices. 3rd ed. Oxford: Oxford University Press, 2001.
49. Hydman J, Björck G, Persson JK, et al. Diagnosis and prognosis of iatrogenic injury of the recurrent laryngeal nerve. Ann Otol Rhinol Laryngol 2009;118:506-11.
50. Schwab ME. Nogo and axon regeneration. Curr Opin Neurobiol 2004;14:118-24.
51. DeFrancesco-Lisowitz A, Lindborg JA, Niemi JP, et al. The neuroimmunology of degeneration and regeneration in the peripheral nervous system. Neuroscience 2014. [Epub ahead of print].
52. Fawcett JW, Keynes RJ. Peripheral nerve regeneration. Annu Rev Neurosci 1990;13:43-60.
53. Ide C. Peripheral nerve regeneration. Neurosci Res 1996;25:101-21.
54. Richner M, Ulrichsen M, Elmegaard SL, et al. Peripheral nerve injury modulates neurotrophin signaling in the peripheral and central nervous system. Mol Neurobiol 2014;50:945-70.
55. Scheib J, Höke A. Advances in peripheral nerve regeneration. Nat Rev Neurol 2013;9:668-76.
56. Cajal YR. eds. Degeneration and regeneration of the nervous system. Oxford: Oxford University Press, 1928.
57. Waller A. Experiments on the section of the glossopharyngeal and hypoglossal nerves of the frog, and observations of the alterations produced thereby in the structure of their primitive fibers. Philos Trans R Soc London (Biol) 1850;140:423-29.
58. Fournier AE, Strittmatter SM. Regenerating nerves follow the road more traveled. Nat Neurosci 2002;5:821-2.
59. Nguyen QT, Sanes JR, Lichtman JW. Pre-existing pathways promote precise projection patterns. Nat Neurosci 2002;5:861-7.
60. Aldskogius H, Svensson M. Neuronal and glial cell responses to axon injury. Advances in Structural Biology 1993;2:191-223.
61. Svensson M, Aldskogius H. The effect of axon injury on microtubule-associated proteins MAP2, 3 and 5 in the hypoglossal nucleus of the adult rat. J Neurocytol 1992;21:222-31.
62. Svensson M, Eriksson P, Persson JK, et al. The response of central glia to peripheral nerve injury. Brain Res Bull 1993;30:499-506.
63. Oppenheim RW, Houenou LJ, Johnson JE, et al. Developing motor neurons rescued from programmed and axotomy-induced cell death by GDNF. Nature 1995;373:344-6.
64. Oppenheim RW, Yin QW, Prevette D, et al. Brain-derived neurotrophic factor rescues developing avian motoneurons from cell death. Nature 1992;360:755-7.
65. Sendtner M, Holtmann B, Kolbeck R, et al. Brain-derived neurotrophic factor prevents the death of motoneurons in newborn rats after nerve section. Nature 1992;360:757-9.
66. Sendtner M, Kreutzberg GW, Thoenen H. Ciliary neurotrophic factor prevents the degeneration of motor neurons after axotomy. Nature 1990;345:440-1.
67. Hydman J, Svensson M, Kuylenstierna R, et al. Neuronal survival and glial reactions after recurrent laryngeal nerve resection in the rat. Laryngoscope 2005;115:619-24.
68. Blinzinger K, Kreutzberg G. Displacement of synaptic terminals from regenerating motoneurons by microglial cells. Z Zellforsch Mikrosk Anat 1968;85:145-57.
69. Randolph GW, Dralle H. International Intraoperative Monitoring Study Group, Electrophysiologic recurrent laryngeal nerve monitoring during thyroid and parathyroid surgery: international standards guideline statement. Laryngoscope 2011;121 Suppl 1:S1-16.
70. Dionigi G, Donatini G, Boni L, et al. Continuous monitoring of the recurrent laryngeal nerve in thyroid surgery: a critical appraisal. Int J Surg 2013;11 Suppl 1:S44-6.
71. Phelan E, Schneider R, Lorenz K, et al. Continuous vagal IONM prevents recurrent laryngeal nerve paralysis by revealing initial EMG changes of impending neuropraxic injury: a prospective, multicenter study. Laryngoscope 2014;124:1498-505.
72. Faaborg-andersen K, Buchthal F. Action potentials from internal laryngeal muscles during phonation. Nature 1956;177:340-1.
73. Blitzer A, Crumley RL, Dailey SH, et al. Recommendations of the Neurolaryngology Study Group on laryngeal electromyography. Otolaryngol Head Neck Surg 2009;140:782-93.
74. Rickert SM, Childs LF, Carey BT, et al. Laryngeal electromyography for prognosis of vocal fold palsy: a meta-analysis. Laryngoscope 2012;122:158-61.
75. Smith LJ, Rosen CA, Niyonkuru C, et al. Quantitative electromyography improves prediction in vocal fold paralysis. Laryngoscope 2012;122:854-9.

76. Wang CC, Chang MH, De Virgilio A, et al. Laryngeal electromyography and prognosis of unilateral vocal fold paralysis-A long-term prospective study. Laryngoscope 2014. [Epub ahead of print].
77. Wang CC, Chang MH, Wang CP, et al. Prognostic indicators of unilateral vocal fold paralysis. Arch Otolaryngol Head Neck Surg 2008;134:380-8.
78. Crumley RL. Repair of the recurrent laryngeal nerve. Otolaryngol Clin North Am 1990;23:553-63.
79. Volk GF, Hagen R, Pototschnig C, et al. Laryngeal electromyography: a proposal for guidelines of the European Laryngological Society. Eur Arch Otorhinolaryngol 2012;269:2227-45.
80. Crumley RL. Laryngeal synkinesis revisited. Ann Otol Rhinol Laryngol 2000;109:365-71.
81. Kater SB, Mattson MP, Cohan C, et al. Calcium regulation of the neuronal growth cone. Trends Neurosci 1988;11:315-21.
82. Kater SB, Mills LR. Regulation of growth cone behavior by calcium. J Neurosci 1991;11:891-9.
83. Gomez TM, Spitzer NC. In vivo regulation of axon extension and pathfinding by growth-cone calcium transients. Nature 1999;397:350-5.
84. Gomez TM, Spitzer NC. Regulation of growth cone behavior by calcium: new dynamics to earlier perspectives. J Neurobiol 2000;44:174-83.
85. Gomez TM, Zheng JQ. The molecular basis for calcium-dependent axon pathfinding. Nat Rev Neurosci 2006;7:115-25.
86. Van den Kerckhoff W, Drewes LR. Transfer of the calcium antagonists nifedipine and nimodipine across the blood brain barrier and their regional distribution in vivo. J Cerebr Blood Flow Metab 1985; 5 Suppl 1:459-60.
87. van der Zee CE, Schuurman T, Traber J, et al. Oral administration of nimodipine accelerates functional recovery following peripheral nerve damage in the rat. Neurosci Lett 1987;83:143-8.
88. Angelov DN, Neiss WF, Streppel M, et al. Nimodipine accelerates axonal sprouting after surgical repair of rat facial nerve. J Neurosci 1996;16:1041-8.
89. Mattsson P, Aldskogius H, Svensson M. Nimodipine-induced improved survival rate of facial motor neurons following intracranial transection of the facial nerve in the adult rat. J Neurosurg 1999;90:760-5.
90. Mattsson P, Janson AM, Aldskogius H, et al. Nimodipine promotes regeneration and functional recovery after intracranial facial nerve crush. J Comp Neurol 2001;437:106-17.
91. Angelov DN, Neiss WF, Gunkel A, et al. Nimodipine-accelerated hypoglossal sprouting prevents the postoperative hyperinnervation of target muscles after hypo glossal-facial anastomosis in the rat. Restor Neurol Neurosci 1997;11:109-21.
92. Hydman J, Remahl S, Björck G, et al. Nimodipine improves reinnervation and neuromuscular function after injury to the recurrent laryngeal nerve in the rat. Ann Otol Rhinol Laryngol 2007;116:623-30.
93. Mattsson P, Björck G, Remahl S, et al. Nimodipine and microsurgery induced recovery of the vocal cord after recurrent laryngeal nerve resection. Laryngoscope 2005;115:1863-5.
94. Rosen CA, Smith L, Young V, et al. Prospective investigation of nimodipine for acute vocal fold paralysis. Muscle Nerve 2014;50:114-8.
95. Sridharan SS, Rosen CA, Smith LJ, et al. Timing of nimodipine therapy for the treatment of vocal fold paralysis. Laryngoscope 2015;125:186-90.
96. Scheller C, Richter HP, Engelhardt M, et al. The influence of prophylactic vasoactive treatment on cochlear and facial nerve functions after vestibular schwannoma surgery: a prospective and open-label randomized pilot study. Neurosurgery 2007;61:92-7; discussion 97-8.
97. Scheller C, Wienke A, Wurm F, et al. Neuroprotective efficacy of prophylactic enteral and parenteral nimodipine treatment in vestibular schwannoma surgery: a comparative study. J Neurol Surg A Cent Eur Neurosurg 2014;75:251-8.
98. Scheller K, Scheller C. Nimodipine promotes regeneration of peripheral facial nerve function after traumatic injury following maxillofacial surgery: an off label pilot-study. J Craniomaxillofac Surg 2012;40:427-34.
99. Scheller K, Scheller C. Nimodipine for peripheral nerve recovery after maxillofacial and vestibular schwannoma surgery. Muscle Nerve 2014;50:1026-7.
100. Strauss C, Romstöck J, Fahlbusch R, et al. Preservation of facial nerve function after postoperative vasoactive treatment in vestibular schwannoma surgery. Neurosurgery 2006;59:577-84; discussion 577-84.

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Electrophysiological neural monitoring of the laryngeal nerves in thyroid surgery: review of the current literature

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Abstract: Recurrent laryngeal nerve (RLN) injury is one of the most common complications of thyroid surgery. RLN injury can cause vocal cord paralysis, affecting the patient's voice and the quality of life. Injury of the external branch of the superior laryngeal nerve (EBSLN) can cause cricothyroid muscle denervation affecting high vocal tones. Thus, securing the laryngeal nerves in these surgeries is of utmost importance. Visual identification of the nerves has long been the standard method for this precaution. Intraoperative neuromonitoring (IONM) has been introduced as a novel technology to improve the protection of the laryngeal nerves and reduce the rate of RLN injury. The aim of this article is to provide a brief description of the technique and review the literature to illustrate the value of IONM. IONM can provide early identification of anatomical variations and unusual nerve routes, which carry a higher risk of injury if not detected. IONM helps in prognosticating postoperative nerve function. Moreover, by detecting nerve injury intraoperatively, it aids in staging bilateral surgeries to avoid bilateral vocal cord paralysis and tracheostomy. The article will discuss the value of continuous IONM (C-IOMN) that may prevent nerve injury by detecting EMG waveform changes indicating impending nerve injury. Herein, we are also discussing anatomy of laryngeal nerves and aspects of its injury.

Keywords: Laryngeal nerves; nerve monitoring; neural monitoring; thyroidectomy

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Introduction

Thyroid surgery is among the most common cervical surgeries. Due to the close proximity of the laryngeal nerves to the surgical field, nerve injury is a common complication of these surgeries. Unilateral paralysis of the recurrent laryngeal nerve (RLN) can cause dysphagia, hoarseness of voice, or respiratory complications due to aspiration (1). The consequences are more severe in bilateral paralysis, which can jeopardize the airway and may necessitate tracheostomy (1). As the external branch of the superior laryngeal nerve (EBSLN) supplies only the cricothyroid muscle, its paralysis is less devastating and can affect the voice variably.

RLN injury is the most common cause of medicolegal litigation after thyroid surgery (2). In cases of bilateral vocal cords paralysis, plaintiffs can be awarded up to 2.5 million dollars (1).

Rates of RLN injury are reported to be as high as 10% (3). Regarding the EBSLN, the reported injury rate varies widely (0-58%) due to difficulty of assessment (4). The published rates of RLN injury are thought to be underestimated, as the less satisfactory results are less commonly reported, and reported RLN injuries are usually from high-volume practices (5,6). Complications related to thyroid surgery, including laryngeal nerve palsy, are reported to be higher in low-volume surgeons (7,8).

Revision neck surgery may be especially challenging due to postoperative changes and scarring. The risk of RLN injury increases threefold for repeat thyroid surgery when

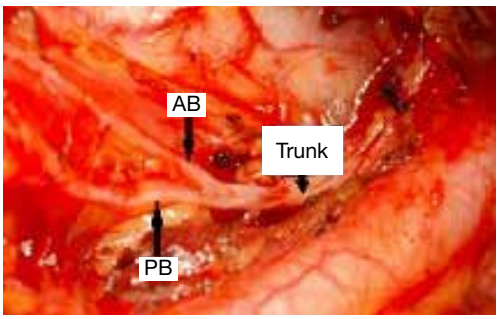

Figure 1 Branching of the main trunk of the RLN into anterior and posterior branches. Trunk, main trunk of RLN; AB, anterior branch; PB, posterior branch; RLN, recurrent laryngeal nerve.

compared to the initial operations (9).

Intraoperative visual identification has been the gold standard for securing the laryngeal nerves during thyroid surgery (10-12). However, an anatomically intact nerve identified by gross visualization does not confirm a functional nerve. Consequently, electrophysiologic intraoperative nerve monitoring (IONM) of the nerves was introduced by Shedd and Durham in 1965 as a novel technique which lowers the risk of RLN injury compared to the traditional visual identification (13).

IONM has been gaining popularity since its introduction. Studies have shown that over 50% of otolaryngologists and general surgeons use it in all or some of their cases (14,15). Neuromonitoring was reported to be more beneficial in video-assisted surgery as it makes the surgeon more comfortable during nerve dissection (5). Keeping detailed records of perioperative visits, including fundamental discussions, is essential. RLN injury should be emphasized as a potential complication and clear documentation in the informed consent is crucial. Nerve stimulating current, response amplitude and latency should be recorded in the operative report during and by the end of surgery.

The aim of our review is to review the literature addressing IONM to assess it safety, feasibility in thyroid surgery. Herein, we are also discussing anatomy of laryngeal nerves and aspects of its injury; and concise description of the basics of neuromonitoring.

Surgical anatomy of the laryngeal nerves

Recurrent laryngeal nerve (RLN)

The RLN is a branch of the vagus nerve. The right RLN originates at the level of the right subclavian artery and loops around it; then ascends in the tracheo-esophageal groove to the larynx. On the left side, it originates in the superior mediastinum at the level of the aortic arch, curves around it, runs superiorly through the thoracic outlet, and travels in the tracheo-esophageal groove near the branches of the inferior thyroid artery. It gives sensory branches to the esophagus and trachea before entering the larynx. Extralaryngeal branching of the RLN into anterior and posterior branches was reported to occur in around 40% of patients (16,17) (*Figure 1*). The motor fibers are usually located in the anterior branch; however they may run in the posterior branch that mostly carries sensory fibers (18). Extralaryngeal branching should be identified to avoid missing any unidentified anterior branch which may lead to postoperative nerve injury (16).

There are four important landmarks to aid mapping the RLN in thyroid surgery (2,19):

(I) The tracheo-esophageal groove, taking into consideration that the course of the RLN near or in the groove varies between individuals, especially on the right side;

(II) The inferior thyroid artery, another variable landmark of the RLN. The relationship of the nerve to the vessel is not constant and is a common site of RLN injury;

(III) The inferior thyroid cartilage cornu, which is palpable manually;

(IV) The entry to the larynx, believed to be the most reliable RLN landmark and the most common site of injury. It is more vulnerable at this point due to close proximity of the nerve to Berry's ligament and the thyroid capsule (2).

External branch of the superior laryngeal nerve (EBSLN)

The EBSLN is a branch of the superior laryngeal nerve, which originates at the C2 spinal level from the vagus nerve and divides into internal and external branches. It then descends behind the carotid sheath and the superior thyroid artery towards the superior pole of the thyroid. The nerve can be located at the laryngeal head of the sternothyroid muscle.

In cases with large goiters or upper pole masses, the upper edge of this muscle could be transected, applying traction to the upper thyroid pole and dissecting the sternohyoid-laryngeal triangle to facilitate EBSLN exposure. The EBSLN runs close to the superior thyroid vessels, a location which makes it vulnerable to injury during

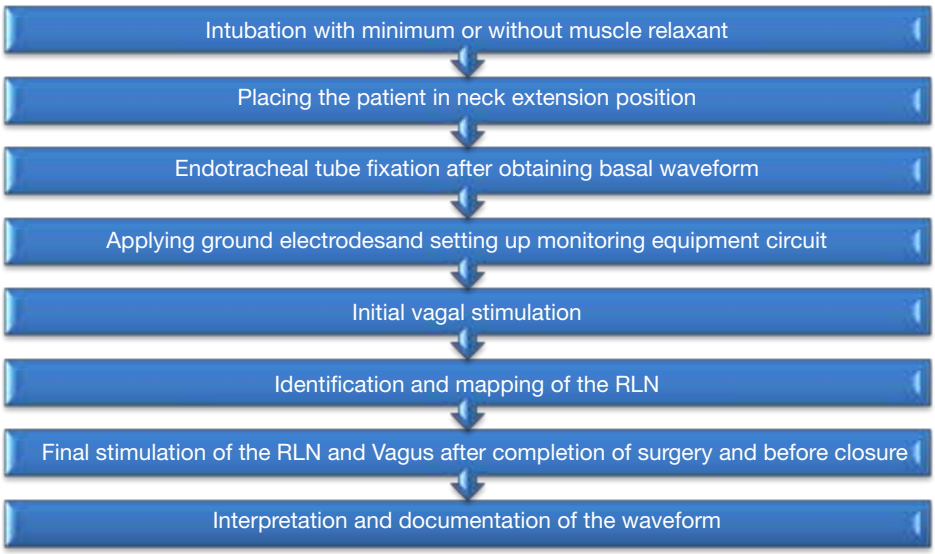

Figure 2 RLN monitoring steps, showing the main standard steps for intraoperative neuromonitoring of RLN. RLN, recurrent laryngeal nerve.

their ligation. Due to the variability of the EBSLN course, classifications were suggested to identify the relationship of the EBSLN to the upper thyroid pole and superior thyroid vessels (20,21). Cernea *et al*. classified EBSLN into type 1 which crosses the superior thyroid vessels more than 1 cm above the upper thyroid pole, type 2A that crosses the vessels less than 1 cm from the upper pole, and type 2B that crosses the vessels below the upper pole (20). In 68-90% of cases, the EBSLN was reported to share with the RLN in innervating the anterior thyroid muscle as the communicating branch (22).

Nerve injury

Laryngeal nerves are mainly injured by traction, suture entrapment, transection or thermal injury. Thermal injury is caused by energy-generating devices that can cause collateral damage to nearby structures. The International Neural Monitoring Study Group classified nerve injury into two categories: segmental, which involves a lesion to a clear-cut segment of the RLN, and global, where all the RLN and vagus are nonconductive which may indicate an intralaryngeal focus of injury (23). The segmental injury may be potentially correctable in case of a suture or clip entrapping the nerve that can be removed to prevent permanent nerve injury.

Revision neck surgery and surgery after radiotherapy have a higher risk of nerve injury due to tissue scarring. In large goiters, Graves' disease and thyroiditis, enlarged glands put nerves under tension, making them more vulnerable to injury. The right non-recurrent inferior laryngeal nerve which is associated with arteria lusoria (aberrant right subclavian artery) carries a higher risk of injury due to its unusual course. Because dissection is more difficult in extralaryngeal branches of the RLN, they are at increased risk of injury compared to single nerves.

IONM technique (*Figure 2*)

Cooperation between the surgeon and the anesthesiologist is essential for successful neuromonitoring. The use of neuromuscular blockers should be carefully considered and avoided if possible, as they reduce response amplitude from the vagus, RLN and EBSLN which may hinder injury detection.

In IONM, an endotracheal tube (ETT) tube equipped with a pair of recording electrodes of suitable size to make direct contact with the vocal cords is used. Due to its safety and simplicity, it is superior to other modalities as glottic observation, laryngeal palpation, postcricoid surface electrodes and intramuscular electrodes (23).

A stimulator probe is used to deliver the electrical current to structures suspected to be neural tissue. For identification and mapping of the RLN and EBSLN, a probe is used to deliver intermittent current when needed. A 2 mA current is used initially for nerve identification and mapping when

overlaid by other tissue. A current of 1 mA can be used to map the nerve once identified and exposed. An automatic periodic stimulation (APS) probe is placed over the vagus nerve for real-time continuous monitoring. The nerve is exposed by dissecting the carotid sheath for 1 cm. It works by delivering a continuous low level stimulation to the vagus to obtain a basic nerve function. It gives a real time feedback by monitoring EMG responses. Continuous IONM (C-IONM) can detect early change in nerve function which may be a warning of impending nerve injury.

The stimulating and recording equipment are connected to an interface connector box, which is connected to grounding electrodes. Both the stimulatory and recording grounding electrodes are placed on the shoulder or on the sternum. The interface box is connected to a monitoring device. Waveform monitors are superior to audio systems with alarms indicating signal abnormality, as visual waveform displays amplitude, threshold and latency data which can differentiate true signals from artifacts.

Respiratory movement EMG waveform is used as proof of correct positioning and contact between recording electrodes and vocal cords. Baseline amplitude of 30-70 mV indicates proper positioning of the ETT (24). Proper positioning of the ETT can be verified by other methods as: fiberoptic laryngoscopic examination, tap test on the larynx or translaryngeal stimulation. The RLN is searched for in the tracheoesophageal groove near the inferior thyroid artery. To localize the EBSLN, the probe can be placed between the laryngeal head of the sternothyroid muscle and the superior thyroid pole (4,25). Visualization of the EBSLN is more challenging than RLN; in a previous study for our group the rate of visualization was about 53% (25). EBSLN visualization was more challenging in obese patients with two-fold chance to visualize it in non-obese patients (25). While RLN response is evaluated by the EMG waveform displayed on the monitor, EBSLN response is evaluated by monitoring cricothyroid muscle twitch.

Feasibility and safety of IONM and medico-legal implications

IONM is considered a feasible and safe addition to traditional visualization in identifying nerves (26,27). It was reported that IONM can reduce the rate of transient RLN injury in thyroid surgery (11,28,29). Interestingly, one study notes the conspicuous absence of IONM use in cases of bilateral RLN injury related to thyroid surgery (30). Another study has shown that users of IONM are less frequently named in lawsuits involving RLN injury, compared with non-users (14). The major motivations for neuromonitoring that surgeons cite are enhanced confidence during operative nerve dissection and diminished medicolegal liability (15).

However, there is no clear consensus in the literature to indicate that IONM decreases RLN injury. This is most probably due in part to the low incidence of injury in hands of high volume surgeons. Other studies showed that IONM did not reduce the prevalence of RLN palsy (31,32). Due to the low rate of RLN palsy, Dralle *et al*. reported that running a statistically powerful study would require millions of patients (11).

Recent guidelines from the American Academy of Otolaryngology-Head and Neck Surgery recommend IONM use in thyroid surgery to ensure voice protection (33). The German Association of Endocrine Surgeons practice guidelines and the International Neural Monitoring Study Group guidelines both support using IONM in all thyroid surgeries (23,34), while the American Head and Neck Society endorses its utilization in thyroid cancer cases, particularly patients with RLN palsy.

IONM was reported to decrease operative time when compared to visual identification alone as it decreases the time needed to identify the RLN (35). Final monitoring signal can prognosticate postoperative nerve function with high reliability. In the case of non-reduced signal, the negative predictive value of IONM can be as high as 97%, while the positive predictive value when signal is lost is only 33-37.8% (11,28).

Preoperative laryngoscopy is proposed to be significant in all patients when counseling and planning extent of surgery (36,37). However, it is believed by others to be more essential in patients with persistent hoarseness of voice, suspicious for cancer or with prior thyroid surgery (33,38). Detection of any preoperative baseline abnormality is essential, as preoperative paralysis of the vocal cords may be an indicator of locally advanced cancer (36). Nonetheless, Kamani *et al*. found that 60% of invaded nerves retained near-normal EMG activity amplitude and normal function of vocal cords preoperatively (39).

Routine postoperative laryngoscopy is recommended, as hoarseness does not necessarily indicate abnormal glottic function (36). Patients with intact nerves may experience hoarseness, while others with a paralyzed cord can be asymptomatic. Laryngoscopy is necessary to differentiate between vocal cord paralysis and intubation-induced causes of hoarseness such as vocal cord polyps.

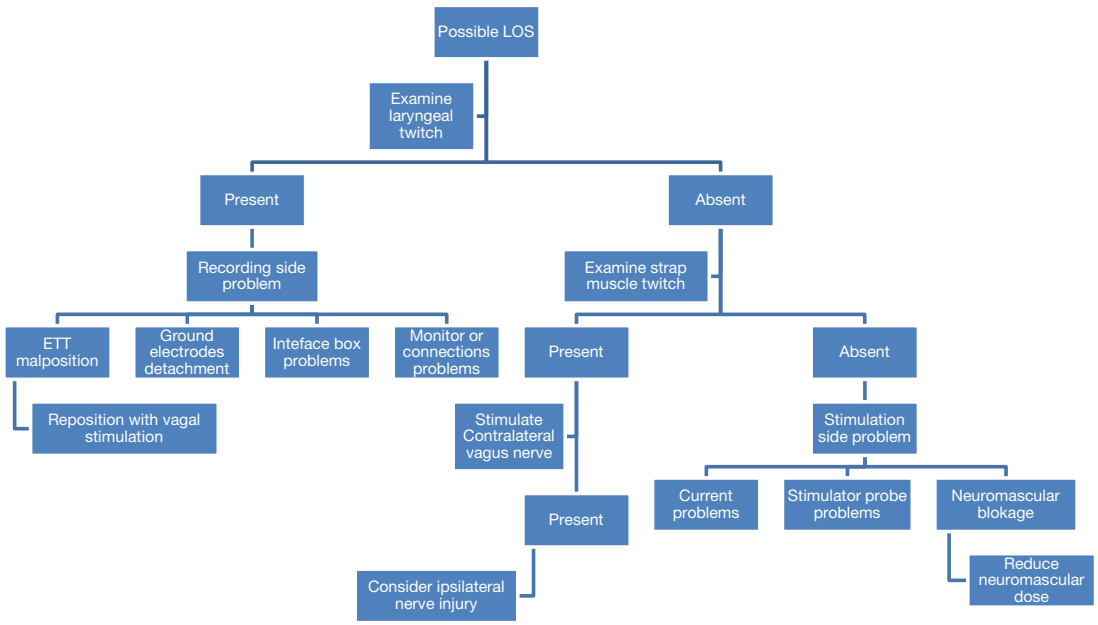

Figure 3 Steps for trouble shooting in case LOS encountered. All equipment problems should be fixed accordingly. In case of bilateral surgery and unilateral confirmed LOS, staging the surgery should be considered. LOS, loss of signal; ETT, endotracheal tube.

IONM can determine the mechanism of injury by tracking surgical maneuvers after which the signal was lost. Compared to visual identification which detects only 10% of nerve injuries, IONM can predict postoperative vocal cord function (2). Postoperative hemi-laryngeal edema can cause vocal cord immobility with normal signal; once the edema subsides, mobility will be regained.

Initial amplitude of 100 mV is essential to ensure the system is functional and any subsequent loss of signal (LOS) is not due to equipment malfunction (*Figure 3* shows stepwise approach for LOS). IONM can diagnose non-RLN which has shorter latency time compared to the recurrent nerve (11). Prolonged latency time can be used in combination with decreased amplitude or complete LOS as an indicator of nerve injury (23,40). Post-dissection amplitude off 200 μV was used as a cutoff to predict RLN injury and showed an accuracy of 99.1% in prognosticating postoperative RLN function (40).

IONM may help in avoiding bilateral RLN injury with its devastating effects on airway which may necessitate tracheostomy. In bilateral surgery, when nerve injury is detected by IONM on the initial side, the procedure could be staged by postponing operation on the other side until vocal cord function can be verified (41,42).

Repetitive nerve stimulation in IONM is safe and does not affect the functional integrity of nerves; there was no decline in amplitude after repetitive stimulation (1,43). Although a current of 1-2 mA is advisable to minimize the potential for false results of high current shunting and is enough for a maximum EMG response, a higher current can be tolerated (44).

Despite IONM is considered safe, it has some limitations. EMG signal can be affected by anesthesia and manipulation of the trachea. In addition, it is difficult to differentiate between nerve injury and loss of contact between the recording electrodes and the vocal cords in case of EMG amplitude or LOS. Intermittent IONM is limited to the short intervals of stimulation, so it usually detects nerve injury after it has occurred. Moreover, it can miss injury proximal to the point of stimulation as it only examines the nerve distal to the point of stimulation.

These limitations of intermittent IONM which can expose the laryngeal nerves to injury proximal to the site of stimulation or the interval gap between two intermittent stimulations are overcome by C-IONM (45). C-IONM is a modality of neuromonitoring that uses a stimulator clip applied to the vagus nerve and delivers interrupted periodic stimulation. It examines the whole course of

RLN by continuous stimulation of the vagus nerve to detect proximal injuries that can be missed by intermittent stimulation distal to the injury. It gives feedback about nerve function at short intervals. If EMG signal decreased or became weak indicating imminent nerve injury, an adverse condition may be reversed before nerve damage is persistent. This is achievable in reversible nerve injury as neuropraxia, in contrast to significant disruption as complete transection of nerves (46). Furthermore, it can detect the most proximal RLN or EBSLN injuries (23). The vagus nerve has varied relation to the carotid artery and the internal jugular vein, so the electrode used in C-IONM should be flexible (46). The procedure was considered safe in a German study of 30 nerves at risk in 24 patients (47). Although continuous monitoring is an improvement in laryngeal nerves monitoring, an intermittent stimulator is still important in mapping the nerves in combination with continuous monitoring. In a prospective multicenter study that included 102 thyroidectomies; C-IONM showed safety and predictability of vocal cord palsy in case of LOS or combined event of decreased amplitude and increased latency (48). Combined events were found to be reversible when the surgical maneuver is stopped or modified saving the nerve from permanent injury (48). Other studies supported its accuracy and reliability in detecting impending nerve injury that can be reversed to save the nerve (49-51).

Conclusions

Although there is no consensus that IONM decreases laryngeal nerve injury when compared to visual identification, it has many advantages over traditional nerve visualization alone. IONM may help prevent bilateral RLN injury by allowing surgeons to stage the surgery when the signal is lost on the initial side, thus avoiding the need for tracheostomy. In addition, IONM can properly prognosticate postoperative nerve function, which is difficult to detect by visual identification, as most of injured nerves appear intact. Neuromonitoring can detect anatomical variation and abnormal courses of the nerves which are at higher risk of injury if not detected. Higher risk patients, including cancer patients, patients with prior surgery and scarring, and patients with large goiters, may benefit most from IONM. C-IONM is an advanced modality of neuromonitoring that can prevent potential nerve injury by detecting signal changes indicating an adverse condition, such as a suture compressing the nerve. C-IONM is also able to detect the most proximal injuries, which may be missed by intermittent monitoring. More large studies are needed to further clarify the benefits of these of these approaches.

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References

1. Caragacianu D, Kamani D, Randolph GW. Intraoperative monitoring: normative range associated with normal postoperative glottic function. Laryngoscope 2013;123:3026-31.
2. Durán Poveda MC, Dionigi G, Sitges-Serra A, et al. Intraoperative monitoring of the recurrent laryngeal nerve during thyroidectomy: A standardized approach (Part 1). World Journal of Endocrine Surgery 2011;3:144-50.
3. Lo CY, Kwok KF, Yuen PW. A prospective evaluation of recurrent laryngeal nerve paralysis during thyroidectomy. Arch Surg 2000;135:204-7.
4. Barczyński M, Randolph GW, Cernea CR, et al. External branch of the superior laryngeal nerve monitoring during thyroid and parathyroid surgery: International Neural Monitoring Study Group standards guideline statement. Laryngoscope 2013;123 Suppl 4:S1-14.
5. Dionigi G, Boni L, Rovera F, et al. Neuromonitoring and video-assisted thyroidectomy: a prospective, randomized case-control evaluation. Surg Endosc 2009;23:996-1003.
6. Snyder SK, Lairmore TC, Hendricks JC, et al. Elucidating mechanisms of recurrent laryngeal nerve injury during thyroidectomy and parathyroidectomy. J Am Coll Surg 2008;206:123-30.
7. Kandil E, Noureldine SI, Abbas A, et al. The impact of surgical volume on patient outcomes following thyroid surgery. Surgery 2013;154:1346-52; discussion 1352-3.
8. Loyo M, Tufano RP, Gourin CG. National trends in thyroid surgery and the effect of volume on short-term outcomes. Laryngoscope 2013;123:2056-63.
9. Kurmann A, Herden U, Schmid SW, et al. Morbidity rate of reoperation in thyroid surgery: a different point of view. Swiss Med Wkly 2012;142:w13643.
10. Stevens K, Stojadinovic A, Helou LB, et al. The impact of recurrent laryngeal neuromonitoring on multi-dimensional voice outcomes following thyroid surgery. J Surg Oncol 2012;105:4-9.
11. Dralle H, Sekulla C, Haerting J, et al. Risk factors of paralysis and functional outcome after recurrent

laryngeal nerve monitoring in thyroid surgery. Surgery 2004;136:1310-22.
12. Snyder SK, Hendricks JC. Intraoperative neurophysiology testing of the recurrent laryngeal nerve: plaudits and pitfalls. Surgery 2005;138:1183-91; discussion 1191-2.
13. Shedd DP, Durham C. Electrical identification of the recurrent laryngeal nerve. I. Response of the canine larynx to electrical stimulation of the recurrent laryngeal nerve. Ann Surg 1966;163:47-50.
14. Sturgeon C, Sturgeon T, Angelos P. Neuromonitoring in thyroid surgery: attitudes, usage patterns, and predictors of use among endocrine surgeons. World J Surg 2009;33:417-25.
15. Singer MC, Rosenfeld RM, Sundaram K. Laryngeal nerve monitoring: current utilization among head and neck surgeons. Otolaryngol Head Neck Surg 2012;146:895-9.
16. Kandil E, Abdel Khalek M, Aslam R, et al. Recurrent laryngeal nerve: significance of the anterior extralaryngeal branch. Surgery 2011;149:820-4.
17. Kandil E, Abdelghani S, Friedlander P, et al. Motor and sensory branching of the recurrent laryngeal nerve in thyroid surgery. Surgery 2011;150:1222-7.
18. Fontenot TE, Randolph GW, Friedlander PL, et al. Gender, race, and electrophysiologic characteristics of the branched recurrent laryngeal nerve. Laryngoscope 2014;124:2433-7.
19. Miller MC, Spiegel JR. Identification and monitoring of the recurrent laryngeal nerve during thyroidectomy. Surg Oncol Clin N Am 2008;17:121-44, viii-ix.
20. Cernea CR, Ferraz AR, Furlani J, et al. Identification of the external branch of the superior laryngeal nerve during thyroidectomy. Am J Surg 1992;164:634-9.
21. Selvan B, Babu S, Paul MJ, et al. Mapping the compound muscle action potentials of cricothyroid muscle using electromyography in thyroid operations: a novel method to clinically type the external branch of the superior laryngeal nerve. Ann Surg 2009;250:293-300.
22. Sañudo JR, Maranillo E, León X, et al. An anatomical study of anastomoses between the laryngeal nerves. Laryngoscope 1999;109:983-7.
23. Randolph GW, Dralle H, Abdullah H, et al. Electrophysiologic recurrent laryngeal nerve monitoring during thyroid and parathyroid surgery: international standards guideline statement. Laryngoscope 2011;121 Suppl 1:S1-16.
24. Durán Poveda MC, Dionigi G, Sitges-Serra A, et al. Intraoperative monitoring of the recurrent laryngeal nerve during thyroidectomy: A standardized approach part 2. World Journal of Endocrine Surgery 2012;4:33-40.
25. Kandil E, Mohamed SE, Deniwar A, et al. Electrophysiologic identification and monitoring of the external branch of superior laryngeal nerve during thyroidectomy. Laryngoscope 2015. [Epub ahead of print].
26. Calò PG, Pisano G, Medas F, et al. Intraoperative recurrent laryngeal nerve monitoring in thyroid surgery: is it really useful? Clin Ter 2013;164:e193-8.
27. Terris DJ, Anderson SK, Watts TL, et al. Laryngeal nerve monitoring and minimally invasive thyroid surgery: complementary technologies. Arch Otolaryngol Head Neck Surg 2007;133:1254-7.
28. Barczyński M, Konturek A, Cichoń S. Randomized clinical trial of visualization versus neuromonitoring of recurrent laryngeal nerves during thyroidectomy. Br J Surg 2009;96:240-6.
29. Cavicchi O, Caliceti U, Fernandez IJ, et al. The value of neurostimulation and intraoperative nerve monitoring of inferior laryngeal nerve in thyroid surgery. Otolaryngol Head Neck Surg 2009;140:866-70.
30. Dralle H, Lorenz K, Machens A. Verdicts on malpractice claims after thyroid surgery: emerging trends and future directions. Head Neck 2012;34:1591-6.
31. Shindo M, Chheda NN. Incidence of vocal cord paralysis with and without recurrent laryngeal nerve monitoring during thyroidectomy. Arch Otolaryngol Head Neck Surg 2007;133:481-5.
32. Atallah I, Dupret A, Carpentier AS, et al. Role of intraoperative neuromonitoring of the recurrent laryngeal nerve in high-risk thyroid surgery. J Otolaryngol Head Neck Surg 2009;38:613-8.
33. Chandrasekhar SS, Randolph GW, Seidman MD, et al. Clinical practice guideline: improving voice outcomes after thyroid surgery. Otolaryngol Head Neck Surg 2013;148:S1-37.
34. Musholt TJ, Clerici T, Dralle H, et al. German Association of Endocrine Surgeons practice guidelines for the surgical treatment of benign thyroid disease. Langenbecks Arch Surg 2011;396:639-49.
35. Sarı S, Erbil Y, Sümer A, et al. Evaluation of recurrent laryngeal nerve monitoring in thyroid surgery. Int J Surg 2010;8:474-8.
36. Randolph GW, Kamani D. The importance of preoperative laryngoscopy in patients undergoing thyroidectomy: voice, vocal cord function, and the preoperative detection of invasive thyroid malignancy. Surgery 2006;139:357-62.
37. Farrag TY, Samlan RA, Lin FR, et al. The utility of evaluating true vocal fold motion before thyroid surgery.

Laryngoscope 2006;116:235-8.
38. Schlosser K, Zeuner M, Wagner M, et al. Laryngoscopy in thyroid surgery--essential standard or unnecessary routine? Surgery 2007;142:858-64; discussion 864.e1-2.
39. Kamani D, Darr EA, Randolph GW. Electrophysiologic monitoring characteristics of the recurrent laryngeal nerve preoperatively paralyzed or invaded with malignancy. Otolaryngol Head Neck Surg 2013;149:682-8.
40. Genther DJ, Kandil EH, Noureldine SI, et al. Correlation of final evoked potential amplitudes on intraoperative electromyography of the recurrent laryngeal nerve with immediate postoperative vocal fold function after thyroid and parathyroid surgery. JAMA Otolaryngol Head Neck Surg 2014;140:124-8.
41. Giordano D, Valcavi R, Thompson GB, et al. Complications of central neck dissection in patients with papillary thyroid carcinoma: results of a study on 1087 patients and review of the literature. Thyroid 2012;22:911-7.
42. Fontenot TE, Randolph GW, Setton TE, et al. Does intraoperative nerve monitoring reliably aid in staging of total thyroidectomies? Laryngoscope 2015. [Epub ahead of print].
43. White WM, Randolph GW, Hartnick CJ, et al. Recurrent laryngeal nerve monitoring during thyroidectomy and related cervical procedures in the pediatric population. Arch Otolaryngol Head Neck Surg 2009;135:88-94.
44. Wu CW, Lu IC, Randolph GW, et al. Investigation of optimal intensity and safety of electrical nerve stimulation during intraoperative neuromonitoring of the recurrent laryngeal nerve: a prospective porcine model. Head Neck 2010;32:1295-301.
45. Schneider R, Przybyl J, Hermann M, et al. A new anchor electrode design for continuous neuromonitoring of the recurrent laryngeal nerve by vagal nerve stimulations. Langenbecks Arch Surg 2009;394:903-10.
46. Dionigi G, Donatini G, Boni L, et al. Continuous monitoring of the recurrent laryngeal nerve in thyroid surgery: a critical appraisal. Int J Surg 2013;11 Suppl 1:S44-6.
47. Lamadé W, Ulmer C, Friedrich C, et al. Signal stability as key requirement for continuous intraoperative neuromonitoring. Chirurg 2011;82:913-20.
48. Phelan E, Schneider R, Lorenz K, et al. Continuous vagal IONM prevents recurrent laryngeal nerve paralysis by revealing initial EMG changes of impending neuropraxic injury: a prospective, multicenter study. Laryngoscope 2014;124:1498-505.
49. Schneider R, Randolph GW, Sekulla C, et al. Continuous intraoperative vagus nerve stimulation for identification of imminent recurrent laryngeal nerve injury. Head Neck 2013;35:1591-8.
50. Schneider R, Bures C, Lorenz K, et al. Evolution of nerve injury with unexpected EMG signal recovery in thyroid surgery using continuous intraoperative neuromonitoring. World J Surg 2013;37:364-8.
51. Van Slycke S, Gillardin JP, Brusselaers N, et al. Initial experience with S-shaped electrode for continuous vagal nerve stimulation in thyroid surgery. Langenbecks Arch Surg 2013;398:717-22.

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Esophageal recurrence of medullary thyroid carcinoma

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Abstract: Medullary thyroid carcinoma (MTC) metastasizes to the regional lymph nodes and to the lungs, liver and bones. Only one case of recurrence of MTC involving the upper gastrointestinal tract has been reported so far. We describe the case of a 38-year-old woman with MTC, who developed an upper esophageal submucosal recurrence after two previous local recurrences treated surgically and one ethanol injection. After resection of the right lateral esophageal wall, calcitonin dropped by 60% and showed a doubling time >1 year. We cannot rule out the role of deep ethanol injection in the involvement of the cervical esophagus wall.

Keywords: Thyroid neoplasms; medullary carcinoma; esophageal recurrence

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Introduction

Medullary thyroid carcinoma (MTC) accounts for about 5% of all thyroid malignant neoplasms. In most cases MTC is sporadic, but in 20-25% it is part of a genetic syndrome (MEN 2A, MEN 2B and familial MTC). For most of the patients, total thyroidectomy, level VI compartmental dissection and lateral neck dissection are the first line treatment. Five-year recurrence-free survival varies between 20-73% and is related to the number of metastatic nodes and postoperative calcitonin and CEA doubling times (1). MTC usually recurs locally but as far as we know there have been no reports on intramural oesophageal recurrences.

Case report

A 38-year-old woman was diagnosed in 2002 with sporadic MTC, on a nodule of the right thyroid lobe. Lateral cervical nodes were positive for metastasis on FNA. Calcitonin levels were 500 pg/mL. A total thyroidectomy, bilateral central compartment dissection, and right modified radical neck dissection (II-V) were performed (*Figure 1*). The histopathological report revealed nodal metastasis in 15 of the 23 nodes removed from the central compartment and in 8 of the 47 nodes resected from the lateral right compartment (pT1N1b), without extrathyroid extension or extranodal extension. The resection was considered R0 and postoperatively calcitonin dropped to 90 pg/mL.

By 2010, the level of calcitonin had raised to 470 pg/mL. Physical examination revealed a subcutaneous lump under the thyroidectomy scar while an ultrasonography identified an enlarged right paratracheal node. After performing a neck-chest-abdomen CT and a PET/CT, there was no evidence of distant metastases. A second surgery was performed and both the subcutaneous nodule and the paratracheal metastatic nodes were resected. The right inferior recurrent laryngeal nerve was infiltrated by the central compartment nodes (*Figure 2*) and had to be resected. The postoperative level of calcitonin was 461 pg/mL. Later in 2012 subcutaneous nodules reappeared under the scar and were once again resected.

We then lost sight of the patient who requested a second opinion from another centre where a further central neck recurrence was treated with repeated percutaneous ethanol injections.

In 2013, the patient was seen again in our unit complaining of dysphagia to solids. Calcitonin was 223 pg/mL. A neck ultrasound revealed two right nodules, probably within

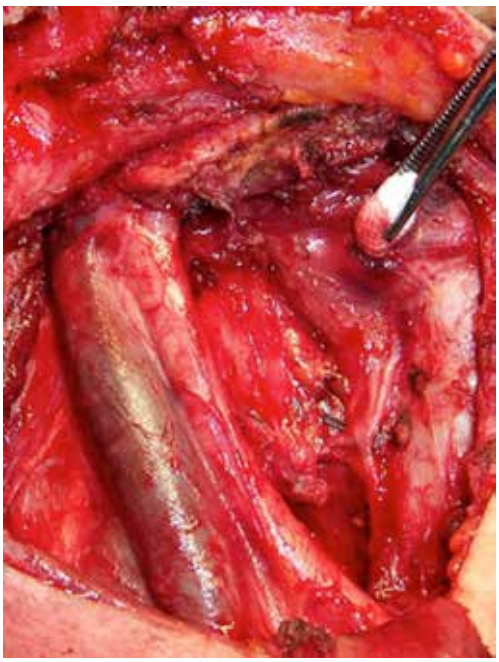

Figure 1 First surgery: total thyroidectomy, bilateral central compartment dissection and right modified radical neck dissection.

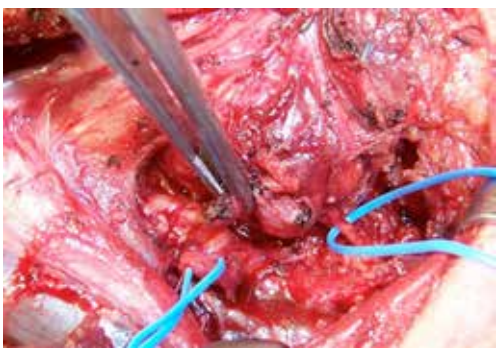

Figure 2 Second surgery: the paratracheal nodes infiltrating the inferior recurrent laryngeal nerve.

the esophageal wall (*Figure 3*). An upper gastrointestinal endoscopy found two submucosal nodules in the cervical oesophagus (*Figure 4*). The patient underwent a resection of the right lateral esophageal wall. There was no evidence of locoregional recurrence (*Figure 5*). Histopathology revealed that both nodules were metastases of MTC located in the submucosal layer of esophagus. There was no infiltration of the muscle layer (*Figure 6*). After surgery, calcitonin dropped to 89 pg/mL and was 155 pg/mL one year later during the follow up (doubling time >1 year).

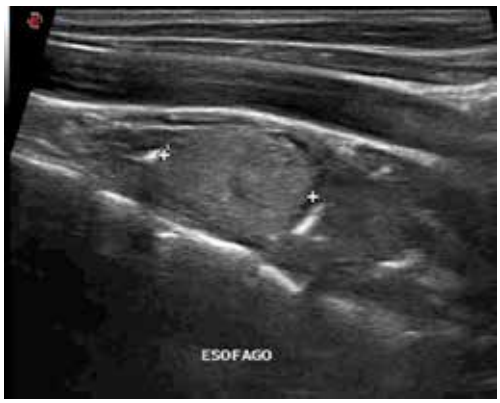

Figure 3 Ultrasound neck exploration revealing two nodules close or within the oesophageal wall.

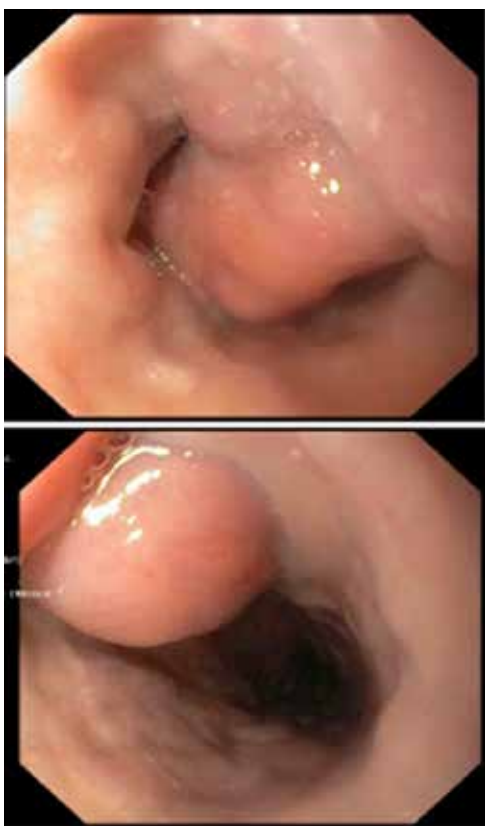

Figure 4 Upper GI endoscopy showing two submucosal nodules in the cervical oesophagus.

Discussion

MTC is known to give metastases via the lymphatic system to locoregional nodes and by hematogenous spread causing distant metastases to the lungs, liver and bones (1). Only

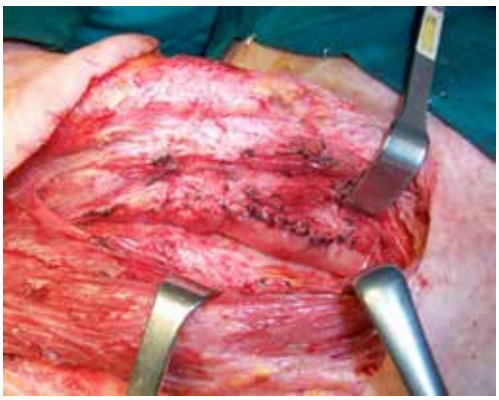

Figure 5 Fourth surgery: partial resection and primary suture of the cervical oesophagus.

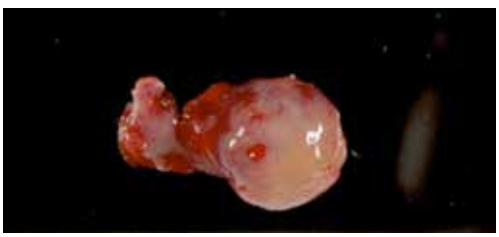

Figure 6 Macroscopic view of the submucosal oesophageal nodule.

a few cases of thyroid carcinoma metastases, mainly of follicular or papillary carcinoma, have been described to occur in the pharyngoesophageal axis. Even fewer of these cases describe limited metastases to the esophagus (2,3). The implantation of papillary or follicular carcinoma cancerous cells has been described a number of times after fine needle biopsy and other invasive procedures (4). This process has been associated with multiple factors such as needle size, number of passages during biopsy, excessive suction, needle withdrawal without releasing suction, and injection of tumour cells during biopsy.

To the best of our best knowledge, there has only been one other case of MTC metastasis to the upper GI tract involving the epiglottis (5). In this case, a 50-year-old woman who had initially undergone total thyroidectomy for MTC had developed mild dyspnea. Laryngoscopy found small nodular formations in the larynx. These were resected using CO_2-laser, with the pathological diagnosis of metastatic MTC.

In our case, the submucosal location of the esophageal nodules, with an uninfiltrated muscular layer suggests metastatic origin of the disease rather than locoregional spread. Yet we cannot exclude the possibility that MTC cells were implanted into the esophageal wall by percutaneous ethanol injections or fine needle biopsy. However, there have been no reports of intraesophageal metastatic implants after these specific procedures.

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References

1. Meijer JA, le Cessie S, van den Hout WB, et al. Calcitonin and carcinoembryonic antigen doubling times as prognostic factors in medullary thyroid carcinoma: a structured meta-analysis. Clin Endocrinol (Oxf) 2010;72:534-42.
2. Lee B, Cook G, John L, et al. Follicular thyroid carcinoma metastasis to the esophagus detected by 18FDG PET/CT. Thyroid 2008;18:267-71.
3. Wisotzki C, Friese M, Ehresmann J, et al. Esophageal metastasis from papillary thyroid cancer: diagnosis by 131I SPECT/CT. Clin Nucl Med 2014;39:e73-4.
4. Moon HJ, Park SH, Hong SW, et al. Extrathyroidal implantation of thyroid tumor cells after needle biopsy and other invasive procedures. Thyroid 2010;20:459-64.
5. Desuter G, Schmitz S, Jamar F, et al. Pharyngoesophagolaryngeal metastases of medullary thyroid carcinoma. A case report. Ann Endocrinol (Paris) 2003;64:448-52.

Negative developing of parathyroid using carbon nanoparticles during thyroid surgery

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Introduction

Subtotal thyroidectomy and total thyroidectomy are two main options to treat thyroid nodules. Due to the special anatomical location of parathyroid, the incidence of permanent hypoparathyroidism due to parathyroid damage is about 9-32% postoperatively (1). This condition can seriously affect the quality of life of patients and post great challenges to surgeons; therefore, it is particularly important to protect the parathyroid during the thyroid surgery.

Given the strong lymphoid tropism of nano-carbon materials, we can black-stain the thyroid and its surrounding lymph nodes without changing the anatomic color of parathyroid, which facilitates the doctors to identify and protect the parathyroid and lowers the risk of resecting the parathyroid by accident or affecting its blood supply; as a result, we may reduce the accidental injury of parathyroid and lower the incidence of hypoparathyroidism.

Principles

Nano-carbon Suspension Injection is a suspension with nanoscale carbon particles. The particles, 150 nm in diameter, have strong lymphatic tropism. As we know, the spaces among capillary endothelial cells range 20-50 nm, whereas those among the endothelial cells of lymph capillaries range 120-150 nm, along with the hypoplastic basement membrane. Therefore, after having been injected into the thyroid tissue, the carbon nanoparticles will not enter the blood vessels; rather, they will rapidly enter the lymphatic vessels and then enter the lymphatic capillaries after having been internized by macrophages; finally, they will accumulate in the lymph nodes, resulting in the black staining of the lymph nodes (2). Meanwhile, the parathyroid still maintains its original color (brown or reddish-brown), remarkably distinguishing from the adjacent black-stained thyroid and lymph nodes.

Procedure

(I) Retract the anterior neck muscles to expose the thyroid gland. Without excessive dissociation, the carbon nanoparticles suspension is slowly injected into the gland using a skin test needle in the upper, middle, and lower poles of the thyroid (0.1 mL each pole). Pull back on the syringe before injecting to make sure the suspension will not be injected into the bloodstream.

(II) After the injection at each point, gently press the site for 1-2 minutes with sterile gauze. Otherwise, the extravasation of the suspension may black-stain the adjacent tissues and thus obscure the surgical field.

(III) The surgical operation can be initiated 10 minutes later. Any damage to the posterior and lateral capsules of the thyroid should be avoided during the surgery to prevent the possibility that the extravasation of the suspension affects the surgical field.

Significance

It can be found during the surgery that the parathyroid still maintains its original color (brown or reddish-brown), remarkably distinguishing from the adjacent black-stained thyroid and lymph nodes, which is helpful for the identification and protection of the parathyroid and its

blood supply. During the thyroidectomy, therefore, the non-black-stained tissues should be preserved as well as their blood supplies whenever possible to maintain the normal functions of the parathyroid. It is particularly useful to identify and protect parathyroid when performing the level VI lymph node dissection.

Acknowledgements

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References

1. Kihara M, Miyauchi A, Kontani K, et al. Recovery of parathyroid function after total thyroidectomy: long-term follow-up study. ANZ J Surg 2005;75:532-6.
2. Hagiwara A, Takahashi T, Sawai K, et al. Lymph nodal vital staining with newer carbon particle suspensions compared with India ink: experimental and clinical observations. Lymphology 1992;25:84-9.

Prediction of ipsilateral and contralateral central lymph node metastasis in unilateral papillary thyroid carcinoma: a retrospective study

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Background: Prophylactic central lymph node dissection (CLND) in patients with papillary thyroid carcinoma (PTC) remains controversial and predictive factors for central lymph node (CLN) metastasis in unilateral PTC cases are not well defined. The aims of this study were to evaluate the rate of ipsilateral and contralateral CLN metastasis and to determine the clinicopathologic factors predictive for ipsilateral and contralateral CLN metastasis in unilateral PTC cases.

Methods: We retrospectively reviewed 218 PTC patients with clinically negative-node neck who have received total thyroidectomy with bilateral CLND. Pearson χ^2 test or Fisher exact test and multivariate analysis were used to evaluate relationships between CLN metastasis and demographic factors such as age, sex and the clinicopathologic factors.

Results: Ipsilateral and contralateral CLN metastasis were present in 47.7% (104/218) and 13.3% (29/218), respectively. Multivariate analysis showed that tumor size (>1 cm) (P=0.016; OR, 2.005) and age <45 years old (P=0.031; OR, 1.539) were the predictors of ipsilateral CLN metastasis, and prelaryngeal lymph node (LN) metastasis (P=0.028; OR, 2.970) and ipsilateral CLN metastasis (P<0.001; OR, 15.128) independently predicted contralateral CLN metastasis.

Conclusions: CLN metastasis was common in PTC patients with clinically node-negative neck and the most common pattern of CLN metastasis was ipsilateral CLN metastasis. Prophylactic ipsilateral CLND may be an optional procedure and should be considered for patients with a tumor size >1 cm. Therapeutic bilateral CLND should be considered in patients with a tumor size >1 cm and especially, if there exists prelaryngeal LN or ipsilateral CLN metastasis on frozen section analysis.

Keywords: Papillary thyroid carcinoma (PTC); lymph node (LN) metastasis; prophylactic central lymph node dissection (CLND)

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Introduction

Papillary thyroid carcinoma (PTC) is the most common histologic type of differentiated thyroid cancer, which is characterized by early lymph node (LN) metastasis (1). Cervical LN metastasis is frequently observed in PTC patients with an average incidence of 60% (2). The most common sites of metastases are the central lymph nodes (CLNs) of the neck (level VI), followed by ipsilateral lateral LNs (3). Therapeutic central compartment neck dissection is well accepted to perform for patients with known LN metastasis diagnosed by physical examination or preoperative ultrasonograph (US) scanning. However, even for clinically node-negative neck PTC, occult CLN metastasis was found common in postoperatively pathological examination (4-6). It has been known that LN metastasis increases the rate of loco-regional recurrence and

mortality of PTC patients. Therefore, the 2009 guidelines of American Thyroid Association (ATA) recommended that prophylactic central lymph node dissection (CLND) may be considered in patients with high-risk thyroid cancer (T3 or T4 classification) (7). However, prophylactic CLND in PTC cases with clinically node-negative neck remains controversial as the lack of convincing evidence of its survival benefits. In addition, recent studies, including a prospective randomized controlled study, showed that the morbidity rate of complications such as hypoparathyroidism or recurrent laryngeal nerve injury was significantly higher in the PTC patients who underwent CLND (8-11). Therefore, the identification of predictive factors of CLN metastasis can help surgeons manage individualized therapy, which is crucial to avoid unnecessary CLND and to minimize postoperative complications. However, predictive factors for CLN metastasis in unilateral PTC cases are not well defined.

The aims of this study were to evaluate the rate of LN metastasis to the ipsilateral and contralateral central neck compartment as well as to determine the predictive factors of ipsilateral and contralateral CLN metastasis in unilateral PTC.

Materials and methods

Study design

We conducted a retrospective study of unilateral PTC patients who underwent total thyroidectomy and bilateral CLND in West China Hospital, Sichuan University from September 2011 to October 2013. All patients were diagnosed with PTC by preoperative fine-needle aspiration biopsy or by intraoperatively on frozen section. Preoperative US and computerized tomography (CT) scan were performed to identify patients with unilateral PTC and no suspicious LN in the neck. No patient previously underwent any cervical surgery, external radiotherapy, or radioactive iodine treatment. Patients with other types of thyroid malignancy or undergoing unilateral CLND were excluded. Patients were also excluded if they had PTC in isthmus (N=9) or bilateral lobes (N=52). A total of 218 patients were finally enrolled into our study. Bilateral CLND is defined as the removal of CLNs [including pretracheal, paratracheal (ipsilateral and contralateral), prelaryngeal and perithyroidal groups] as well as nodes along the recurrent laryngeal nerves (10,12). Dissections were carried out in accordance to anatomical parameters established by the ATA (7). Specimens were separated and marked according to location within the central compartment and sent for histopathologic examination. The electronic clinical and pathological records collected included sex, age, tumor size, perithyroidal invasion, chronic lymphatic thyroiditis and central compartment LN involvement. Moreover, the number of total and positive LNs in each central region was also determined. This study was approved by the Institutional Review Board of Sichuan University, China, and all patients provided informed consents.

All patients were preoperatively examined by the fiberoptic laryngoscopy to evaluate the mobility of vocal cord and reevaluated after surgery. Vocal cord palsy as confirmed by laryngoscopy was considered permanent if it lasted for more than 6 months. While temporary recurrent laryngeal nerve injury was defined as vocal cord palsy persisting for less than 6 months. Postoperative hypoparathyroidism was also evaluated. Patients who developed hypocalcemia were administered oral calcium and vitamin D supplements, and those who developed significant symptoms were administered intravenous calcium gluconate. Temporary hypoparathyroidism was defined as the level of parathyroid hormone <1.60 pmol/L postoperatively. Permanent hypoparathyroidism was defined as the level of parathyroid hormone <1.60 pmol/L persisting more than 6 months after surgery.

Statistical analysis

Statistical analysis was performed using SPSS version 19.0 software. Univariate analysis (Pearson χ^2 test or Fisher exact test) and multivariate analysis were used to evaluate relationships between CLN metastasis and demographic factors such as age, sex and the clinicopathologic factors. A P value <0.05 was considered to be statistically significant.

Results

Patient characteristics and pathology

In our study, 170 women (78.0%) and 48 men (22.0%) were enrolled, and the mean age was 43.2±12.1 years, with a range of 10-78 years. Of these patients, 59.2% (129/218) were <45 years of age, and 40.8% (89/218) were ≥45 years of age. The median size of primary tumor was 1.1 cm (range, 0.1-4.0 cm), 134 patients (61.5%) had a primary tumor ≤1 cm, and 84 (38.5%) had a primary tumor >1 cm.

Among 218 patients, 104 patients (47.7%) had ipsilateral CLN metastasis, 29 (13.3%) had bilateral CLN metastasis,

31 (14.2%) had prelaryngeal LN metastasis, and 100 (45.9%) had pretracheal LN metastasis. The mean ± SD numbers of total and positive LNs collected during CLND were 5.5±3.7 (range, 1-21) and 1.3±2.2 (range, 0-8) in the ipsilateral paratracheal region, 4.0±3.4 (range, 1-17) and 0.3±0.8 (range, 0-6) in the contralateral paratracheal region, 0.8±1.3 (range, 1-6) and 0.2±0.6 (range, 0-3) in the prelaryngeal region, and 3.9±3.6 (range, 1-21) and 1.1±2.0 (range, 0-20) in the pretracheal region, respectively (*Table 1*).

Univariate and multivariate analyses of risk factors

In univariate analysis, ipsilateral CLN metastasis was more prevalent in patients who were male, <45 years of age, or had a tumor >1 cm (P<0.05). Multivariate analysis revealed that tumor size >1 cm (P=0.016; OR, 2.005) and age <45 years old (P=0.031; OR, 1.539) were the predictive factors of ipsilateral CLN metastasis (*Table 2*). The rate of contralateral CLN metastasis was 13.3%. Contralateral CLN metastasis was significantly associated with prelaryngeal LN metastasis (P=0.002), pretracheal LN metastasis (P=0.002), and ipsilateral CLN metastasis (P<0.001) by univariate analysis (*Table 3*). *Table 4* shows the results of multivariate analysis. Prelaryngeal LN metastasis (P=0.028; OR, 2.970) and ipsilateral CLN metastasis (P<0.001; OR, 15.128) were the independent predictive factors of contralateral CLN metastasis. Perithyroidal invasion and chronic lymphatic thyroiditis were not significantly related to the presence ipsilateral or contralateral CLN metastasis (*Tables 3,5*).

Table 1 Demographic and clinicopathologic characteristics of patients with unilateral PTC

Variables	Value
No. of patients	218
Female/male sex, No. (%)	170 (78.0)/48 (22.0)
Age	
Mean (SD), y	43.2 (12.1)
<45 y/≥45 y, No. (%)	129 (59.2)/89 (40.8)
Primary tumor	
Tumor size, median, cm	1.1
≤1 *vs*. >1 cm, No. (%)	134 (61.5)/84 (38.5)
Perithyroidal invasion, No. (%)	85 (39.0)
Number of dissected nodes, mean ± SD [range]	
Ipsilateral paratracheal lymph nodes	5.5±3.7 [1-21]
Contralateral paratracheal lymph nodes	4.0±3.4 [1-17]
Pretracheal lymph nodes	3.9±3.6 [1-21]
Prelaryngeal lymph nodes	0.8±1.3 [1-6]

PTC, papillary thyroid carcinoma; No., number; SD, standard deviation; y, years.

Postoperative complications

Eighty-nine of the 218 patients (40.8%) developed transient hypocalcemia requiring calcium supplementation. Of these patients, 2 (0.9%) had permanent hypoparathyroidism. Vocal cord palsy was observed in eight patients. Two patients underwent intentional unilateral recurrent laryngeal nerve resection due to direct tumor invasion. The remaining six patients recovered from hoarseness and showed normal cord mobility within 6 months after surgery.

Discussion

This retrospective study systematically examined the pattern of CLN metastasis in 218 patients with diagnosed with unilateral cN0 PTC. The presence of metastatic LNs at all specific subsites of the central compartment was accurately assessed by standard histologic examination of dissected neck specimens. We found that the rate of occult CLN metastasis was high, 64.7%, in patients with unilateral cN0 PTC and ipsilateral CLN metastasis was the most frequent

Table 2 Multivariate logistic regression for ipsilateral central lymph node metastasis

Variables	β (SE)	P value	OR	95% CI (OR)	
				Lower	Upper
Male	–0.545 (0.343)	0.112	0.580	0.296	1.136
Age <45 y	0.617 (0.287)	0.031	1.539	1.307	2.946
Tumor size >1 cm	0.696 (0.290)	0.016	2.005	1.136	3.538
Constant	0.318 (0.344)				

SE, standard error; OR, odds ratio; CI, confidence interval; y, years.

Table 3 Clinicopathologic factors in relation to contralateral central lymph node (CLN) metastasis

Variables (n=218)	Contralateral CLN metastasis, number (%)		P value
	Present (n=29)	Absent (n=189)	
Gender			
Female	19 (11.2)	151 (88.8)	
Male	10 (20.8)	38 (79.2)	0.082
Age, years			
<45	22 (17.1)	107 (82.9)	
≥45	7 (7.9)	82 (92.1)	0.050
Tumor size, cm			
≤1	14 (10.4)	121 (89.6)	
>1	15 (18.1)	68 (81.9)	0.104
Perithyroidal invasion			
Yes	17 (13.1)	113 (86.9)	
No	12 (13.6)	76 (86.4)	0.905
Chronic lymphatic thyroiditis			
Yes	7 (13.2)	46 (86.8)	
No	22 (13.3)	143 (86.7)	0.981
Ipsilateral CLN metastasis			
Yes	27 (26.0)	77 (74.0)	
No	2 (1.8)	112 (98.2)	0.000
Prelaryngeal LN metastasis			
Yes	10 (32.3)	21 (67.7)	
No	19 (10.2)	168 (89.8)	0.002*
Pretracheal LN metastasis			
Yes	21 (20.8)	80 (79.2)	
No	8 (6.8)	109 (93.2)	0.002

*, Fisher's exact test.

involved region in central neck compartment. The pattern of CLN metastasis from PTC was similar to those observed in previous studies (5,6).

The incidence of occult nodal metastasis of PTC in central compartment has been reported to vary between 30% and 90% (2). Eun *et al*. (6) reported that the rate of CLN metastasis is 36.4% in PTC cases with clinically node-negative neck. Another report showed that CLN metastasis associated with PTC is present in 52.3% (79/151) of cases (5). These results including ours indicate that LNs in the central compartment generally are most commonly involved in metastasis, and it is necessary to perform routine CLND in primary surgery. However, to date, prophylactic CLND in clinically node-negative PTC patients are still a matter of debate. Some authors recommend routine CLND to prevent long-term recurrence and decrease postoperative thyroglobulin (Tg) levels, citing the high risk of cervical LN metastasis in PTC (13-15). Furthermore, several prospective studies have demonstrated that prophylactic CLND is able to improve accuracy in staging and selecting patients for Radioiodine (RAI) and with a lower risk complication when compared to that with reoperative surgery (14,16,17). While others suggest that this procedure increases the risk of postoperative complications, such as hypothyroidism or the recurrent laryngeal nerves injury, without any demonstrable long-term survival benefits (9,18,19).

High percentage of occult CLN metastasis was also reported in papillary thyroid microcarcinoma (PTMC) in previous studies (20,21) and it is widely accepted that tumor size is closely related with CLN metastasis. Previous studies have reported that tumor size of greater than 1 cm was associated with a higher rate of ipsilateral CLN metastasis, and our result was consistent with the results

Table 4 Multivariate logistic regression for contralateral CLN metastasis

Variables	β (SE)	P value	OR	95% CI (OR)	
				Lower	Upper
Prelaryngeal pN (+)	1.088 (0.496)	0.028	2.970	1.123	7.853
Pretracheal pN (+)	0.600 (0.479)	0.210	1.822	0.713	4.659
Ipsilateral CLN pN (+)	2.717 (0.760)	0.000	15.128	3.411	67.088
Constant	−4.430 (0.760)				

SE, standard error; OR, odds ratio; CI, confidence interval; pN (+), positive for pathologic lymph nodes metastasis; CLN, central lymph node.

Table 5 Clinicopathologic factors in relation to ipsilateral central lymph node metastasis

Variables (n=218)	Ipsilateral central lymph node metastasis, number (%)		
	Present (n=104)	Absent (n=114)	P value
Gender			
Female	75 (44.1)	95 (55.9)	
Male	29 (60.4)	19 (39.6)	0.046
Age, years			
<45	70 (54.3)	59 (45.7)	
≥45	34 (38.2)	55 (61.8)	0.020
Tumor size, cm			
≤1	55 (40.7)	80 (59.3)	
>1	49 (59.0)	34 (41.0)	0.009
Perithyroidal invasion			
Yes	65 (50.0)	65 (50.0)	
No	39 (44.3)	49 (55.7)	0.410
Chronic lymphatic thyroiditis			
Yes	24 (45.3)	29 (54.7)	
No	80 (48.5)	85 (51.5)	0.685

(5,22). Although some LN metastasis may be treated with radioactive iodine, the addition of nodal dissection could reduce the need for reoperation in the central compartment and with lower postoperative Tg levels (23). LN metastasis in PTC may associate with various factors such as gender, primary tumor size, capsular invasion, extracapsular extension, multifocality, and *BRAF*-mutated gene expression (1,4,6,22). On multivariate analysis in our study, tumor size >1 cm was an independent predictive factor of ipsilateral CLN metastasis in cases of PTC, which was similar to previous studies (4,6,22). These results including ours indicate that the rate of ipsilateral CLN metastasis is significantly higher in cases of tumor with a maximal diameter of greater than 1 cm, and prophylactic ipsilateral CLND with thyroidectomy should be considered as an option when managing these patients. Although several studies (4,6) found no correlation between age and ipsilateral CLN metastasis, Lee *et al.* (5) found a higher prevalence of ipsilateral CLN metastasis in patients with age <45 years old. Similarly, our study also showed that age <45 years old was the predictive factor of ipsilateral CLN metastasis.

Tumor with perithyroidal invasion has been repeated demonstrated closely related to increased rates of central compartmental LN metastases in PTC, which was also independent predictor of both pathological and clinical outcomes. However, Eun *et al.* (6) have found no correlation between perithyroidal invasion and CLN metastasis in a prospective multicenter study of 140 patients. Perithyroidal invasion was also not significantly associated with CLN metastasis in our study. The different result we observed may have been due to the rate of perithyroidal invasion in our study was lower than previous studies (45.8-54.3%) (22,24).

The rate of contralateral CLN metastasis was 13.3% (29/218). Of these patients, 2 (6.90%) had isolated contralateral CLN metastasis without ipsilateral CLN involvement in our study. Multivariate analysis in our study showed that ipsilateral CLN metastasis was an independent predictor of contralateral CLN metastasis, which was consistent with previous reports (5,22,25). Additionally, we also found the rate of contralateral CLN metastasis was significantly higher in cases with histologically proven metastasis to the prelaryngeal LN (P=0.028). It is accepted that prelaryngeal LN positivity was associated with further nodal metastasis to the central and lateral neck compartments and with heavier nodal burden (26-29). As our study reported, the incidence of ipsilateral CLN metastasis was high, while that of contralateral CLN metastasis was relatively low, with most metastases observed in patients with tumors size >1 cm. This may guide the extent of prophylactic CLND in the management of patients with unilateral PTC. Although the ATA guidelines do not recommend elective central neck dissection in patients with small, noninvasive cN0 PTCs or in most patients with follicular cancer, our findings indicate that patients with larger tumor size (>1 cm) should undergo unilateral or bilateral CLND with thyroidectomy in the initial surgery and for most patients with tumor size >1 cm, total thyroidectomy and ipsilateral CLND should be sufficient (7).

Hypocalcemia was more commonly seen in PTC patients with thyroidectomy and CLND than with thyroidectomy alone. In our study, transient hypoparathyroidism was found in 40.8% (89/218), which was similar to those observed in previous studies (26.6-49.5%) (6,24,30). Considering the mentioned morbidities in preceding paragraphs, preoperative identification of patients with PTC at greater risk of metastases to the central compartment would be valuable. Sometimes LN metastasis in the central compartment cannot be detected by palpation and does not appear abnormal in preoperative imaging. Preoperative US have been reported as a rapid, low-cost, noninvasive, and reliable method for detecting neck metastasis of head

and neck cancer, but with a limitation because of low sensitivity (31-33). To evaluate the status of CLN metastasis accurately, intraoperative palpation or inspection has emerged as an alternative approach to preoperative imaging. Intraoperative frozen biopsy appears to be a supplementary, safe and efficacious tool to guide the use and determine the extent of CLND (15,34). Based on the results of this study, therapeutic bilateral CLND may be considered in patients with a tumor size >1 cm and especially, if there exists prelaryngeal LN and ipsilateral CLN metastasis on frozen section analysis.

Our findings indicate that CLN metastasis is common in PTC patients with clinically node negative neck and prophylactic ipsilateral CLND may be an optional procedure and should be considered for patients with a tumor size >1 cm. However, we cannot determine the cause-and-effect relationship between the risk and variables due to our study was conducted with a retrospective design. Furthermore, owing to the short duration of follow-up, tumor recurrence and survival after central compartment dissection were not well studied. Further investigation with a long follow-up time is necessary to determine whether the studied parameters are associated with prognosis.

Conclusions

The most common pattern of CLN metastasis in unilateral PTC patients with clinically node-negative neck was ipsilateral CLN metastasis. Tumor size >1 cm was an independent predictive factor of ipsilateral CLN metastasis and prelaryngeal LN metastasis and ipsilateral CLN metastasis were the independent predictive factors of contralateral CLN metastasis. Prophylactic ipsilateral CLND may be an optional procedure and should be considered for patients with a tumor size >1 cm. Therapeutic bilateral CLND should be considered in patients with a tumor size >1 cm and especially, if there exists prelaryngeal LN or ipsilateral CLN metastasis on frozen section analysis.

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References

1. Nam IC, Park JO, Joo YH, et al. Pattern and predictive factors of regional lymph node metastasis in papillary thyroid carcinoma: a prospective study. Head Neck 2013;35:40-5.
2. Rotstein L. The role of lymphadenectomy in the management of papillary carcinoma of the thyroid. J Surg Oncol 2009;99:186-8.
3. Machens A, Hinze R, Thomusch O, et al. Pattern of nodal metastasis for primary and reoperative thyroid cancer. World J Surg 2002;26:22-8.
4. Joo JY, Park JY, Yoon YH, et al. Prediction of occult central lymph node metastasis in papillary thyroid carcinoma by preoperative BRAF analysis using fine-needle aspiration biopsy: a prospective study. J Clin Endocrinol Metab 2012;97:3996-4003.
5. Lee KE, Chung IY, Kang E, et al. Ipsilateral and contralateral central lymph node metastasis in papillary thyroid cancer: patterns and predictive factors of nodal metastasis. Head Neck 2013;35:672-6.
6. Eun YG, Lee YC, Kwon KH. Predictive factors of contralateral paratracheal lymph node metastasis in papillary thyroid cancer: prospective multicenter study. Otolaryngol Head Neck Surg 2014;150:210-5.
7. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167-214.
8. Conzo G, Calò PG, Sinisi AA, et al. Impact of prophylactic central compartment neck dissection on locoregional recurrence of differentiated thyroid cancer in clinically node-negative patients: a retrospective study of a large clinical series. Surgery 2014;155:998-1005.
9. Palestini N, Borasi A, Cestino L, et al. Is central neck dissection a safe procedure in the treatment of papillary thyroid cancer? Our experience. Langenbecks Arch Surg 2008;393:693-8.
10. White ML, Gauger PG, Doherty GM. Central lymph node dissection in differentiated thyroid cancer. World J Surg 2007;31:895-904.
11. Viola D, Materazzi G, Valerio L, et al. Prophylactic central compartment lymph node dissection in papillary thyroid carcinoma: clinical implications derived from the first

prospective randomized controlled single institution study. J Clin Endocrinol Metab 2015;100:1316-24.
12. American Thyroid Association Surgery Working Group, American Association of Endocrine Surgeons, American Academy of Otolaryngology-Head and Neck Surgery, et al. Consensus statement on the terminology and classification of central neck dissection for thyroid cancer. Thyroid 2009;19:1153-8.
13. Nixon IJ, Ganly I, Patel SG, et al. Observation of clinically negative central compartment lymph nodes in papillary thyroid carcinoma. Surgery 2013;154:1166-72; discussion 1172-3.
14. Raffaelli M, De Crea C, Sessa L, et al. Prospective evaluation of total thyroidectomy versus ipsilateral versus bilateral central neck dissection in patients with clinically node-negative papillary thyroid carcinoma. Surgery 2012;152:957-64.
15. Sadowski BM, Snyder SK, Lairmore TC. Routine bilateral central lymph node clearance for papillary thyroid cancer. Surgery 2009;146:696-703; discussion 703-5.
16. Raffaelli M, De Crea C, Sessa L, et al. Can intraoperative frozen section influence the extension of central neck dissection in cN0 papillary thyroid carcinoma? Langenbecks Arch Surg 2013;398:383-8.
17. Carling T, Long WD 3rd, Udelsman R. Controversy surrounding the role for routine central lymph node dissection for differentiated thyroid cancer. Curr Opin Oncol 2010;22:30-4.
18. Giordano D, Valcavi R, Thompson GB, et al. Complications of central neck dissection in patients with papillary thyroid carcinoma: results of a study on 1087 patients and review of the literature. Thyroid 2012;22:911-7.
19. Chisholm EJ, Kulinskaya E, Tolley NS. Systematic review and meta-analysis of the adverse effects of thyroidectomy combined with central neck dissection as compared with thyroidectomy alone. Laryngoscope 2009;119:1135-9.
20. Park JP, Roh JL, Lee JH, et al. Risk factors for central neck lymph node metastasis of clinically noninvasive, node-negative papillary thyroid microcarcinoma. Am J Surg 2014;208:412-8.
21. Roh JL, Kim JM, Park CI. Central cervical nodal metastasis from papillary thyroid microcarcinoma: pattern and factors predictive of nodal metastasis. Ann Surg Oncol 2008;15:2482-6.
22. Koo BS, Choi EC, Yoon YH, et al. Predictive factors for ipsilateral or contralateral central lymph node metastasis in unilateral papillary thyroid carcinoma. Ann Surg 2009;249:840-4.
23. Popadich A, Levin O, Lee JC, et al. A multicenter cohort study of total thyroidectomy and routine central lymph node dissection for cN0 papillary thyroid cancer. Surgery 2011;150:1048-57.
24. Kim WW, Park HY, Jung JH. Surgical extent of central lymph node dissection in clinically node-negative papillary thyroid cancer. Head Neck 2013;35:1616-20.
25. Lim YC, Choi EC, Yoon YH, et al. Central lymph node metastases in unilateral papillary thyroid microcarcinoma. Br J Surg 2009;96:253-7.
26. Oh EM, Chung YS, Lee YD. Clinical significance of Delphian lymph node metastasis in papillary thyroid carcinoma. World J Surg 2013;37:2594-9.
27. Iyer NG, Kumar A, Nixon IJ, et al. Incidence and significance of Delphian node metastasis in papillary thyroid cancer. Ann Surg 2011;253:988-91.
28. Kim WW, Yang SI, Kim JH, et al. Experience and analysis of Delphian lymph node metastasis in patients with papillary thyroid carcinoma. World J Surg Oncol 2012;10:226.
29. Isaacs JD, McMullen TP, Sidhu SB, et al. Predictive value of the Delphian and level VI nodes in papillary thyroid cancer. ANZ J Surg 2010;80:834-8.
30. Roh JL, Kim JM, Park CI. Central lymph node metastasis of unilateral papillary thyroid carcinoma: patterns and factors predictive of nodal metastasis, morbidity, and recurrence. Ann Surg Oncol 2011;18:2245-50.
31. Kim SS, Lee BJ, Lee JC, et al. Preoperative ultrasonographic tumor characteristics as a predictive factor of tumor stage in papillary thyroid carcinoma. Head Neck 2011;33:1719-26.
32. Wu LM, Gu HY, Qu XH, et al. The accuracy of ultrasonography in the preoperative diagnosis of cervical lymph node metastasis in patients with papillary thyroid carcinoma: A meta-analysis. Eur J Radiol 2012;81:1798-805.
33. Lee DW, Ji YB, Sung ES, et al. Roles of ultrasonography and computed tomography in the surgical management of cervical lymph node metastases in papillary thyroid carcinoma. Eur J Surg Oncol 2013;39:191-6.
34. Lim YS, Choi SW, Lee YS, et al. Frozen biopsy of central compartment in papillary thyroid cancer; quantitative nodal analysis. Head Neck 2013;35:1319-22.

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The presentation of lymph nodes in Hashimoto's thyroiditis on ultrasound

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Background: Comprehensive neck ultrasound (US) examination has become an essential component of preoperative workup for patients with thyroid cancer. Regional cervical lymph nodes may be involved in cases of Hashimoto's thyroiditis (HT). This study seeks to examine the sonographic pattern of lymph nodes in patients with HT.

Methods: This is a retrospective study looking at patients with confirmed diagnoses of HT on final surgical pathology who underwent preoperative comprehensive neck US. We compared preoperative ultrasound for patients with HT to euthyroid patients with goiter. Data collected included number, size and ultrasonographic features of cervical lymph nodes.

Results: We included a total of 417 patients: 202 patients with HT in the study group, and 215 patients with goiter and euthyroid status in the control group. Patients with HT had a higher number of total cervical lymph nodes than the control group (2.00±2.35 *vs.* 0.76±1.36 mm; P<0.0001), most notably in cervical levels III and IV (P<0.05 for both).

Conclusions: HT seems to be associated with an ultrasonographic pattern of increased number of enlarged cervical lymph nodes, particularly in levels III, and IV.

Keywords: Hashimoto's thyroiditis (HT); lymph nodes; ultrasound (US)

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Introduction

Hashimoto's thyroiditis (HT) is the most common type of thyroiditis and the most common autoimmune disease, with an annual incidence worldwide of about 1 case per 1,000 persons (1,2). In the United States and other countries where there is sufficient dietary iodine, it is the most common cause of hypothyroidism (3).

The key factor in the development of autoimmune thyroiditis is the breakdown of immune tolerance. The initial production and clonal expansion of self-reactive cells occurs in the regional lymph nodes. Later, lymphoid tissue develops directly in the thyroid gland (4,5). The cells lining the thyroid follicles (thyrocytes), which are the target for these autoreactive lymphocytes, are progressively destroyed, ultimately leading to hypothyroidism (4). The inflammation is primarily mediated by circulating antibodies against thyroid tissue (6). High serum thyroid peroxidase antibody concentrations are present in 90% of patients with HT, and high serum thyroglobulin antibody concentrations are present in 20% to 50% of these patients (3,7).

HT is characterized pathologically by lymphocytic infiltration of the interstitium, mainly lymphocytes with some plasma cells and macrophages (1,3). The lymphoid tissue is distributed within and around the lobules, and often exhibits large follicles with prominent germinal centers (1,4). The inflammatory process also results in oxyphilic changes of follicular epithelial cells, parenchymal atrophy of thyroid tissue, and varying degrees of fibrosis, imparting a firm consistency to the thyroid (8).

Table 1 Clinical and biochemical characteristics of Hashimoto's and control groups

Characteristics	Hashimoto's group	Control group	P value
Sex (female/male)	179/123	187/28	0.66
Right thyroid lobe volume (mL)	21.20±27.34	29.96±36.72	0.08
Left thyroid lobe volume (mL)	17.09±23.17	24.53±36.22	0.034
TSH (U/mL)	10.85±30.91	1.44±1.18	<0.001

TSH, thyroid stimulating hormone.

Neck ultrasound (US) has become the most commonly used imaging tool in patients with thyroid diseases (9,10). Thyroid US of patients with HT generally reveals diffuse enlargement of the gland, a heterogenous background, and a general decrease in echogenicity. Other sonographic findings of HT often include hypervascularity and the presence of hypoechoic micronodules with an echogenic rim (11-13).

Despite the known involvement of lymphoid tissue in the pathogenesis of HT, little investigation has been done into the pattern of cervical lymphadenopathy in these patients (14). This is of particular importance given the long debate over the relationship between HT and thyroid cancer, specifically papillary carcinoma of the thyroid (PTC) (15,16). Lymphadenopathy is often considered a finding concerning for malignancy (17). However, more recent studies have found that the presence of benign, enlarged cervical lymph nodes is common in HT patients (14,18,19). It is important to determine whether the lymphadenopathy is a result of the malignancy or the thyroiditis.

This study therefore seeks to describe the cervical lymph node findings on US in patients with HT, including size, number, anatomic location and ultrasonographic characteristics. The characterization of the sonographic pattern of lymph nodes in patients with HT may assist in improving the diagnosis of HT, as well as preventing unnecessary testing of patients for malignancy based solely on cervical lymphadenopathy.

Materials and methods

This is a retrospective study of 417 patients from Tulane University Medical Center visiting from January 2013 to September 2014. Of our patients, 366 (87.77%) were female and the average age was 52.53±14.96 years. All patients underwent a preoperative comprehensive neck US and the diagnosis of HT was made based upon final surgical pathology. As the control group, 215 patients with euthyroid goiter were selected (28 males, 187 females). All ultrasounds were performed by a single surgeon who is the senior author on this paper.

For each patient included in the study, we recorded the following: age; gender; duration of disease (expressed in days after diagnosis); thyroid volume by ultrasound; number of cervical lymph nodes, cervical level (I-VI), size (short-axis diameter, long-axis diameter, short axis: long axis-ratio), and presence or absence of fatty hilum; thyroid stimulating hormone (TSH) level; and dose of Levothyroxine (if applicable).

Statistical methods included Fisher's exact test for the categorical variables and two-tailed Student's *t*-test for the continuous variables. Statistical significance was set as (α=0.05). All the analyses were carried out using SAS 9.2 for Windows (SAS Institute Inc., Cary, NC, USA).

Results

Our population consisted of a total of 417 patients with thyroid disease. The study group included 202 patients with HT, and the control group included 215 patients with nontoxic goiter. Disease duration for documented HT averaged 861.59 days. Gender representation in the study population overall was 87.77% female (N=366).

In the group of 215 patients with nontoxic goiter females represented 86.98% (N=187), while in the HT group females represented 88.61% (N=179) for a total of 366 females out of 417 patients overall. In the HT group, mean age was 51.11±14.92 years while the control group's mean age was 53.90±14.91 years. There was no significant difference between the control group and the HT group in terms of age or gender distribution. These measurements are summarized in *Table 1*.

As expected, TSH levels were higher in the HT group (10.85±30.91 mIU/L HT group *vs.* 1.44±1.18 mIU/L controls, P<0.001). Mean right thyroid lobe volume as measured on ultrasound was 29.96±36.72 milliliters (mL)

Table 2 Diameter (mm), and S/L ratio of each level neck nodes in Hashimoto's thyroiditis and control groups

US characteristics	Hashimoto's group (N=202), mean ± SD	Control group (N=214), mean ± SD	P value
Level I nodes			
Long-axis diameter (mm)	11.15±5.00	8.93±6.44	0.11
Short-axis diameter (mm	5.45±3.23	2.32±2.80	0.007
S/L ratio	0.43±2.09	0.45±0.21	0.16
Level II nodes			
Long-axis diameter (mm)	11.68±10.99	10.50±4.53	0.41
Short-axis diameter (mm)	4.09±2.09	4.08±2.65	0.99
S/L ratio	0.43±2.09	0.42±2.65	0.92
Level III nodes			
Long-axis diameter (mm)	9.35±5.63	8.36±5.07	0.31
Short-axis diameter (mm)	3.53±1.86	3.27±2.47	0.61
S/L ratio	0.43±0.26	0.40±0.19	0.53
Level IV nodes			
Long-axis diameter (mm)	8.50±6.47	10.64±2.94	0.054
Short-axis diameter (mm)	4.19±3.19	3.86±1.57	0.92
S/L ratio	0.52±0.19	0.32±0.05	<0.001
Level V nodes			
Long-axis diameter (mm)	6.96±2.88	5.05±4.13	0.21
Short-axis diameter (mm)	3.00±1.62	2.52±1.84	0.56
S/L ratio	0.52±0.25	1.26±1.19	0.19
Level VI nodes			
Long-axis diameter (mm)	4.93±2.89	10.52±0.84	0.002
Short-axis diameter (mm)	2.95±1.54	7.70± (just 1 record)	<0.001
S/L ratio	0.72±0.10	0.75± (just 1 record)	0.58

S/L rato, short axis diameter/long axis diameter ratio; US, ultrasound.

in controls and 21.20±27.34 mL in the HT group (P=0.08). Mean left thyroid lobe volume as measured on ultrasound was 24.53±36.22 mL in controls and 17.09±23.17 mL in the study group. The left lobe volume as measured by ultrasound was significantly larger in the control group as compared to the study group (24.53±36.22 *vs.* 17.09±23.17 mL, P=0.034).

The average number of total enlarged nodes per patient identified on ultrasound in the control group was significantly lower than the HT population, 0.76±1.36 *vs.* 2.00±2.35 nodes (P<0.001). The mean number of nodes was significantly higher in Levels I, III, and IV: 0.09±0.32 nodes in the control group for Level I *vs.* 0.33±0.79 nodes in the HT group (P<0.001), at Level III 0.22±0.50 nodes in the control group *vs.* 0.63 nodes ±1.08 in the HT group (P<0.001), and at Level IV 0.06±0.25 nodes in the control group *vs.* 0.19±0.44 nodes in the HT group (P=0.044). The mean number of nodes at Levels II, V, and VI was not significantly different between the two groups. The mean number of nodes at Level II was 0.21±0.67 in the controls and 0.34±0.72 in the HT group; at Level V it was 0.04±0.21 in the controls and 0.08±0.32 in the HT group, and at Level VI it was 0.02±0.18 in the controls and 0.03±0.27 in the HT group.

Measurements in the Level IV compartment revealed a short-to-long axis ratio of 0.32±0.05 in the control group and 0.52±0.19 in the HT group, (P<0.001). All other lymph node measurements are listed in *Table 2*.

Node status was characterized as benign appearing in 92.91% of the control group (N=131) and 94.44% (N=306) of the HT group. Node status was characterized as suspicious for malignancy by ultrasonographic features in 7.09% (N=10) of the control group and 5.56% (N=18)

Table 3 Clinical and biochemical characteristics of Hashimoto's and control groups

Characteristics	Hashimoto's group	Control group	P value
Total number of neck nodes	2.00±2.35	0.76±1.36	<0.001
Nodes with hilus	3.36±2.00	2.11±1.43	0.53
Level I nodes	0.33±0.79	0.09±0.32	<0.001
Level II nodes	0.34±0.72	0.21±0.67	0.48
Level III nodes	0.63±1.08	0.22±0.50	<0.001
Level IV nodes	0.19±0.44	0.06±0.25	0.044
Level V nodes	0.08±0.32	0.04±0.21	0.66
Level VI nodes	0.03±0.27	0.02±0.18	0.43

of the HT group (P=0.53). Fatty hilum was identified on 3.36±2.00 lymph nodes per HT subject and 2.11±1.43 lymph nodes per goiter subject (P<0.001). These measurements are summarized in *Table 3*.

Discussion

Evaluation of lymph nodes is a critical component in the diagnosis of patients with thyroid pathology, particularly considering the frequency of co-existing benign and malignant disease and the propensity of malignant thyroid disease to metastasize to regional lymph nodes. Imaging modalities used to evaluate lymph nodes in the setting of thyroid disease must therefore have accurate, validated radiologic criteria for the differentiation of benign and malignant lymph nodes.

In this study, the aim was to evaluate size and number of cervical lymph nodes in HT to establish an accurate radiologic threshold. Lymph node size criteria for biopsy are commonly used for many malignancies of the head and neck, including thyroid cancers, although there is conflicting data regarding their accuracy (20,21). Because reactive lymph nodes and those involved in malignancy can be equal in size, importance must be placed on appropriately interpreting sonographic findings in context (22).

The association between many autoimmune disorders and enlarged lymph nodes demands a similar investigation into HT. The ultrasonographic patterns of lymphadenopathy in autoimmune thyroiditis may allow for the creation of size-driven cutoffs. Indeed, HT has been linked to an increased presence of benign hyperplastic lymphadenopathy (18,23). Our results are similar to a study that identified those paratracheal lymph nodes more often in patients with chronic autoimmune thyroiditis versus controls. Importantly, regional lymph nodes are known to be involved in early disease; activation of T cells in thyroid draining nodes precedes the clonal expansion of autoreactive T and B cells, while subsequently, lymphoid tissue often develops in the gland itself (5,24).

The benign lymphadenopathy common to autoimmune thyroiditis may mimic pathologies such as malignancy (25). Unnecessary and invasive interrogations of lymph nodes are often performed solely based on these characteristic histologic features of T-zone dysplasia with hyperplastic follicles, (1,26). In addition to size criteria for biopsy, suspicion for malignancy based on other morphologic features would likely increase the specificity of sonographic studies, reduce false positive results, and decrease unnecessary invasive procedures (20,27).

Previous studies of PTC metastases demonstrated frequent involvement of Levels II, III, and IV lymph node segments (28). This suggests that these lymph nodes may directly drain the gland, and would be the most likely to be involved in other benign thyroid pathology (29). In our study, lymph nodes in Levels III and IV showed a statistically significant increase in number identified over the control group. This is consistent with the proposed pattern of lymph nodal drainage seen in inflammatory thyroid disease. However, no significant difference in size of short- or long-axis was detected at any level of lymph node between the HT and control groups.

Biopsy of enlarged cervical lymph nodes based solely on size as a marker for potential malignancy is myopic and outdated; size is only one parameter that may be useful in the evaluation for thyroid cancer. Current accepted practice involves surveillance for well-differentiated thyroid malignancy, and observance for lymph nodes sized 5-8 mm with benign features on imaging (29). Benign lymph node features, such as fatty or echogenic hilum, may help guide further evaluation. These features are usually present in the

setting of inflammation and help to delineate malignant versus benign processes (30). In our study, Level IV demonstrated a large increase in the S/L ratio (P≤0.001) between the control and HT groups: 0.32±0.05 in the controls and 0.52±0.19 in the HT group. The clinician should note that, although this data is statistically significant, a difference of only 0.2 cm may be difficult to discern in the clinical setting.

Our data demonstrated no significant difference in S/L ratio between patients with HT and goiter at all other levels (20). Our knowledge of the pathogenesis of HT calls into question standard size-based cutoffs for biopsy, and a recent study supported this conclusion. In this study we showed that HT seems to be associated with an increased number of enlarged cervical lymph nodes, particularly in levels III, and IV. However, our data do not suggest any difference in size of lymph nodes at any level between patients with inflammatory versus non-inflammatory thyroid pathology.

A limitation of this study is that patients in the HT group were examined during different stages of the disease process. While all patients' diagnoses were confirmed on surgical pathology, not all had been treated with levothyroxine. As described above, the thyroid gland and lymph nodes in these patients undergoes inflammatory changes secondary to prolonged attack by the host immune system. It is less certain, however, if the levothyroxine therapy would lessen the inflammatory changes in the lymph nodes. It is also uncertain if the lymph nodes mimic the same fluctuations in size and inflammation as the thyroid gland throughout the course of the disease (31). To that end, it would be of benefit to have larger studies that stratify patients based on TSH level, a known marker of inflammatory status.

Conclusions

HT patients present with an increased number of enlarged cervical lymph nodes, seen mainly in levels III and IV. However, there is no significant increase in lymph node size or suspicious features.

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References

1. Caturegli P, De Remigis A, Rose NR. Hashimoto thyroiditis: clinical and diagnostic criteria. Autoimmun Rev 2014;13:391-7.
2. Vanderpump MP, Tunbridge WM, French JM, et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clin Endocrinol (Oxf) 1995;43:55-68.
3. Pearce EN, Farwell AP, Braverman LE. Thyroiditis. N Engl J Med 2003;348:2646-55.
4. Ahmed AM, Ahmed NH. History of disorders of thyroid dysfunction. East Mediterr Health J 2005;11:459-69.
5. Chistiakov DA. Immunogenetics of Hashimoto's thyroiditis. J Autoimmune Dis 2005;2:1.
6. Armengol MP, Juan M, Lucas-Martín A, et al. Thyroid autoimmune disease: demonstration of thyroid antigen-specific B cells and recombination-activating gene expression in chemokine-containing active intrathyroidal germinal centers. Am J Pathol 2001;159:861-73.
7. Slatosky J, Shipton B, Wahba H. Thyroiditis: differential diagnosis and management. Am Fam Physician 2000;61:1047-52, 1054.
8. Amani HK. Histopathologic and immunohistochemical features of Hashimoto thyroiditis. Indian J Pathol Microbiol 2011;54:464-71.
9. Pedersen OM, Aardal NP, Larssen TB, et al. The value of ultrasonography in predicting autoimmune thyroid disease. Thyroid 2000;10:251-9.
10. Lee JH, Anzai Y. Imaging of thyroid and parathyroid glands. Semin Roentgenol 2013;48:87-104.
11. Butch RJ, Simeone JF, Mueller PR. Thyroid and parathyroid ultrasonography. Radiol Clin North Am 1985;23:57-71.
12. Yeh HC, Futterweit W, Gilbert P. Micronodulation: ultrasonographic sign of Hashimoto thyroiditis. J Ultrasound Med 1996;15:813-9.
13. Anderson L, Middleton WD, Teefey SA, et al. Hashimoto thyroiditis: Part 1, sonographic analysis of the nodular form of Hashimoto thyroiditis. AJR Am J Roentgenol 2010;195:208-15.
14. Sahlmann CO, Meller J, Siggelkow H, et al. Patients with autoimmune thyroiditis. Prevalence of benign lymphadenopathy. Nuklearmedizin 2012;51:223-7.
15. Cunha LL, Ferreira RC, Marcello MA, et al. Clinical and pathological implications of concurrent autoimmune thyroid disorders and papillary thyroid cancer. J Thyroid Res 2011;2011:387062.
16. Jankovic B, Le KT, Hershman JM. Clinical Review: Hashimoto's thyroiditis and papillary thyroid carcinoma: is there a correlation? J Clin Endocrinol Metab

2013;98:474-82.
17. Stein SA, Wartofsky L. Primary thyroid lymphoma: a clinical review. J Clin Endocrinol Metab 2013;98:3131-8.
18. Serres-Créixams X, Castells-Fusté I, Pruna-Comella X, et al. Paratracheal lymph nodes: a new sonographic finding in autoimmune thyroiditis. J Clin Ultrasound 2008;36:418-21.
19. Paksoy N, Yazal K. Cervical lymphadenopathy associated with Hashimoto's thyroiditis: an analysis of 22 cases by fine needle aspiration cytology. Acta Cytol 2009;53:491-6.
20. Steinkamp HJ, Cornehl M, Hosten N, et al. Cervical lymphadenopathy: ratio of long- to short-axis diameter as a predictor of malignancy. Br J Radiol 1995;68:266-70.
21. van den Brekel MW, Castelijns JA, Snow GB. The size of lymph nodes in the neck on sonograms as a radiologic criterion for metastasis: how reliable is it? AJNR Am J Neuroradiol 1998;19:695-700.
22. Chan JM, Shin LK, Jeffrey RB. Ultrasonography of abnormal neck lymph nodes. Ultrasound Q 2007;23:47-54.
23. Brancato D, Citarrella R, Richiusa P, et al. Neck lymph nodes in chronic autoimmune thyroiditis: the sonographic pattern. Thyroid 2013;23:173-7.
24. Ahmed R, Al-Shaikh S, Akhtar M. Hashimoto thyroiditis: a century later. Adv Anat Pathol 2012;19:181-6.
25. Patel BN, Kamaya A, Desser TS. Pitfalls in sonographic evaluation of thyroid abnormalities. Semin Ultrasound CT MR 2013;34:226-35.
26. Kojima M, Nakamura S, Oyama T, et al. Autoimmune disease-associated lymphadenopathy with histological appearance of T-zone dysplasia with hyperplastic follicles. A clinicopathological analysis of nine cases. Pathol Res Pract 2001;197:237-44.
27. Lo CP, Chen CY, Chin SC, et al. Detection of suspicious malignant cervical lymph nodes of unknown origin: diagnostic accuracy of ultrasound-guided fine-needle aspiration biopsy with nodal size and central necrosis correlate. Can Assoc Radiol J 2007;58:286-91.
28. Eskander A, Merdad M, Freeman JL, et al. Pattern of spread to the lateral neck in metastatic well-differentiated thyroid cancer: a systematic review and meta-analysis. Thyroid 2013;23:583-92.
29. Stack BC Jr, Ferris RL, Goldenberg D, et al. American Thyroid Association consensus review and statement regarding the anatomy, terminology, and rationale for lateral neck dissection in differentiated thyroid cancer. Thyroid 2012;22:501-8.
30. Ahuja AT, Ying M. Sonographic evaluation of cervical lymph nodes. AJR Am J Roentgenol 2005;184:1691-9.
31. Korzeniowska K, Jarosz-Chobot P, Szypowska A, et al. L-thyroxine stabilizes autoimmune inflammatory process in euthyroid nongoitrous children with Hashimoto's thyroiditis and type 1 diabetes mellitus. J Clin Res Pediatr Endocrinol 2013;5:240-4.

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A cost analysis of thyroid core needle biopsy *vs*. diagnostic surgery

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Background: Twenty percent of thyroid fine needle aspiration (FNA) is indeterminate. Because 3 in 4 of these are actually benign, a method of clarifying the pathology could help patients to avoid diagnostic thyroidectomy. Recently, core needle biopsy (CNB) has been proven to be highly reliable for this purpose. However, there are no reports of any potential cost benefit provided by CNB. Here we analyzed the impact on management costs of CNB compared with traditional diagnostic surgery in indeterminate FNA.

Methods: Over 24 months, 198 patients with thyroid indeterminate cytology underwent CNB at Ospedale Israelitico of Rome or diagnostic surgery at the Department of Surgery of Sapienza University of Rome. We tabulated costs of the medical instruments, operating theater, surgical team, patient recovery, and pathologic examination for each method.

Results: In CNB group, 42.4% of patients had benign lesions and avoided surgery, 20.8% was cancer, and the remaining 36.8% uncertain. The malignancy rate in CNB group was 26.4%, and mean cost of CNB per nodule was 1,032€. In diagnostic surgery group, 24.7% had cancer and 75.3% had benign lesions, and mean expense for each thyroidectomy was 6,364€. In an ideal cohort of 100 patients with indeterminate FNA, the cost of CNB is 33.8% lower than that of diagnostic surgery.

Conclusions: CNB can detect a large proportion of the benign thyroid nodules that are classified as indeterminate by FNA. These patients can avoid diagnostic thyroidectomy and hospitals can reduce their surgical costs by one-third.

Keywords: Thyroid; core needle biopsy (CNB); surgery; cytology; cost-effectiveness

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Introduction

Cytology by fine needle aspiration (FNA) is used worldwide to evaluate both palpable and non-palpable thyroid nodules. It is highly accurate, reproducible, and cost effective (1,2). However, 20% of these biopsies are given the pathologic classification of indeterminate neoplasm (IN). These samples are classified as Thy-3 according to British Thyroid Association guidelines (3), Class 3 by American Association of Clinical Endocrinologists/Association Medici Endocrinology/European Thyroid Association guidelines (1), or Category III-IV using the Bethesda System for Reporting Thyroid Cytopathology (4), with the latter dividing the uncertain reports into two categories of cancer risk. The samples classified as IN represent the gray zone of FNA results, in which cytologic evaluation cannot discriminate benign from malignant neoplasia (5). Traditionally, patients with IN cytology have required diagnostic thyroidectomy (1,2), with about 3 in 4 nodules ultimately being ruled benign (6). A method that

will identify these benign nodules can help patients to avoid unnecessary surgery and is therefore highly desirable.

Over the last decade, there has been investigation into potential markers for benign thyroid lesions (6-10). Unfortunately, there are no clinical, molecular, cytologic, ultrasonographic, or scintigraphic features exclusively associated with benign neoplasia; these examinations are useful only for thyroid cancer risk stratification (6-11). Recently, however, core needle biopsy (CNB) has been identified as a highly reliable approach to thyroid diagnosis (12). CNB allows for microhistologic analysis of IN thyroid tissue, a more accurate evaluation than FNA cytology. Up to 98% of IN lesions are able to be classified as malignant or benign when CNB is used for follow-up analysis (13-19), allowing patients with benign nodules to avoid surgery. Although the popularity of CNB has risen worldwide, the potential cost benefit provided by its use has not yet been reported.

Our aim was to analyze the cost effectiveness of using CNB in patients with previous IN pathology on FNA.

Material and methods

Patients

Between January 2012 and December 2013, a consecutive series of 125 patients (101 females, 24 males; mean age, 46.4 years) underwent CNB at Ospedale Israelitico, Rome, Italy. Each patient had a single nodule, and all had previously undergone FNA with a result of IN. All cytologic examinations were conducted by an expert cytopathologist (LG). All microhistologic CNB specimens were evaluated by an experienced pathologist (AC).

During the same period, 73 consecutive patients (65 females, 8 males; mean age, 51.4 years) with IN cytology on FNA underwent diagnostic surgery at the Department of Surgical Sciences, Sapienza University, Rome.

The study was conducted according to the Declaration of Helsinki and was approved by institute ethical committee. Informed consent was obtained by all patients.

Cost analysis

All CNB procedures were performed in the outpatient surgery department. The overall cost for each patient included the price of two cutting needles (45€ each), other surgical instruments, the operating theater, the surgical team, and the cost of microhistologic examination. The cost of diagnostic surgery included all medical instruments and medications used for the procedure, patient recovery costs, the operating theater, the surgical team, and the cost of histologic examination.

We used our results to construct an ideal series of 100 patients with indeterminate thyroid nodules by FNA in order to estimate the potential impact on expenses of performing CNB *vs*. diagnostic surgery.

Statistical analysis

Means and standard deviations were compared using t-test. The rate of malignancy recorded in the two groups was compared using the chi-square test. All statistical analyses were performed using Graph Pad Prism (Graph Pad Software Inc., La Jolla, CA, USA).

Results

Core needle biopsy (CNB)

Of the 125 patients with FNA followed by CNB, 53 (42.4%) had benign lesions and were able to avoid surgery. A total of 26 patients (20.8%) had malignancy and were surgically treated. The remaining 46 patients (36.8%) had indeterminate results on CNB and underwent diagnostic surgery. Of these 46, a total of 7 had cancer. The overall rate of malignancy was 26.4% (n=33). The mean cost of CNB for a single nodule was 1,032€ (*Table 1*). In those patients with malignant or indeterminate results on CNB, the total cost included thyroidectomy.

Diagnostic surgery

Of the 73 patients who underwent diagnostic surgery, 18 (24.7%) had cancer and 55 (75.3%) had benign lesion. The mean recovery duration was 2.4 days, and the mean expense for each patient was 6,364€ (*Table 1*).

Comparison of the results

There was no significant difference in the rate of malignancy between the groups (26.4% in the CNB group and 24.7% in the diagnostic surgery group). The mean patient age and nodule size were no different between groups (*Table 2*). No operative difficulties were recorded in patients undergoing surgery after CNB.

Table 1 Comparison of costs deriving from diagnostic surgery or CNB performed in a single patient with previous indeterminate (Thy-3, Class-3, Category III-IV) thyroid nodule at FNA cytology

Variables	Diagnostic surgery	CNB
Medical instruments (needle, syringes, drugs, anesthetics, scalpels, etc.)	230	90
Operating theater	2,700	675
Operators (Medical Doctors)	558	93
Anesthetists	372	–
Nurses	144	18
Recovery	2,760	–
Histopathologic report*	175	125
Office visit control after the procedure	25	25
Total expense	6,364	1,032

–, costs are reported in Euros; *, fares from Italian Society of Anatomic Pathology and Cytology (SIAPEC). CNB, core needle biopsy; FNA, fine needle aspiration.

Table 2 Characteristics of the two groups included in the study

Characteristics	Diagnostic surgery	CNB
Patients	73	125
Females/males	65/8	101/24
Age	51.4	46.4
Rate of malignancy	24.7	26.4

CNB, core needle biopsy.

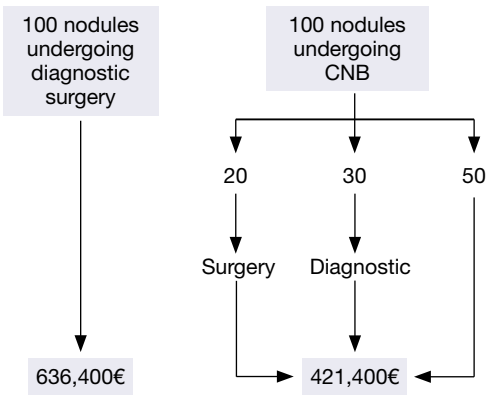

Figure 1 Total expense to diagnose and treat an ideal series of 100 nodules with previous indeterminate (Thy-3/Class 3/Category III-IV) FNA cytology by CNB and "diagnostic" surgery. FNA, fine needle aspiration; CNB, core needle biopsy.

Impact of CNB on treatment expense

The cost of a single CNB was lower than that of diagnostic surgery (*Table 1*). To compare the expense, we constructed an ideal cohort of 100 patients with IN cytology on FNA. Of these, 50 nodules would be benign, with patients able to avoid surgery. A total of 20 would be malignant and treated by thyroidectomy, and 30 patients would have indeterminate results on CNB and would require surgery for diagnosis. The total expense incurred by 100 patients submitting to CNB is 33.8% lower than the expense of diagnostic surgery, with a saving of 215,000€ (*Figure 1*).

Discussion

Cytological indeterminate nodules represent a major dilemma for thyroidologists. These lesions make up about 20% of thyroid cytology results, with 70-80% ultimately being determined benign. A large number of researchers have attempted, unsuccessfully, to discover molecular or clinical markers that are able to predict the likelihood of malignancy in patients with IN (6-11). Traditionally, thyroidectomy has been required to obtain a definite diagnosis, increasing costs in a large number of patients with benign nodules. Recently, CNB has been reported to be highly accurate in identifying the majority of benign nodules with prior uncertain cytology, allowing patients to avoid diagnostic thyroidectomy. This should theoretically reduce the expense associated with treatment. Furthermore, a very good prognosis has been reported for patients with thyroid cancers previously classified as indeterminate at cytology (20,21).

We reviewed a large series (198 patients) with indeterminate cytology that underwent different diagnostic approaches at two institutions. CNB had a much lower cost than routine diagnostic thyroidectomy, reducing the total surgical expense by about one-third. In Italy, 44,000 thyroidectomies are annually performed, with 11,000 of these patients diagnosed with malignancy. We may estimate that about 3,000 nodules are assessed as indeterminate at FNA each year. If all of these patients undergo diagnostic surgery, the cost would be about 19 million Euros; CNB would therefore allow a savings of about 6 million Euros. We did not take into account other expenses and consequences of surgery, such as lost work days, potential

postoperative complications, chronic treatment and follow-up of athyreotic patients, and hypocalcaemia. All of these may be avoided if benign pathology is able to be confirmed using CNB.

A combined performance of repeated FNA plus CNB might be considered in indeterminate lesions. Tow relevant studies (16,17) used that in large series of nodules, and the results showed that CNB has higher accuracy than repeated FNA, but the combination of the two biopsies improves the rate of diagnosis. This approach could reduce the number of thyroidectomies and save the expense to manage these patients.

Some limitations of the present study have to be addressed. First, here we reported a series of thyroid nodules enrolled over the period 2012-2013 and classified as indeterminate by current Italian reporting system. More recently, the latter guidelines, in agreement with international ones (4,22), suggested a sub-classification of the indeterminate lesions in two classes (i.e., TIR-3a and TIR-3b) which are associated with different malignancy risk (i.e., <10% and 15-30%, respectively) (23). The results of our study have to be confirmed in these sub-categories. In addition, incidental contralateral thyroid cancer cannot be excluded by CNB of a benign lesion. Also, a patient with a large symptomatic nodule may be selected for surgery regardless of benign results on CNB. Finally, our cost analysis was based on an ideal cohort of 100 patients; a prospective study is needed to confirm our results.

In conclusion, CNB can provide a definitive diagnosis in a large proportion of patients with indeterminate thyroid nodules by FNA cytology. Those patients with benign nodules can therefore avoid diagnostic thyroidectomy. The use of CNB reduces the cost of treatment by about one-third.

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References

1. Gharib H, Papini E, Paschke R, et al. AACE/AME/ETA Task Force on Thyroid Nodules. American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European Thyroid Association medical guidelines for clinical practice for the diagnosis and management of thyroid nodules: executive summary of recommendations. J Endocrinol Invest 2010;33:51-6.
2. Cooper DS, Doherty GM, Haugen BR, et al. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2006;16:109-42.
3. British Thyroid Association, Royal College of Physicians. Guidelines for the management of thyroid cancer (Perros P, ed) 2nd edition. Report of the Thyroid Cancer Guidelines Update Group. London: Royal College of Physicians, 2007.
4. Cibas ES, Ali SZ. The Bethesda System for Reporting Thyroid Cytopathology. Thyroid 2009;19:1159-65.
5. Baloch ZW, Sack MJ, Yu GH, et al. Fine-needle aspiration of thyroid: an institutional experience. Thyroid 1998;8:565-9.
6. Trimboli P, Treglia G, Guidobaldi L, et al. Clinical characteristics as predictors of malignancy in patients with indeterminate thyroid cytology: a meta-analysis. Endocrine 2014;46:52-9.
7. Bartolazzi A, Orlandi F, Saggiorato E, et al. Italian Thyroid Cancer Study Group (ITCSG). Galectin-3-expression analysis in the surgical selection of follicular thyroid nodules with indeterminate fine-needle aspiration cytology: a prospective multicentre study. Lancet Oncol 2008;9:543-9.
8. Saggiorato E, De Pompa R, Volante M, et al. Characterization of thyroid 'follicular neoplasms' in fine-needle aspiration cytological specimens using a panel of immunohistochemical markers: a proposal for clinical application. Endocr Relat Cancer 2005;12:305-17.
9. Trimboli P, Condorelli E, Catania A, et al. Clinical and ultrasound parameters in the approach to thyroid nodules cytologically classified as indeterminate neoplasm. Diagn Cytopathol 2009;37:783-5.
10. Treglia G, Caldarella C, Saggiorato E, et al. Diagnostic performance of (99m)Tc-MIBI scan in predicting the malignancy of thyroid nodules: a meta-analysis. Endocrine 2013;44:70-8.
11. Trimboli P, Treglia G, Sadeghi R, et al. Reliability of real-time elastography to diagnose thyroid nodules previously read at FNAC as indeterminate: a meta-analysis. Endocrine 2014. [Epub ahead of print].
12. Trimboli P, Crescenzi A. Thyroid core needle biopsy: taking stock of the situation. Endocrine 2015;48:779-85.
13. Park KT, Ahn SH, Mo JH, et al. Role of core needle biopsy and ultrasonographic finding in management of indeterminate thyroid nodules. Head Neck 2011;33:160-5.
14. Zhang S, Ivanovic M, Nemcek AA Jr, et al. Thin core needle biopsy crush preparations in conjunction with fine-needle aspiration for the evaluation of thyroid nodules: a complementary approach. Cancer 2008;114:512-8.

15. Screaton NJ, Berman LH, Grant JW. US-guided core-needle biopsy of the thyroid gland. Radiology 2003;226:827-32.
16. Sung JY, Na DG, Kim KS, et al. Diagnostic accuracy of fine-needle aspiration versus core-needle biopsy for the diagnosis of thyroid malignancy in a clinical cohort. Eur Radiol 2012;22:1564-72.
17. Na DG, Kim JH, Sung JY, et al. Core-needle biopsy is more useful than repeat fine-needle aspiration in thyroid nodules read as nondiagnostic or atypia of undetermined significance by the Bethesda system for reporting thyroid cytopathology. Thyroid 2012;22:468-75.
18. Nasrollah N, Trimboli P, Guidobaldi L, et al. Thin core biopsy should help to discriminate thyroid nodules cytologically classified as indeterminate. A new sampling technique. Endocrine 2013;43:659-65.
19. Nasrollah N, Trimboli P, Rossi F, et al. Patient's comfort with and tolerability of thyroid core needle biopsy. Endocrine 2014;45:79-83.
20. Trimboli P, Bongiovanni M, Rossi F, et al. Differentiated thyroid cancer patients with a previous indeterminate (Thy 3) cytology have a better prognosis than those with suspicious or malignant FNAC reports. Endocrine 2015;49:191-5.
21. Rago T, Scutari M, Latrofa F, et al. The large majority of 1520 patients with indeterminate thyroid nodule at cytology have a favorable outcome, and a clinical risk score has a high negative predictive value for a more cumbersome cancer disease. J Clin Endocrinol Metab 2014;99:3700-7.
22. Perros P, Boelaert K, Colley S, et al. British Thyroid Association. Guidelines for the management of thyroid cancer. Clin Endocrinol (Oxf) 2014;81:1-122.
23. Nardi F, Basolo F, Crescenzi A, et al. Italian consensus for the classification and reporting of thyroid cytology. J Endocrinol Invest 2014;37:593-9.

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Parathyroid cancer

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Abstract: Parathyroid carcinoma is an exceedingly rare endocrine malignancy first described in 1933. It accounts for between 0.5% and 5% of all cases of primary hyperparathyroidism. Parathyroid carcinoma is unusual among endocrine malignancies, being more hormonally active than its benign counterpart. Parathyroid carcinoma poses a diagnostic challenge both clinically and histologically due to the lack of features which can definitively distinguish malignant from benign disease early in its clinical course. Here, we describe the clinical features of the disease, and present the current opinion on optimal management. Further, we analyse the most recent histological advances made to aid in the diagnosis and management of this rare, but potentially devastating, disease.

Keywords: Parathyroid gland; parathyroid cancer; endocrine malignancy; primary hyperparathyroidism

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Introduction

Parathyroid carcinoma is an exceedingly rare endocrine malignancy first described by Sainton and Millot in 1933 (1,2). It accounts for between 0.5% and 5% of all cases of primary hyperparathyroidism (3-9). Further, it is the least commonly seen endocrine cancer worldwide (4). Parathyroid carcinoma is unusual among endocrine malignancies, being more hormonally active than its benign counterpart (10). Parathyroid carcinoma poses a diagnostic challenge both clinically and histologically due to the lack of features which can definitively distinguish malignant from benign disease early in its clinical course.

A high index of clinical suspicion in cases of severe primary hyperparathyroidism is therefore required to correctly diagnose parathyroid malignancy and thus offer patients complete primary excision of the parathyroid tumour and surrounding structures—the only known curative treatment. The diagnosis of parathyroid carcinoma is difficult to ascertain on initial histology with many cases being incorrectly labelled as benign. Metastases, occurring later in the disease process, are the only unequivocal criterion of malignancy. The course of parathyroid carcinoma is indolent but progressive with patients succumbing to the effects of uncontrolled hypercalcaemia associated with local recurrence and distant metastases rather than the effect of tumour load, often after a long period of disease-free survival (4).

Clinical presentation

While parathyroid adenomas show a female preponderance parathyroid carcinoma has an equal sex distribution with carcinoma patients being on average one decade younger than those with adenoma, usually in the fourth or fifth decade of life (8,11,12).

Parathyroid carcinoma commonly present with more severe hypercalcaemia than may be associated with primary hyperparathyroidism caused by benign parathyroid adenomas. This is due to the relatively higher levels of parathyroid hormone (PTH). While symptoms such as malaise, nausea, vomiting, mood disturbance and weight loss are largely common to all causes of hypercalcaemia, patients presenting with manifestations of parathyroid bone disease: osteitis fibrosa cystica, subperiosteal bone resorption, 'salt and pepper' skull, absence of lamina dura, diffuse osteopenia, osteoporosis, bone pain and pathological fracture should arouse suspicion of parathyroid carcinoma (3,4,13). In benign

parathyroid disease overt bone disease is unusual in the Western world; however of note is that historically primary hyperparathyroidism presented with large increases in serum calcium and target organ damage due to late presentation with the disease. In countries with poor healthcare infrastructure, therefore, the distinction between benign and malignant disease using the severity of symptoms can be challenging (3).

Concomitant bone and renal disease occurs in 50% of parathyroid carcinomas manifesting as nephrocalcinosis, reduced GFR and renal colic (4). However, completely asymptomatic presentation of parathyroid cancer has been reported in 7-46% of patients in several previous studies, making the symptoms of severe hypercalcaemia with renal involvement highly suggestive, but not a pre-requisite, for the suspicion of parathyroid carcinoma (4,14-16). A palpable neck mass is an additional indicator of the possibility of malignant disease occurring in 15-76% of malignancies and seldom in benign causes (4,5,13,15,17-20).

Laboratory testing

Laboratory testing of PTH and serum calcium aids diagnosis although there is no agreed threshold level for malignancy. Calcium levels in carcinoma are typically above 14 mg/dL *vs*. under 11.2 mg/dL in benign parathyroid disease. In fact PTH levels are typically 5-10 times higher than the upper range of normal while benign disease usually shows a more modest increase (4,14,17,18,20,21). Although severe hyperparathyroidism associated with a benign disease process is uncommon it is not unreported and elevated PTH therefore has not been shown to be statistically significant in the differentiation between benign and malignant disease. In addition to calcium levels, alkaline phosphatase (ALP) levels have been shown to be significantly higher in parathyroid carcinoma than in benign disease—with levels under 300 IU/L making carcinoma unlikely (16). Raised ALP reflects that action of PTH on the bone and it has been mooted by Bae *et al*. that as PTH causes loss of cortical bone before cancellous bone, a raise in ALP may be a useful diagnostic marker before skeletal manifestations such as fractures (16).

The measurement of human chorionic gonadotrophin (hCG) levels in parathyroid cancer is currently being researched. After the incidental finding of raised baseline serum hCG levels in patients with parathyroid cancer Rubin *et al*. found that persistently raised or increasing urinary hCG levels in parathyroid cancer correlate with a more aggressive stage of disease related to pathological fracture and death. This has led to the hypothesis that urinary hCG levels may have the potential to discriminate between benign and malignant parathyroid disease (22). This hypothesis is supported by Stock *et al*. who found elevations in alpha and beta sub-units of hCG which fell after surgical cure (23). Further investigation is required to delineate the role of hCG testing in the diagnosis and prognosis of parathyroid malignancy.

Non-functional parathyroid carcinoma

Non-functioning parathyroid carcinoma represents between 10% and 25% of parathyroid carcinomas (24). Although first reported by De Quervain in 1904 (25), non-functional parathyroid carcinoma remains an exceedingly rare malignancy with fewer than 30 cases reported in the literature worldwide (26,27). Symptoms are caused by local growth and invasion of surrounding tissues and patients succumb to systemic tumour burden rather than the effects of uncontrolled hypercalcaemia (8,26). Wilkins and Lewis have reported an older age range for non-functional parathyroid carcinomas with most patients presenting in their sixth or seventh decade (26). Neck mass at presentation is more common than with functional parathyroid carcinoma, with half of patients presenting with a neck mass between 5 and 11 cm in size (26).

Diagnosis in this case is based almost entirely on histological findings, metastases or local recurrence as patients are normocalcaemic at diagnosis with PTH and ALP in the normal range. A high proportion—up to 80%—present with a neck mass often associated with dysphagia, hoarseness or vocal cord paralysis and dyspnoea (4,20,26).They are often misdiagnosed as thyroid or thymic carcinoma due to the symptoms of locally advanced disease. Immunohistochemistry for PTH, thyroglobulin, thyroid transcription factor 1 and calcitonin can help to ascertain the correct diagnosis (3). Again adequate primary surgical excision is paramount with overall survival directly correlating with the margin status of the initial resection (28).

Predisposition

The aetiology of parathyroid carcinoma is largely unknown. Several authors have reported a potential role of previous neck irradiation and end-stage renal failure however the role is less clear for the development of parathyroid carcinoma than for benign parathyroid adenomas

(3,11,13,18,29-31). Increased risk of parathyroid carcinoma has been reported in association with hereditary syndromes of hyperparathyroidism, particularly hyperparathyroidism-jaw tumour (HPT-JT) syndrome. This is a rare autosomal disorder causing primary hyperparathyroidism and fibro-osseous lesions in the maxilla and mandible. In HPT-JT, approximately 15% of patients develop malignant parathyroid disease (8,32). Recently parathyroid malignancy has also been reported in association with multiple endocrine neoplasia (MEN) type 1 and MEN 2A (33-36).

Imaging

Imaging is useful, as in benign disease, for localisation of a tumour, but cannot reliably distinguish between benign and malignant disease. Ultrasound and 99m Tc-sestamibi scan are the most commonly employed diagnostic imaging studies utilised for parathyroid disease. Ultrasound provides general information on the size and location of the mass with tumours larger than 3 cm significantly more likely to constitute carcinoma than adenoma (37). Features including inhomogeneity, hypoechogenicity and irregularity of borders have been shown to correlate with malignancy, but these features may also be seen in benign parathyroid tumours (38). If carcinoma is a proposed differential diagnosis then a fine needle aspirate for cytology (FNAC) must be avoided due to the risk of seeding the tumour (39,40). Some authors have suggested that parathyroid carcinomas tend to be localised to the inferior glands; however, others have found no association with either the location or number of parathyroid glands involved and malignancy (9,16,27,41).

99m Tc-sestamibi scan enables the identification of abnormal and ectopic parathyroid tissue and is commonly used in the diagnosis of benign lesions (8,37). If malignancy is suspected, then higher resolution studies are of value (42). Contrast computed tomography (CT) can accurately localise the lesion and its relationship with or invasion into surrounding structures. Magnetic resonance imaging (MRI) with gadolinium and fat suppression provides the best imaging of the soft tissues of the neck (37). Both CT and MRI are commonly used when planning en-bloc resection of the lesion and surrounding structures. In the case of recurrent disease, MRI is considered superior as surgical clips in the surgical field can cause artefact when using CT (37).

FDG-PET has been used in cases of parathyroid adenoma, but there is little in the literature on its use in parathyroid cancer (43-45). Evangelista *et al.* in a case study used FDG-PET/CT as an additional imaging study in five patients with parathyroid cancer. Increased FDG uptake on the basis of suspicious CT changes not corresponding with physiological patterns of uptake were recorded as evidence of recurrence/metastases (37). The benefit of FDG-PET/CT is in its delivery of both anatomical and functional information allowing small tumour deposits to be detected but post-operative inflammation can cause false positive results limiting its use to a minimum of 3 to 6 months post-surgery (37). Due to the small number of studies neither the sensitivity nor specificity can be assessed but it may prove to be a useful tool in the early identification of metastases/recurrence (37,46,47). More recent studies have assessed the use of ^{11}C-choline and Fluorine-18-fluorodeoxyglucose as substrates for PET/CT studies. Early results are promising in identifying the parathyroid glands more accurately than standard FDG-PET/CT studies, although this has not yet been demonstrated specifically for parathyroid carcinoma (43,48).

Selective venous catheterisation and PTH measurement can be utilised if the above measures have failed to localise the lesion, however they are invasive (8).

Intra-operative diagnosis

As clinical features can be inconclusive in the differentiation between benign and malignant disease the intra-operative appearance of the tumour is a useful diagnostic tool. Intra-operative features which arouse suspicion of parathyroid carcinoma are a large (>3 cm), irregular firm mass, occasionally lobulated and usually surrounded by a dense fibrous capsule that gives it a white or grey-brown hue. Conversely adenomas are smaller, soft, round and red-brown in colour. Malignancies infiltrate and adhere to surrounding structures—commonly the ipsilateral thyroid and strap muscles, the ipsilateral recurrent laryngeal nerve, oesophagus and trachea (2,5). Lymph node metastases are present at operation in 3-19% of cases and distant metastases in 3-4% of patients (6,7,14,18-20). Surgeons do not recognise parathyroid cancer in up to 25% of cases—not surprising due to the rarity of the condition and often lack of pre-operative suspicion (49).

Frozen sections are not helpful in distinguishing benign from malignant disease. Excisional biopsy is not recommended due to the risk of intraoperative seeding of malignant tissue. Exploration of all four glands may be required as carcinoma of multiple glands has been documented in the literature, although there is no agreed consensus on this (50,51).

Histological diagnosis

Metastasis remains the only definitive marker of malignancy. No TNM staging system is available for parathyroid carcinoma firstly because the disease dose not uniformly metastasise to the lymph nodes and secondly because the size of the tumour does not appear to play a role in prognosis (1,18). The histological criteria for parathyroid carcinoma most commonly used is that established by Schantz and Castleman in 1973 based on the evaluation of 70 parathyroid carcinomas: presence of parenchymal mitoses, trabeculated parenchyma including thick fibrous band and capsular or vascular invasion (52). However, many of these features can also be observed in atypical parathyroid adenomas. Capsular or lymphovascular invasion remains the most specific marker of parathyroid carcinoma (4).

Neoplastic cells, generally chief cells, are arranged in a lobular pattern and separated by dense trabeculae, with mitotic figures. Invasion of the capsule is common; with vascular invasion less frequently noted (10-15%) (48). Capsular invasion is characterized by a 'tongue-like' protrusion though the collagenous fibres and should be distinguished from pseudoinvasion because of 'trapping' of tumour within the capsule which can be seen in adenomas (31).

Many of the features described by Schantz and Castleman—adherence to surrounding tissues, fibrous bands, trabecular growth and mitoses—are not pathognomonic of malignancy and can be found in parathyroid adenomas. The diagnostic value of vascular and capsular invasion is still debated (53,54). Interestingly, up to 50% of patients with metastatic parathyroid carcinomas were initially classified as benign on histology in a large study by Sandelin *et al*. (55). Therefore that distinction between benign and malignant parathyroid tumours is very difficult to make on initial histology meaning that histology is often inconclusive leaving a dilemma for the surgeon who has not performed an en-bloc excision whether to return to ensure clear margins or pursue a course of watchful waiting for recurrence and metastases. Some authors have suggested a watchful waiting approach in which reoperation is postponed until tumour recurrence (13,18). However insufficient excision is associated with higher rates of recurrence: one study citing local recurrence in 8% of en bloc resections versus 51% tumour excisions (19).

New tumour markers

Due to the difficulties with accurate differentiation between benign and malignant tumours on histology, recent research has been focused on identifying immunohistochemical tumour markers. Several oncogenes and tumour suppressor genes have been linked to parathyroid carcinoma (1). Loss of chromosome 13 has been reported by several authors. This deletion codes for the retinoblastoma (Rb) and hereditary breast carcinoma susceptibility (BRCA2) tumour suppressor genes (56-58). Immunohistochemical studies have shown loss of Rb immunostaining in parathyroid cancer (59). Cyclin D1 or parathyroid adenoma 1 (PRAD1) oncogene has been shown to be overexpressed in parathyroid carcinoma and so have also been proposed to play a role in the malignant transformation of parathyroid tumours (1).

HPT-JT syndrome has provided the best evidence for a defined gene in parathyroid malignancy. CDC73 gene mutations (formerly HRPT2)—is the gene responsible for HPT-JT syndrome and parathyroid cancer. Carcinoma occurs in 15% HPT-JT as opposed to under 1% of primary hyperparathyroidism (3). CDC73 mutations were found in 4/4 sporadic parathyroid carcinomas and 0/25 sporadic parathyroid adenomas by Howell *et al*. (33) Shattuck *et al*. found CDC73 mutations in 10/15 patients with parathyroid carcinoma (60). Cetani *et al*. identified the mutation in 9/11 parathyroid carcinomas and 0/4 sporadic atypical adenomas (30,35). Most of the mutations are nonsense and are predicted to result in the lack of or reduced protein expression of parafibromin protein. The prevalence of CDC73 mutations in parathyroid cancer may be as high as 76.6% (3). Germline mutations have been found in 1/3 of subjects suggesting that a subset of parathyroid cancer patients may have a HPT-JT syndrome (35,60,61). CDC73 mutations are found rarely in sporadic benign parathyroid adenomas as demonstrated by Carpten *et al*. finding CDC73 mutation in only 0.8% (1/120) cases of benign parathyroid adenoma (33,35,62,63). It has been proposed that CDC73 mutations may constitute an early event that may lead to parathyroid malignancies and that mutations in CDC73 mutations may be a marker of malignant potential in both familial and sporadic parathyroid carcinomas.

CDC73 encodes the protein parafibromin (parathyroid disease and fibro-osseous lesions). The idea of parafibromin as a tumour suppressor protein has arisen from the observation that parathyroid tumours carrying CDC73 mutations are frequently associated with the loss of parafibromin expression or function. It is hypothesised that after bi-allelic CDC73 inactivation the inhibitor effect of parafibromin on cyclin D1 activity is lost, leading to neoplastic transformation in susceptible tissue such as the

parathyroid glands (64).

CDC73 inactivation has been strongly linked with parathyroid carcinoma with the use of parafibromin as a marker. The loss of nuclear expression of parafibromin has been reported to be 96% specific and 99% sensitive in identifying parathyroid malignancies (65). Further studies have reported successful identification of malignancies using parafibromin however with lower specificity and sensitivities (61,66,67). Absent nuclear staining of parafibromin also characterises HPT-JT associated adenomas.

Without a gold standard test to identify parathyroid carcinoma a high index of suspicion for this rare malignancy is essential.

Treatment

Surgery

Most authors recommend en bloc excision at initial surgery as the only chance of cure (8). En bloc resection refers to the complete excision of the tumour with clear macroscopic margins, generally with ipsilateral thyroid lobe and normal ipsilateral parathyroid gland excision. If there is invasion of surrounding structures, such as the strap muscles, these should be incorporated into the resection. However, the difficulties inherent in the pre-operative and intra-operative diagnosis of parathyroid carcinoma mean that this opportunity for excision at initial surgery is often missed. Adequate surgical excision requires as a minimum the removal of the ipsilateral lobe of the thyroid (49,68,69); however, many authors recommend a more radical excision including the thyroid isthmus, skeletonisation of the trachea, and excision of any skeletal muscle intimately related to the tumour. The normal ipsilateral parathyroid gland should also be excised with the specimen. This extensive resection is not routinely performed (5).

It is imperative to avoid rupturing the tumour capsule due to the risk of seeding the surgical field. The recurrent laryngeal nerve is only resected if found to be involved and non-functioning—several authors recommending pre-operative assessment of vocal cord function to pre-empt the need for resection (8). Parathyroid carcinoma and adenoma may exist concurrently, so it has been suggested that all parathyroid glands be identified, and excised if necessary. However, there is no agreed consensus on four gland exploration: this point remains controversial. Regional lymph node dissection is indicated only if involvement suspected on pre-operative scanning or intra-operatively. Prophylactic neck dissection has been shown to have no effect on survival, but can increase morbidity (70).

Intra-operative PTH testing (rapid PTH test) has been shown to be useful, especially in surgically naïve patients, as PTH levels can fall significantly after resection of disease, but often not as rapidly as with the resection of benign disease in which PTH levels can normalise within 15 to 30 minutes. However, Givi and Shah have commented on the difficulty posed for the surgeon if levels do not decrease after excision has been completed either due to remaining unidentified tumour in the neck or metastatic disease (8).

Due to the rarity of the disease no prospective data regarding the initial surgical approach exists. Although strongly recommended in the literature, en-bloc resection at primary surgery is only performed in approximately 12-52% of cases (7,11,19). This is important as several studies have found that the recurrence rate in patients who have undergone en-bloc resection is 33% as opposed to 50% in patient who have undergone sub-optimal resection (19,49). Munson *et al*. have suggested that this group of patients may benefit from adjuvant radiotherapy treatment; however this is debated in the literature (28).

Patients are followed-up closely with serial PTH, calcium and ALP blood testing and ultrasound every 3 months. Calcium replacement is organised accordingly—most patients require intravenous calcium replacement soon post-operatively but can then be weaned onto oral calcium replacement and calcitriol (13).

With persistent or recurrent disease it is important to exclude metastases to the lung or bone prior to re-exploration of the neck. It is recommended that at least two non-invasive studies seeking distant metastases should be negative before re-exploration of the neck is planned. However, surgery for recurrent disease is generally palliative, for both relief of local pressure symptoms and for treatment of hypercalcaemia. There is little consensus in the literature as to how or when such surgery should be performed (13,21). Complications of both initial and especially subsequent neck exploration include: recurrent laryngeal nerve injury, transient and permanent hypoparathyroidism, oesophageal or tracheal injury and neck haematoma.

The localisation and treatment of distant disease, although not undertaken with a curative aim, can successfully improve symptoms and lower the serum calcium levels in 68-86% of cases from which the majority of parathyroid cancer patients succumb (14,21). Subsequent re-operations have lower success rates due to the rarity of the disease and its

indolent nature, survival benefit has not been definitively demonstrated with re-operation. Several authors have reported the palliative effect of decreasing tumour burden and improving symptoms by lowering serum calcium levels.

Radiotherapy

Parathyroid carcinoma has been generally believed to be insensitive to radiotherapy for either primary or metastatic disease, but several recent case series have suggested that adjuvant radiotherapy may reduce the incidence of local recurrence and increase disease-free survival (14,15,28). Research from M. D. Anderson has shown that local recurrence appears to be lower if adjuvant radiotherapy is given after initial surgery independent of the type of surgery and the stage of the disease (1). It is difficult to assess the efficacy of adjuvant radiotherapy as many patients have long disease-free intervals after parathyroidectomy alone and the numbers included in these studies are small, however there may be a role of adjuvant radiotherapy in parathyroid cancer (8).

Other treatments

Chemotherapy has not been demonstrated to be beneficial in parathyroid carcinoma. Although short-term responses have been demonstrated with single-agent dacarbazine (70) and combination chemotherapy with flurouracil, cyclophosphamide and dacarbazine in patients with metastatic disease but no survival benefit was shown (71). Reports of response remain limited to case reports (72).

Radiofrequency ablation therapy has been used to treat multiple unresectable metastases in the lung (1,73). A combination of RFA and transcatheter arterial embolization has been used to treat multiple metastatic lesions in the liver (74). Both reports showed improvement in serum calcium and PTH levels. Recurrent disease in the neck has been treated with ultrasound-guided percutaneous alcohol injection and short-term improvements in calcium and PTH levels (75).

Medical treatment

Major morbidity and death in patients with parathyroid carcinoma is due to uncontrolled hyercalcaemia and not tumour burden. Medical management is the mainstay of treatment in patients awaiting surgical intervention and those with unresectable disease. Urgent management with intravenous rehydration and bisphosphonates although initially often effective in decreasing serum calcium levels become less efficacious with subsequent treatments. Oral bisphosphonates have been found to have no effect in parathyroid cancer. Calcitonin can decrease serum calcium but is only transiently effective. Octreotide (long-acting somatostatin analogue) has also been shown to be effective in limited numbers of patients in decreasing PTH levels (76,77).

Calcimimetics have emerged as a more effective treatment than bisphosphonates in controlling hypercalcaemia. Calcimimetics are allosteric modulators of the parathyroid calcium-sensing receptor and act by binding to these receptors and increasing their sensitivity to extracellular calcium (8,78-81). This causes a decrease in PTH secretion by parathyroid cells. Second generation calcimimetic cinacalcet has been shown to decrease serum calcium by 1 mg/dL in 62% of patients. The greatest decrease in calcium levels was seen in those with the highest starting calcium levels. However despite the decreases in serum calcium levels there was no significant decrease in PTH which remains unexplained (79). Cinacalcet has the added advantage of safe usage in patients with chronic renal sufficiency which effects 84% patients with recurrent disease (82). Most of patients tolerated the drug well with nausea and vomiting being the most common side-effect. If ineffective, dialysis against a low-calcium dialysate is necessary (82).

Immunotherapy targeting PTH has been reported. Immunisation with synthetic human and bovine PTH peptides results in production of anti-PTH antibodies and has been shown to decrease serum calcium by more than 1 mmol/L in a patient with parathyroid cancer and unresectable metastases (83). Tumour shrinkage in addition to an improvement in serum calcium and PTH has been demonstrated in another patient (84). However immunotherapy remains largely experimental and results are limited to case studies.

Denosumab, a monoclonal antibody targeting the receptor activator of nuclear factor kappa-b ligand with potent anti-resorptive actions in bone, will be tested for efficacy in controlling the hypercalcaemia seconday to parathyroid cancer (85).

Recurrence

Recurrence is very common in parathyroid carcinoma with 25-100% of patients cited as developing local recurrence after surgery, most studies citing 50% (49). Recurrence is

detected on average 2-4 years after the initial operation and these patients have a mean survival of 5-6 years after the initial diagnosis (4,14,15,17-19,21,70). Approximately 25% of patients develop distant metastases at some stage of the disease. Distant metastases are rarely present at initial diagnosis. Metastases have been documented as long as 20 years after first diagnosis (13,86). Five-year survival rate from case series and registry are fairly consistent at 76-85% and 10-year survival rates range from 49-77% (7,11,15,21).

Recurrence presents as a slowly increasing PTH and serum calcium level. The most common sites of metastases are to cervical lymph nodes (30%), lungs (40%) and liver (10%) via both haematogenous and lymphatic routes (87). The localisation of metastases is undertaken using the techniques for identifying the initial disease. Ultrasound is effective in localising local metastases to lymph nodes in the neck. Sestamibi scans can localise both local and distant metastases. If further surgical intervention is planned CT and MRI scans are undertaken.

Resectable disease, either local or distant is managed surgically as removal of functioning tumour offers best control of hypercalcaemia (13,21). As a result of this multiple operations to remove maximal amount of tumour are often justified as a palliative measure. Morbidity associated with multiple surgical interventions is cited to be as low as 6.9% (if sacrifice of the recurrent laryngeal nerve is excluded) (21). Patients require on average two to three operations during the course of their disease (8). Decreasing the tumour burden reduces the levels of PTH and calcium therefore lessening the symptoms of hypercalcaemia. Although effective in offering symptomatic relief, the surgical resection of metastases rarely offers the chance of cure (88).

Reports in which the initial treatment was en bloc excision have a longer survival and a longer disease-free period than patients treated with tumour excision alone (70). Reports have shown that 28-50% of patients remain alive with no recurrence at follow-up (14,18,19,48). Although surgery, adjuvant radiotherapy, radio-frequency ablation and calcimimetics have shown responses to clinical parameters there is insufficient information to determine the effect on survival. Prognosis appears to be worse in non-functional parathyroid carcinoma as local invasion and distant metastases are more likely at the time of diagnosis (20,26).

Prognosis

Parathyroid cancer follows a progressive course in which the tumour invades surrounding structures, local lymph nodes and also haematogenously to the lungs, liver and skeleton. The most important factor in prognosis is the completeness of the initial surgical resection, dependant on pre-operative suspicion of parathyroid cancer. Survival rates for complete excision at initial operation have been cited as up to 90% at 5 years and 67% at 10 years (89). Poor prognostic indicators include lymph node metastases at initial presentation, distant metastases and non-functioning parathyroid carcinoma (19). Clayman *et al*. have suggested males under 45 years old with higher calcium levels (>13 mg/dL) have a more aggressive disease process (1). Recurrence of 25-100% has been cited with a general consensus of 50% of patients developing recurrence after surgical excision (4,49). Once recurrence has occurred then the chances of cure are remote and treatment is generally focused on surgical intervention to decrease tumour burden for symptomatic control and medical control of hypercalcaemia in the case of unresectable disease.

Summary

Designing clinical trials for new treatments is very challenging due to the rarity of parathyroid cancer. Recently increased research into the molecular biology of parathyroid cancer may enable the *CDC73* gene to be targeted for new therapeutic options. However, currently a high index of suspicion for this rare malignancy and adequate en-bloc excision of the tumour at initial surgery offer the best chance of cure and elongated disease-free survival in parathyroid cancer.

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References

1. Clayman GL, Gonzalez HE, El-Naggar A, et al. Parathyroid Carcinoma: Evaluation and Interdisciplinary Management. Cancer 2004;100:900-5.
2. Sainton P, Millot J. Malegne dun adenoma parathyroidiene eosinophile; au cours de Recklinghausen. Annales Anatomie Pathologique 1933;10:813.
3. Marococci C, Cetani F, Rubin MR, et al. Parathyroid carcinoma. J Bone Miner Res 2008;23:1869-80.
4. Sharretts JM, Kebebew E, Simonds WF. Parathyroid cancer. Semin Oncol 2010;37:580-90.

5. Holmes EC, Morton DL, Ketcham AS. Parathyroid carcinoma: a collective review. Ann Surg 1969;169:631-40.
6. Fujimoto Y, Obara T, Ito Y, et al. Surgical treatment of ten cases of parathyroid carcinoma: importance of an initial en bloc tumor resection. World J Surg 1984;8:392-400.
7. Lee PK, Jarosek SL, Virnig BA, et al. Trends in the incidence and treatment of parathyroid cancer in the United States. Cancer 2007;109:1736-41.
8. Givi B, Shah JP. Parathyroid Carcinoma. Clin Oncol (R Coll Radiol) 2010;22:498-507.
9. Cohn K, Silverman M, Corrado J, et al. Parathyroid carcinoma: the Lahey Clinic experience. Surgery 1985;98:1095-1100.
10. Ricci G, Assenza M, Barreca M, et al. Parathyroid carcinoma: the importance of high clinical suspicion for a correct management. Int J Surg Oncol 2012;2012:649148.
11. Hundahl SA, Flemming ID, Fremgen AM, et al. Two hundred eighty-six cases of parathyroid carcinoma treated in the U.S. between 1985-1995: a National Cancer Data Base Report. The American College of Surgeons Commission on Cancer and the American Cancer Society. Cancer 1999;86:538-44.
12. Rawat N, Khetan N, Williams DW, et al. Parathyroid carcinoma. Br J Surg 2005;92:1345-53.
13. Shane E. Clinical review 122: Parathyroid carcinoma. J Clin Endocrinol Metab 2001;86:485-93.
14. Wynne AG, van Heerden J, Carney JA, et al. Parathyroid carcinoma: clinical and pathologic features in 43 patients. Medicine 1992;71:197-205.
15. Busaidy NL, Jimenez C, Habra MA, et al. Parathyroid carcinoma: a 22-year experience. Head Neck 2004; 26:716-26.
16. Bae JH, Choi HJ, Lee Y, et al. Preoperative predictive factors for parathyroid carcinoma in patients with primary hyperparathyroidism. J Korean Med Sci 2012;27:890-5.
17. Shane E, Bilezikian JP. Parathyroid carcinoma: a review of 62 patients. Endocr Rev 1982;3:218-26.
18. Obara T, Fujimoto Y. Diagnosis and treatment of patients with parathyroid carcinoma: an update and review. World J Surg 1991;15:738-44.
19. Koea JB, Shaw JH. Parathyroid cancer: biology and management. Surg Oncol 1999;8:155-65.
20. Fernandez-Ranvier GG, Khanafshar E, Jensen K, et al. Parathyroid carcinoma, atypical parathyroid adenoma, or parathyromatosis? Cancer 2007;110:255-64.
21. Kebebew E, Arici C, Duh QY, et al. Localization and reoperation results for persistent and recurrent parathyroid carcinoma. Arch Surg 2001;136:878-85.
22. Rubin MR, Bilezikian JP, Birken S, et al. Human chorionic gonadotropin measurements in parathyroid carcinoma Eur J Endocrinol 2008;159:469-74.
23. Stock JL, Weintraub BD, Rosen SW, et al. Human chorionic gonadotropin subunit measurement in primary hyperparathyroidism. J Clin Endocrinol Metab 1982;54:57-63.
24. Piciu D, Irime A, Kontogeorgos G, et al. Highly aggressive pathology of non-functional parathyroid carcinoma. Orphanet J Rare Dis 2013;8:115-20.
25. De Quervain F. Parastruma maligna aberrata. Deutsche Zeitschr Chir 1904;100:334-52.
26. Wilkins BJ, Lewis JS. Non-functional parathyroid carcinoma: a review of the literature and report of a case requiring extensive surgery. Head Neck Pathol 2009;3:140-9.
27. Giessler GA, Beech DJ. Nonfunctional parthyroid carcinoma. J Natl Med Assoc 2001;93:251-5.
28. Munson ND, Foote RL, Northcutt RC, et al. Parathyroid carcinoma: is there a role for adjuvant radiation therapy? Cancer 2003;98:2378-84.
29. Favia G, Lumachi F, Polistina F, et al. Parathyroid carcinoma: sixteen new cases and suggestions for correct management. World J Surg 1998;22:1225-30.
30. Cetani F, Pardi E, Banti C, et al. HRPT2 gene analysis and diagnosis of parathyroid carcinoma. Expert Rev Endocrinol Metab 2008;3:377-89.
31. DeLellis RA. Parathyroid carcinoma: an overview. Adv Anat Pathol 2005;12:53-61.
32. Chen JD, Morrison C, Zhang C, et al. Hyperparathyroidism-jaw tumour syndrome. J Intern Med 2003;253:634-42.
33. Howell VM, Haven CJ, Kahonski K, et al. HRPT2 mutations are associated with malignancy in sporadic parathyroid tumours. J Med Genet 2003;40:657-63.
34. Shattuck TM, Kim TS, Costa J, et al. Mutational analysis of RB and BRCA2 as candidate tumour suppressor genes in parathyroid carcinoma. Clin Endocrinol (Oxf) 2003;59:180-9.
35. Cetani F, Pardi E, Viacava P, et al. A reappraisal of the Rb1 gene abnormalities in the diagnosis of parathyroid carcinoma. Clin Endocrinol (Oxf) 2004;60:99-106.
36. Jenkins PJ, Satta MA, Simmgen M, et al. Metastatic parathyroid carcinoma in the MEN2A syndrome. Clin Endocrinol 1997;47:747-51.
37. Evangelista L, Sorgato N, Torresan F, et al. FDG-PET/CT and parathyroid carcinoma: Review of literature and illustrative case series. World J Clin Oncol 2011;2:348-54.

38. Hara H, Igarashi A, Yano Y, et al. Ultrasonic features of parathyroid carcinoma. Endocr J 2001;48:213-7.
39. Agarwal G, Dhingra S, Mishra SK, et al. Implantation of parathyroid carcinoma alone fine needle aspiration track. Langenbecks Arch Surg 2006;391:623-6.
40. Spinelli C, Bonadio AG, Berti P, et al. Cutaneous spreading of parathyroid carcinoma after fine needle aspiration cytology. J Endocrinol Invest 2000;23:255-7.
41. Busaidy N, Jimenez C, Habra MA, et al. Two decades of experience with parathyroid carcinoma. Proc Am Soc Clin Oncol 2003;22:516.
42. Fraker DL. Update on the management of parathyroid tumours. Curr Opin Oncol 2000;12:41-8.
43. Gardner CJ, Wieshmann H, Gosney J, et al. Localisation of metastatic parathyroid carcinoma by 18F FDG PET scanning. J Clin Endocrinol Metab 2010;95:4844-5.
44. Neumann DR, Esselstyn CB, Siciliano D, et al. Preoperative imaging of parathyroid carcinoma by positron emission tomography. Ann Otol Rhinol Laryngol 1994;103:741-5.
45. Arslan N, Rydzewski B. Detection of a recurrent parathyroid carcinoma with FDG positron emission tomography. Clin Nucl Med 2002;27:221-2.
46. Neumann DR, Esselstyn CB, Kim EY. Recurrent postoperative parathyroid carcinoma: FDG-PET and sestamibi-SPECT findings. J Nucl Med 1996;37:2000-1.
47. Neumann DR, Esselstyn CB, MacIntyre WJ, et al. Regional body FDG-PET in postoperative recurrent hyperparathyroidism. J Comput Assist Tomogr 1997;21:25-8.
48. Orevi M, Freedman N, Mishani E, et al. Localization of parathyroid adenoma by 11C-choline PET/CT: preliminary results. Clin Nucl Med 2014;39:1033-8.
49. Kebebew E. Parathyroid carcinoma. Curr Treat Options Oncol 2001;2:347-354.
50. Sahasranam P, Tran MT, Mohamed H, et al. Multiglandular parathyroid carcinoma: a case report and brief review. South Med J 2007;100:841-4.
51. Kameyama K, Takami H. Double parathyroid carcinoma. Endocr J 2003;50:477-9.
52. Schantz A, Castleman B. Parathyroid carcinoma. A study of 70 cases. Cancer 1973;31:600-5.
53. Smith JF, Coombs RR. Histological diagnosis of carcinoma of the parathyroid gland. J Clin Pathol 1984;37:1370-8.
54. Tamler R, Lewis MS, LiVolsi VA, et al. Parathyroid carcinoma: ultrasonographic and histologic features. Thyroid 2005;15:744-5.
55. Sandelin K, Tulllgren O, Farnebo LO. Clinical course of metastatic parathyroid cancer. World J Surg 1994;18:594-8.
56. Cryns VL, Thor A, Xy HJ. Loss of the retinoblastoma tumor-suppressor gene in parathyroid carcinoma. N Engl J Med 1994;330:757-61.
57. Yoshimoto K, Endo H, Tsuyuguchi M, et al. Familial isolated primary hyperparathyroidism with parathyroid carcinomas: clinical and molecular features. Clin Endocrinol (Oxf) 1998;48:67-72.
58. Pearce SH, Trump D, Wooding C, et al. Loss of heterozygosity studies at the retinoblastoma and breast cancer susceptibility (BRCA2) loci in pituitary, parathyroid, pancreatic and carcinoid tumors. Clin Endocrinol Oxf) 1996;45:195-200.
59. Subramaniam P, Wilkinson S, Shepherd JJ. Inactivation of retinoblastoma gene in malignant parathyroid growths: a candidate genetic trigger? Aust N Z J Surg 1995;65:714-6.
60. Shattuck TM, Valimaki S, Obara T, et al. Somatic and germline mutations of the HRPT2 gene in sporadic parathyroid carcinoma. N Engl J Med 2003;349:1722-9.
61. Cetani F, Ambrogini R, Viacava P, et al. Should parafibromin staining replace HRPT2 gene analysis as an additional tool for histologic diagnosis of parathyroid carcinoma? Eur J Endocrinol 2007;156:547-54.
62. Krebs LJ, Shattuck TM, Arnold A. HRPT2 mutational analysis of typical sporadic parathyroid adenomas. J Clin Endocrinol Metab 2005;90:5015-7.
63. Carpten JD, Robbins CM, Villablanca A, et al. HRTP2, encoding parafibromin, is mutated in hyperparathyroidism-jaw tumor syndrome. Nat Genet 2002;32:676-80.
64. Woodard GE, Lin L, Zhang JH, et al. Parafibromin, product of the hyperparathyroidism-jaw tumor syndrome gene HRPT2, regulates cyclin D1/PRAD1 expression. Oncogene 2005;24:1272-6.
65. Tan MH, Morrison C, Wang P, et al. Loss of parafibromin immunoreactivity is a distinguishing feature of parathyroid carcinoma. Clin Cancer Res 2004;10:6629-37.
66. Juhlin CC, Villablanca A, Sandelin K, et al. Parafibromin immaunorectivity: its use as an additional diagnostic marker for parathyroid tumor classification. Endocr Relat Cancer 2007;14:501-12.
67. Gill AJ, Clarkson A, Grimm O, et al. Loss of nuclear expression of parafibromin distinguishes parathyroid carcinomas and hyperparathyroidism-jaw tumor (HPT-JT) syndrome-related adenomas from sporadic parathyroid adenomas and hyperplasias. Am J Surg Pathol 2006;30:1140-9.
68. Hoelting T, Weber T, Werner J, et al. Surgical treatment

of parathyroid carcinoma. Oncol Rep 2001;8:931-4.
69. Shortell CK, Andrus CH, Phillips CE Jr, et al. Carcinoma of the parathyroid gland: a 30-year experience. Surgery 1991;110:704-8.
70. Sandelin K, Auer G, Bondeson L, et al. Prognostic factors in parathyroid cancer: a review of 95 cases. World J Surg 1992;16:724-31.
71. Calandra DB, Chejfec G, Foy BK, et al. Parathyroid carcinoma: biochemical and pathologic response to DTIC. Surgery 1984;96:1132-7.
72. Bukowski RM, Sheeler L, Cunningham J, et al. Successful combination chemotherapy for metastatic parathyroid carcinoma. Arch Intern Med 1984;144:399-400.
73. Tochio M, Takaki H, Yamakado K, et al. A case report of 20 lung radiofrequency ablation sessions for 50 lung metastases from parathyroid carcinoma causing hyperparathyroidism. Cardiovasc Intervent Radiol 2010;33:657-9.
74. Artinyan A, Guzman E, Maghami E, et al. Metastatic parathyroid carcinoma to the liver treated with radiofrequency ablation and transcatheter arterial embolization. J Clin Oncol 2008;26:4039-41.
75. Montenegro FL, Chammas MC, Juliano AG, et al. Ethanol injection under ultrasound guidance to palliate unresectable parathyroid carcinoma. Arq Bras Endocrinol Metabol 2008;52;707-11.
76. Koyano H, Shishiba Y, Shimizu T, et al. Successful treatment by surgical removal of bone metastasis producing PTH: new appeoach to the management of metastatic parathyroid carcinoma. Intern Med 1994;33:697-702.
77. Denney AM, Watts NB. The effect of octreotide on parathyroid carcinoma. J Clin Endocrinol Metab 2004;89:1016.
78. Szmuilowicz ED, Utiger RD. A case of parathyroid carcinoma with hypercalcaemia responsive to cinacalcet therapy. Nat Clin Pract Endocrinol Metab 2006;2:291-6.
79. Silverberg SJ, Rubin MR, Faiman C, et al. Cinacalcet hydrochloride reduces the serum calcium concentration in inoperable parathyroid carcinoma. J Clin Endocrinol Metab 2007;92:3803-8.
80. Collins MT, Skarulis MC, Bilezikian JP, et al. Treatment of hypercalcaemia secondary to parathyroid carcinoma with a novel calcimimetic agent. J Clin Endocrinol Metab 1998;83:1083-8.
81. Nemeth EF, Steffey ME, Hammerland LG, et al. Calcimimetics with potent and selective activity on the parathyroid calcium receptor. Proc Natl Acad Sci U S A 1998;95:4040-5.
82. Witteveen JE, Haak HR, Kievit J, et al. Challenges and pitfalls in the management of parathyroid carcinoma: 17-year follow-up of a case and review of the literature. Horm Cancer 2010;1:205-14.
83. Bradwell AR, Harvey TC. Control of hypercalcaemia of the parathyroid carcinoma by immunisation. Lancet 1999;353:370-3.
84. Betea D, Bradwell AR, Harvey TC, et al. Hormonal and biochemical normalization and tumor shrinkage induced by anti-parathyroid hormone immunotherapy in a patient with metastatic parathyroid carcinoma. J Clin Endocrinol Metab. 2004;89:3413-20.
85. Lumachi F, Brunello A, Roma A, et al. Cancer-induced hypercalcaemia. Anticancer Res 2009;29:1551-5.
86. Hundley JC, Albertson DA, Bradley RF, et al. Resection of pulmonary metastasis from parathyroid carcinoma. Am Surg 2003;69:779-83.
87. Hakaim AG, Powsner R, Cho SI. Parathyroid carcinoma: 50-year experience at The Cleveland Clinic Foundation. Cleve Clin J Med 1993;60:331-5.
88. Flye MW, Brennan MF. Surgical resection of metastatic parathyroid carcinoma. Ann Surg 1981;193:425-35.
89. Kleinpeter KP, Lovato JF, Clark PB, et al. Is parathyroid carcinoma indeed a lethal disease? Ann Surg Oncol 2005;12:260-6.

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Different surgical approaches in parathyroid adenoma resections

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Abstract: Three patients were referred to our clinic for the management of a persistent symptomatic primary hyperparathyroidism. Pre-operative imageological localization revealed evidence of an adenoma. Here we are presenting three video demonstrating the different surgical approaches of parathyroid adenoma resection, with the use of an intraoperative gamma probe and nerve monitoring.

Keywords: Video-assisted thoracoscopic approach parathyroidectomy; robotic trans-axillary parathyroidectomy; remote access parathyroidectomy; scarless parathyroidectomy

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The first patient presented is a 76-year-old that had previously undergone two prior parathyroid surgeries, presented to our clinic with an elevated calcium and parathyroid hormone (PTH) level (*Figure 1*). A Tc-99m sestamibi-computed tomography scan was performed which revealed a mass in the anterior mediastinum consistent with a parathyroid adenoma. We subsequently performed a radioguided parathyroidectomy via video-assisted thoracoscopic surgery (VATS) with the use of three ports. An intraoperative gamma probe and nerve monitoring was used to assist the exploration and localization of the adenoma. Circumferential dissection and resection was performed with the use of simple electrocautery. No further elevations in gamma counts were noted on inspection of the mediastinum. Intraoperative PTH testing was used to confirm cure. Since the intraoperative PTH levels confirmed surgical cure, the operation was terminated. The patient was followed for one year postoperatively and had remained eucalcemic. In conclusion, radioguided parathyroidectomy via VATS combined with intraoperative PTH testing is an effective approach for patients with ectopic mediastinal parathyroid adenomas (2).

The second patient underwent a robotic transaxillary resection of a retroesophageal parathyroid adenoma in the thymus (*Figure 2*). The patient was placed in a supine position on the operating room table, and a wedge was placed under the patient's shoulder blades to allow slight hyperextension of the neck. The patient's ipsilateral arm was positioned so that the shoulder was flexed to approximately 160°, and internally rotated. The elbow was flexed to approximately 90°. The upper arm was positioned parallel to the head, and the forearm was placed immediately superior to the head (4,5).

Located on the contralateral operative side, the center console of the da Vinci Si system was aligned to the level of the thyroid gland. A 5-6-cm longitudinal incision was made along the outer border of the pectoralis major muscle. The avascular plane between the sternal and clavicular heads of the sternocleidomastoid muscle was identified and separated. The lateral border of the strap musculature was raised off the anterior surface of the thyroid parenchyma and extended cranially to the level of the cricothyroid cartilage and inferiorly to the lower border of the inferior pole. The robot was positioned over the patient, and the robotic arms were extended to attain maximal range of motion. A 5-mm curved harmonic scalpel, a 5-mm Maryland retractor, and an 8-mm Prograsp dissector were secured into the robotic arms. The arms were aligned along the incision while keeping the robotic arms maximally separated. The camera was placed at the inferior border of the incision directly below the bladed retractor at a 20° angle pointed downward. The camera and instruments were

Figure 1 Video-assisted thoracoscopic approach parathyroidectomy (1). Available online: http://www.asvide.com/articles/192

Figure 2 Robotic transaxillary resection of retro-esophageal parathyroid adenoma in thymus (3).
Available online: http://www.asvide.com/articles/193

deployed under direct visualization. The assistant surgeon also maintained a clear field with laparoscopic suction as needed. The parathyroid adenoma was identified in the inferior pole of the left thyroid lobe. The console surgeon then proceeded to perform a parathyroid adenoma resection robotically in a conventional fashion. The specimen was removed with a laparoscopic grasper through the axilla. The function of the nerve was confirmed intraoperatively using an extended tip nerve monitor (6,7). Intraoperative PTH testing was used to confirm cure. The patient remained eucalcemic one year postoperatively.

The third patient presented underwent radioguided parathyroidectomy for a parathyroid adenoma in the retroesophageal groove (8) (*Figure 3*). Intraoperative ultrasound was used to mark the incision superficial to the adenoma. A 1-inch incision was made at the base of the

Figure 3 Radio-guided parathyroidectomy for retro-esophageal parathyroid adenoma (9).
Available online: http://www.asvide.com/articles/194

neck. The platysma was then identified and divided. The sternothyroid, and sternohyoid muscles were identified and separated from the thyroid lobe. An intraoperative gamma probe was used to confirm the location of the parathyroid adenoma in the retroesophageal groove. Intraoperative nerve monitoring was used to identify and stimulate the recurrent laryngeal nerve. Circumferential dissection and resection of the adenoma was performed using simple electrocautery and a harmonic scalpel. The patient's PTH level at the time of incision was 229 pg/mL. The level decreased to 153, 104, and 78 pg/mL when measured at 5, 10, and 15 minutes, respectively, after excision of the adenoma, confirming that no other hyperfunctioning parathyroid glands were present. The patient was found eucalcemic one year postoperatively.

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References

1. Mohamed SE, Li X, Khadra H, et al. Video-assisted thoracoscopic approach parathyroidectomy. Asvide 2014;1:180. Available online: http://www.asvide.com/articles/192
2. Kandil E, Wassef SN, Alabbas H, et al. Minimally invasive

video-assisted thyroidectomy and parathyroidectomy with intraoperative recurrent laryngeal nerve monitoring. Int J Otolaryngol 2009;2009:739798.
3. Mohamed SE, Li X, Khadra H, et al. Robotic transaxillary resection of retro-esophageal parathyroid adenoma in thymus. Asvide 2014;1:181. Available online: http://www.asvide.com/articles/193
4. Kandil E, Abdelghani S, Noureldine SI, et al. Transaxillary gasless robotic thyroidectomy: a single surgeon's experience in North America. Arch Otolaryngol Head Neck Surg 2012;138:113-7.
5. Kandil E, Noureldine S, Abdel Khalek M, et al. Initial experience using robot- assisted transaxillary thyroidectomy for Graves' disease. J Visc Surg 2011;148:e447-51.
6. Kandil E, Winters R, Aslam R, et al. Transaxillary gasless robotic thyroid surgery with nerve monitoring: initial two experince in a North American center. Minim Invasive Ther Allied Technol 2012;21:90-5.
7. Kandil EH, Noureldine SI, Yao L, et al. Robotic transaxillary thyroidectomy: an examination of the first one hundred cases. J Am Coll Surg 2012;214:558-64; discussion 564-6.
8. Winters R, Friedlander P, Noureldine S, et al. Preoperative parathyroid needle localization: a minimally invasive novel technique in reoperative settings. Minim Invasive Surg 2011;2011:487076.
9. Mohamed SE, Li X, Khadra H, et al. Radio-guided parathyroidectomy for retro-esophageal parathyroid adenoma. Asvide 2014;1:182. Available online: http://www.asvide.com/articles/194

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"Parathyroidectomy in pregnancy"—a single centre experience with review of evidence and proposal for treatment algorithim

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Background: As many as 25% of women with primary hyperparathyroidism (PHPT) present during their child bearing years. However there is a paucity of data about management of PHPT in pregnancy, despite its association with severe complications including foetal loss. A recent review called for early surgical intervention to optimise maternal and foetal outcomes. We present our experience of parathyroidectomy in five pregnant patients, representing the largest series reported to date, alongside a review of literature to formulate a best evidence approach to management.

Methods: A retrospective case series of five patients managed at a single tertiary referral centre in London, UK. Data analysed include patient demographics, clinical features, pre- and post-operative biochemical markers, pathology findings, surgical procedure, complications, and outcome of pregnancy.

Results: Parathyroidectomy was safely carried out in all five patients during their second trimester. Cure was achieved by excision of adenoma in four patients at first operation with no reported complications. One patient with severe preoperative hypercalcaemia of >3 mmol/L suffered persistent severe hypercalcaemia despite three gland excision, with subsequent genetic testing revealing a mutation consistent with familial hypocalciuric hypercalcaemia (FHH).

Conclusions: This case series illustrates the challenges and successes of managing PHPT in pregnancy. Parathyroidectomy can be safely carried out with excellent outcomes for both mother and child. However, a modified approach to diagnosis and localisation studies is required. We propose a model for investigation and approach to management of such patients.

Keywords: Primary hyperparathyroidism (PHPT); pregnancy; parathyroidectomy; familial hypocalciuric hypercalcaemia (FHH)

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Introduction

Primary hyperparathyroidism (PHPT) is a common endocrine disorder, affecting approximately 0.15% of the population (1). There is a greater prevalence amongst women, and as many as 25% of women may present during their childbearing years (2). However, there is a relative lack of data regarding the incidence of PHPT in pregnant women, with less than 200 cases described in previous reports (3-5). Potential explanations for this may be the physiological changes of pregnancy such as hypoalbuminaemia and increased glomerular filtration rate which may blunt the calcium response to PHPT (4). In addition, many PHPT patients present either with nonspecific symptoms or no symptoms at all, which may make the clinical diagnosis difficult to distinguish from pregnancy associated symptoms.

Management of these patients also poses a difficult question. The largest review of PHPT in pregnancy was carried out by Norman *et al.* and reviewed 32 patients with a total of 77 pregnancies (6). This study demonstrated an astonishingly high degree of risk to mother and foetus, with as many as 67% of mothers and 80% of foetuses

experiencing harm. These findings were echoed by a recent and comprehensive literature review carried out by Diaz-Soto *et al.* (7). Reported maternal complications include nephrolithiasis, pancreatitis, and muscle weakness. The risk of pancreatitis is notably higher in pregnant patients with a frequency of approximately 10% in comparison to the 1% risk faced by non-pregnant patients with PHPT (7). The risk to the foetus includes intrauterine growth retardation, permanent hypoparathyroidism, prematurity, and intrauterine foetal loss. Severe hypercalcaemia carries a particularly bleak prognosis, with perinatal loss in up to 25%, although even mild forms are associated with a 3- to 5- fold increase in the rate of pregnancy loss (7). The risk was such that, although most elective surgery is normally delayed until after delivery, the recommendation has been made that parathyroidectomy be performed during pregnancy for all PHPT patients.

Despite this call for early intervention, there is a relative paucity of data regarding the best evidence approach to the optimal approach to undertaking parathyroidectomy in pregnancy. Sporadic cases have been reported with a variety of strategies for workup and operative approaches (8-10); but there are no available guidelines for perioperative workup and procedures. The aim of this series was to examine our experience in five cases of parathyroidectomy performed during pregnancy. To date, this is the largest case series report of surgical management of PHPT in pregnancy. Using this experience and a review of relevant literature, we then propose a step wise approach to management of the pregnant patient with PHPT.

Methods

This is a case series comprising five patients who underwent parathyroidectomy during pregnancy at our tertiary referral centre at St Thomas' Hospital, London, England. Data collected included patient demographics and presenting features, pre- and post-operative biochemical markers, imaging, intraoperative findings, and postoperative maternal and foetal course.

Results

The demographic characteristics of the five patients and their presenting characteristics are detailed in *Table 1*.

The results of preoperative biochemical and radiological investigations, where available, are presented in *Table 2*.

The operative procedure, postoperative findings, and complications related to operation, delivery, or neonate are presented in *Table 3*.

Final pathology in patients A-D revealed parathyroid adenoma in each; in patient E the parathyroid glands were hyperplastic but otherwise normal. Subsequent testing of patient E and her offspring revealed a mutation of the calcium sensing receptor (CaSR) consistent with familial hypocalciuric hypercalcaemia (FHH).

Conclusions

This case series illustrates both the successes and pitfalls which can be encountered when undertaking parathyroidectomy.

Diagnosis

As many as 80% of patients with PHPT may have no symptoms at all, and many cases may be picked up as an incidental finding of unexplained hypercalcaemia (11). Diagnosis of PHPT is classically based upon laboratory findings of elevated serum calcium with an inappropriately elevated PTH. Dias-Soto *et al.* (7) state that PHPT in pregnancy is probably underdiagnosed due to the masking effect of the maternal physiological adaptations lowering the observed serum calcium levels. Although standard antenatal screening in the UK does not include markers of PHPT, we would echo the call by Diaz-Soto *et al.* for measurement of calcium and PTH in pregnant patients with "classic" symptoms such as pancreatitis, fractures, or hyperemesis gravidarum; or indeed any symptoms of pregnancy which are prolonged and unexplained.

Differential diagnosis of hypercalcaemia includes PHPT and the rare autosomal dominant condition FHH. Urinary calcium excretion and the ratio of calcium:creatinine (Ca:Cr) clearance can be used to clarify diagnosis: PHPT demonstrates a high or high-normal calcium excretion with a Ca:Cr ratio of greater than 0.02; while FHH demonstrates a low urinary calcium excretion and Ca:Cr ratio of less than 0.01 (12). FHH is widely understood to demonstrate only a "mild" elevation in serum calcium and is often termed "Familial Benign Hypocalciuric Hypercalcaemia" due to the observed mild clinical syndrome (13). To our knowledge, this is the first report of evidence that FHH can cause extreme elevations of serum calcium, much greater than the "modest" elevations previously reported.

Clarity of diagnosis of PHPT and exclusion of FHH can be particularly difficult, as demonstrated by the case of Patient E. Patent E displayed characteristics of PHPT, with extreme elevation of serum calcium and inappropriate

Table 1 Demographics and clinical features at presentation

Patient	Age	Date of operation	Trimester of pregnancy at diagnosis	Trimester of pregnancy at operation	Co-morbidities	Symptoms of PHPT
A	31	27/4/2009	Pre-pregnancy	2	Li-fraumeni syndrome (nephroblastoma, lung metastases, breast cancer)	Asymptomatic-incidental finding
B	24	3/8/2009	2	2	None	Nephrocalcinosis
C	29	18/6/2013	2	2	HIV positive	Nephrocalcinosis, abdominal pain
D	28	26/3/2013	2	2	Crohn's disease	Asymptomatic-incidental finding
E	29	6/11/2012	2	2	None	Abdominal pain

PHPT, primary hyperparathyroidism.

Table 2 Preoperative biochemical and radiological investigations

Patient	Preoperative calcium (mmol/L)	Preoperative PTH (ng/L)	Preoperative vitamin D (nmol/L)	Preoperative urinary calcium excretion (mmol/L)	Preoperative ultrasound	Preoperative sestamibi scanning
A	2.88	113	-	-	Performed (positive)	Performed 2007 then lost to follow up
B	3.64	286	53	7.2	Performed (positive)	No
C	3.29	101	23	-	Performed (positive)	No
D	2.78	42	-	11.8	Performed (negative)	No
E	3.18	70	57	8.6	Performed (negative)	No

Table 3 Operative procedure and postoperative findings

Patient	Operation performed	Postoperative calcium (mmol/L)	Postoperative PTH (ng/L)	Postoperative complications	Delivery complications	Neonatal complications
A	Focused single gland excision	2.4	24	None	None	None
B	Focused single gland excision	2.25	43	None	None	None
C	Focused single gland excision	2.11	<6	None	None	None
D	Unilateral neck exploration with single gland excision	2.37	19	None	None	None
E	Bilateral neck exploration with three gland excision	2.82	20	Persistent hypercalcaemia	None	Hypercalcaemia

elevation of PTH. Bilateral neck exploration and excision of three glands was undertaken, but postoperatively showed no signs of improvement. With best medical management patient E completed her pregnancy with no significant complications, and delivered a healthy child who also demonstrated hypercalcaemia. After delivery, it was discovered that both patient E and her child had a congenital abnormality of the CaSR, consistent with FHH. Only extensive genetic testing, a lengthy and expensive process, can definitively confirm the diagnosis of FHH. Clearly, this is not practical to adopt as genetic testing as standard practice when there is clear time pressure to proceed to operation in these pregnant patients. Therefore, we would advocate an approach of building a likely diagnosis based on several pieces of key evidence. Firstly, and crucially based on our experience, we would no longer include an extreme elevation of serum calcium (above 3 mmol/L) alone as a key diagnostic factor for PHPT. Equally, an absolute reliance on hypocalciuria is not advisable for diagnosis of FHH as even confirmed patients may demonstrate normal urinary calcium excretion (14) and PHPT patients may demonstrate hypocalciuria if there is concomitant vitamin D deficiency. The presence of a single parathyroid mass on ultrasound may also falsely reassure one of the diagnoses of PHPT, as ultrasound can have a false positive rate of up to 21% (15). In summary: we would recommend a diagnostic approach which takes account of all three of these preoperative tests (serum calcium, urinary calcium markers of excretion and Ca:Cr ratio, and ultrasonography) and make a judgement of the balance of probability based upon them. Where there remains real and unacceptable uncertainty over diagnosis, the use of a calcimimetic such as cinacalcet has been demonstrated to have been used safely in pregnancy (16), and could be considered as a holding measure to control hypercalcaemia whilst genetic testing took place.

Localisation

The evolution of imaging techniques has seen a sea change in the approach to parathyroid surgery over the last 20 years, with accurate preoperative localisation studies permitting a "minimally invasive parathyroidectomy" (MIP) that targets only the identified likely culprit lesion. This has largely replaced the more traditional "bilateral neck exploration" as the gold standard operation for PHPT. The most accurate of the preoperative localisation studies is the 99m-technetium scan, which utilises the propensity for preferential uptake of the radioisotope by hyperfunctioning parathyroid tissue to correctly identify the site of adenoma in 88% of cases (17). Advances in CT scanning through rapid scanning and fine resolution have given rise to the development of "4D CT" imaging for identification of parathyroid adenomas, These images are developed through a four phase scanning technique with injection of an iodine rich contrast, allowing for examination of the uptake and washout of contrast by highly vascular tissue (i.e., parathyroid adenomas) within the neck and mediastinum. This has allowed 4D CT to be used for accurate localisation of the correct quadrant of disease, with reported accuracy of up to 87% (18).

Diagnostic tests using either high dose radiation or radioisotopes are almost universally avoided during pregnancy due to theoretical teratogenicity, and we would advocate the use of ultrasonography as the first line localising investigation in pregnant patients. Ultrasonography has accuracy of up to 79% in experienced hands (17), and for this reason we would suggest that all pregnant patients with PHPT have localisation scans at a specialist centre to maximise the likelihood of success. Specialist centres may also have the facility to offer ultrasound guided fine needle aspirate of lesions, with measurement of the PTH within the aspirate. This technique offers an excellent reported rate for confirmation of the parathyroid origin of tissue (up to 100% accuracy) (19) but is of course dependent of the successful localisation of a lesion to target for aspiration. If ultrasonography fails to identify a lesion, the surgeon is then faced with two options: to undertake BNE, or to request a 99m technetium scan. The woman should be counselled as to the risks and of each; namely the risk of recurrent laryngeal nerve palsy in BNE and the risk of administering radioactive material to the developing foetus with a 88% chance of successful localisation. There have been reports of the use of 99m-technetium in three parathyroidectomies and in several other procedures, with no reported immediate foetal or maternal complications. However, as is so often the case in pregnancy, large scale trials with long term follow up have not been conducted. The risk of radioisotope administration is therefore largely unquantified. By contrast, the risk of BNE to the recurrent laryngeal nerves has been extensively documented and is less than 1% (20). Therefore, in cases such as patient D where ultrasonography has failed to identify a culprit lesion, we would advocate proceeding to a planned bilateral neck exploration. In this case, the lesion was found at the first side of exploration and the procedure could be halted successfully (thus reducing yet further the risk of nerve injury).

MIP and BNE have similar success rates of 95% of

patients achieving long term cure (21), but for the 5% failed first operation there then is the question of how to approach reoperative surgery. Again, the possibility of 99m-technetium scanning could be raised with the patient, although its usefulness is actually significantly reduced in the previously operated neck. Other options for localisation include noninvasive techniques such as MRI scanning (43-71% success) (17) or invasive PTH venous sampling (71-90%) (22). A recent report has suggested promising results in the use of intraoperative ultrasound guided methylene blue administration in the reoperative neck (23), and in future this may become a useful investigation in pregnant patients requiring reoperation.

Safety

The safety of operation is well illustrated by this series of patients, with no complications perioperatively or at delivery. There was one foetal complication of hypercalcaemia; however this was related to the child's underlying pathological process of FHH rather than as a result of the operation. All our cases were operated on in the second trimester, and in several cases this required a rapid turnaround from time of first presentation to date of admission for surgery. There have been reports of parathyroidectomy being safely carried out in the third trimester (24), and this may be an option for women who present late into their pregnancy. However, there is no evidence to suggest superiority of outcomes in third trimester operating; indeed there may be exposure to unacceptable risk if operation is delayed. Therefore, it would be our recommendation that operation be carried out in the second trimester as soon as all preoperative investigations have been completed.

Operative approaches

As discussed above, the operative choice between MIP and BNE depends on the success of localisation techniques and also on surgeon experience. A review of operative approach in parathyroidectomy from 2010 stated that pregnancy is a positive predictive factor for BNE approach (25). However, there at least two case reports of focused parathyroidectomy being successfully carried out in pregnant patients with positive localisation studies (10,26).

An innovative compromise approach for the patient with negative localisation studies may be the "minimally invasive video assisted parathyroidectomy" (MIVAP) technique, which uses a small midline incision with retraction and endoscopic magnification to explore all four glands. This technique has been described by Bendinelli *et al*. (8) who describe a 15-mm incision through which all four glands could be explored, identified, and an adenoma removed. At present, MIVAP is rarely used in the adult patient due to the ability to perform MIP under direct vision. However, for the surgeon who has the skills and experience to perform MIVAP confidently can offer this approach as an excellent option for the patient with negative localisation studies.

The development of intra-operative of PTH monitoring (IOPTH) has provided endocrine surgeons with another useful adjunct during parathyroidectomy. The technique calls for serial measurements of IOPTH at induction of anaesthesia, or just prior to excision of the presumed culprit lesion followed by measurements at 5 and 10 minutes post-excision. The most widely used standard, the Miami criteria, uses a fall in IOPTH by 50% or greater at 10 minutes post-excision as evidence of successful operation (27). IOPTH monitoring can give reassurance to the surgeon that the target lesion has been correctly identified; and that exploration can be limited to that target site. IOPTH monitoring has been used successfully during pregnancy, as demonstrated by two case reports where excision of a single adenoma has been by fall in IOPTH in line with the Miami criteria. Limitations of IOPTH include the additional cost (although this has to be balanced against cost saved by limiting time spent on unnecessary exploration of the neck); and the lack of evidence of its efficacy in identifying multigland disease or double adenoma. However, where facilities for IOPTH monitoring are available, it may provide a useful adjunct to the surgeon performing parathyroidectomy in the pregnant patient and particularly in those with negative localisation studies.

Stepwise model

We have synthesised a summary of our experience and literature review into an evidence based stepwise model for planning approach to parathyroidectomy in the pregnant patient (*Figure 1*). In particular we would highlight the importance of a multidisciplinary team in managing these patients and their pregnancy. Given that the women in this series were all between the ages of 24-31, the number and severity of co-morbidities encountered is quite remarkable. To our knowledge there is no recognised association between Li-Fraumeni, HIV infection, or Crohn's disease with PHPT. Rather, it is a reminder of the complexity of managing these patients which is best

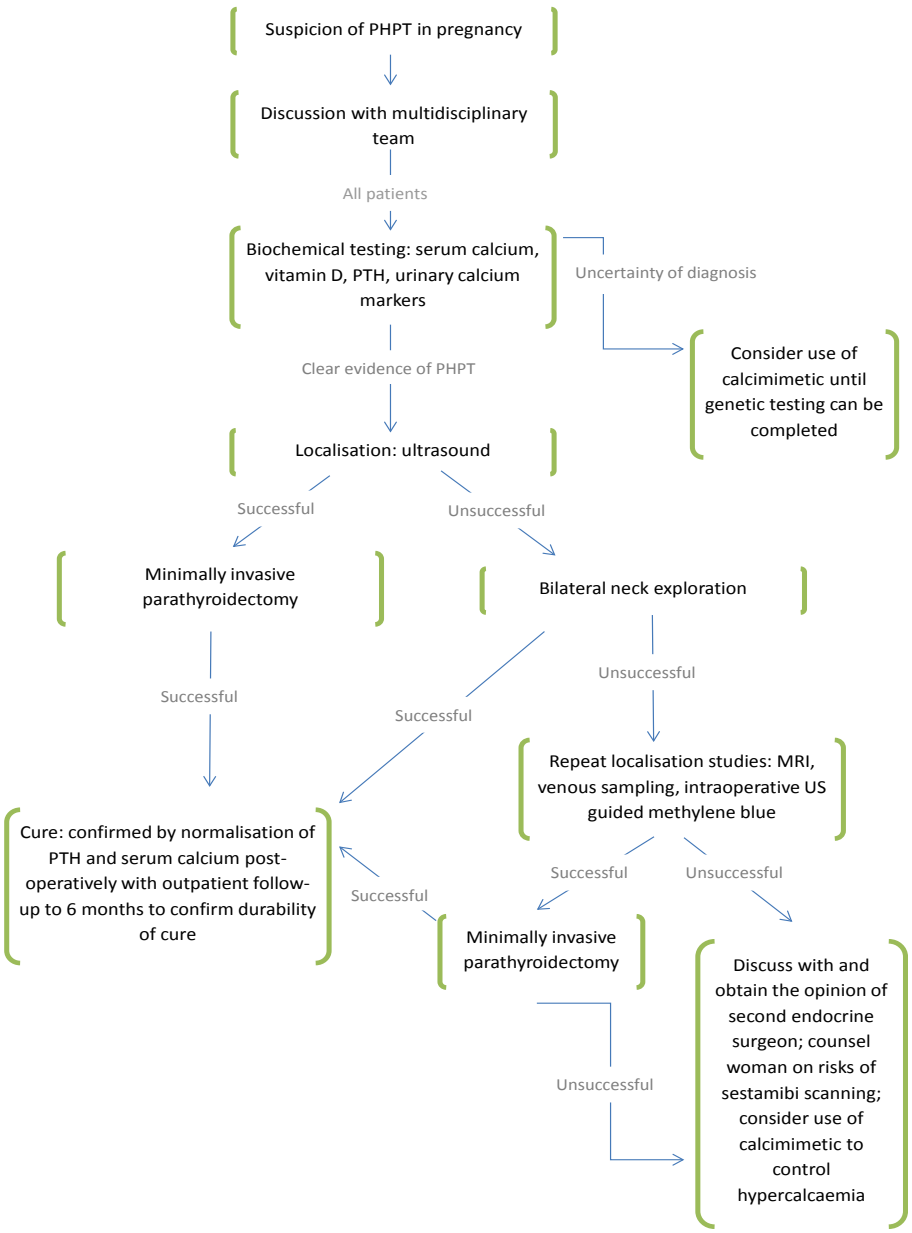

Figure 1 Stepwise best evidence model for approach to parathyroidectomy in pregnancy.

approached by a diverse multidisciplinary team. From time of first presentation, planning should be undertaken by a team experienced in parathyroid surgery and include the surgeon, anaesthetist, an experienced endocrine radiologist, obstetrician, neonatologist, and physicians involved in management of co-morbidities. We believe that by adopting a model based on best available evidence, coordinated by a multidisciplinary team, will prove beneficial in the management of parathyroidectomy in pregnancy.

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References

1. Pallan S, Rahman MO, Khan AA. Hyperparathyroidism: diagnosis and management—a clinical review. BMJ 2012;344:e1013.

2. Heath H 3rd, Hodgson SF, Kennedy MA. Primary hyperparathyroidism: incidence, morbidity, and potential economic impact in a community. N Engl J Med 1980;302:189-93.
3. Schnatz PF, Curry SL. Primary hyperparathyroidism in pregnancy: evidence-based management. Obstet Gynecol Surv 2002;57:365-76.
4. Amaya García M, Acosta Feria M, Soto Moreno A, et al. Primary hyperparathyroidism in pregnancy. Gynecol Endocrinol 2004;19:111-4.
5. Jesudason WV, Murphy J, England RJ. Primary hyperparathyroidism in pregnancy. J Laryngol Otol 2004;118:891-2.
6. Norman J, Politz D, Politz L. Hyperparathyroidism during pregnancy and the effect of rising calcium on pregnancy loss: a call for earlier intervention. Clin Endocrinol (Oxf) 2009;71:104-9.
7. Diaz-Soto G, Linglart A, Sénat MV, et al. Primary hyperparathyroidism in pregnancy. Endocrine 2013;44:591-7.
8. Bendinelli C, Nebauer S, Quach T, et al. Is minimally invasive parathyroid surgery an option for patients with gestational primary hyperparathyroidism? BMC Pregnancy Childbirth 2013;13:130.
9. Petousis S, Kourtis A, Anastasilakis CD, et al. Successful surgical treatment of primary hyperparathyroidism during the third trimester of pregnancy. J Musculoskelet Neuronal Interact 2012;12:43-4; quiz 45.
10. Malekar-Raikar S, Sinnott BP. Primary hyperparathyroidism in pregnancy-a rare cause of life-threatening hypercalcemia: case report and literature review. Case Rep Endocrinol 2011;2011:520516.
11. Bilezikian JP, Silverberg SJ. Asymptomatic primary hyperparathyroidism. N Engl J Med 2004;350:1746-51.
12. Endres DB. Investigation of hypercalcemia. Clin Biochem 2012;45:954-63.
13. Christensen SE, Nissen PH, Vestergaard P, et al. Familial hypocalciuric hypercalcaemia: a review. Curr Opin Endocrinol Diabetes Obes 2011;18:359-70.
14. Pasieka JL, Andersen MA, Hanley DA. Familial benign hypercalcaemia: hypercalciuria and hypocalciuria in affected members of a small kindred. Clin Endocrinol (Oxf) 1990;33:429-33.
15. Jaskowiak N, Norton JA, Alexander HR, et al. A prospective trial evaluating a standard approach to reoperation for missed parathyroidadenoma. Ann Surg 1996;224:308-20; discussion 320-1.
16. Edling KL, Korenman SG, Janzen C, et al. A pregnant dilemma: primary hyperparathyroidism due to parathyromatosis in pregnancy. Endocr Pract 2014;20:e14-7.
17. Johnson NA, Tublin ME, Ogilvie JB. Parathyroid imaging: technique and role in the preoperative evaluation of primary hyperparathyroidism. AJR Am J Roentgenol 2007;188:1706-15.
18. Hunter GJ, Schellingerhout D, Vu TH, et al. Accuracy of four-dimensional CT for the localization of abnormal parathyroid glands in patients with primary hyperparathyroidism. Radiology 2012;264:789-95.
19. Erbil Y, Barbaros U, Salmaslioglu A, et al. Value of parathyroid hormone assay for preoperative sonographically guided parathyroid aspirates for minimally invasive parathyroidectomy. J Clin Ultrasound 2006;34:425-9.
20. Harris SC. Thyroid and parathyroid surgical complications. Am J Surg 1992;163:476-8.
21. Sackett WR, Barraclough B, Reeve TS, et al. Worldwide trends in the surgical treatment of primary hyperparathyroidism in the era of minimally invasive parathyroidectomy. Arch Surg 2002;137:1055-9.
22. Ito F, Sippel R, Lederman J, et al. The utility of intraoperative bilateral internal jugular venous sampling with rapid parathyroid hormone testing. Ann Surg 2007;245:959-63.
23. Candell L, Campbell MJ, Shen WT, et al. Ultrasound-guided methylene blue dye injection for parathyroid localization in the reoperative neck. World J Surg 2014;38:88-91.
24. Schnatz PF. Surgical treatment of primary hyperparathyroidism during the third trimester. Obstet Gynecol 2002;99:961-3.
25. Norman J, Politz D. Prospective study in 3,000 consecutive parathyroid operations demonstrates 18 objective factors that influence the decision for unilateral versus bilateral surgical approach. J Am Coll Surg 2010;211:244-9.
26. Pothiwala P, Levine SN. Parathyroid surgery in pregnancy: review of the literature and localization by aspiration for parathyroid hormone levels. J Perinatol 2009;29:779-84.
27. Carneiro DM, Solorzano CC, Nader MC, et al. Comparison of intraoperative iPTH assay (QPTH) criteria in guiding parathyroidectomy: which criterion is the most accurate? Surgery 2003;134:973-9; discussion 979-81.

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Parathyroid carcinoma: a silent presentation

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Abstract: Primary hyperparathyroidism is most commonly diagnosed in the setting of benign parathyroid adenoma(s). However, it can also rarely be caused by parathyroid malignancy and when it is, the clinical manifestations far supercede the presentation of benign parathyroid adenoma. We report a case of suspected benign parathyroid adenoma induced primary hyperparathyroidism in which pathologic diagnosis of parathyroid carcinoma was made. Due to the lack of signs and symptoms, this indicates parathyroid malignancy can be masked clinically as benign adenomas, until a histologic diagnosis can be ascertained.

Keywords: Hyperparathyroidism; mutation; parathyroid

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Introduction

Parathyroid carcinoma is the rarest endocrine malignancy and represents 1% of all cases of primary hyperparathyroidism (1). Patients often present with severe fatigue, nephrolithiasis, pathologic fractures, brown tumors, hypercalcemic crises, and if not recognized, obdurate hypercalcemia (2). Serum calcium and PTH levels are also much higher in parathyroid cancer patients than in patients with functional parathyroid adenoma; however, patients have been identified with non-functional non-secreting cancers, and they are often associated with a poor prognostic outcome. Non-functional parathyroid carcinomas represents 1.9% of all parathyroid carcinomas, whereas parathyroid adenomas are often benign and have no significant clinical presentation (3,4). Additionally, a palpable nodule located in the parathyroid region(s) is highly indicative of malignancy (2). The patient was completely asymptomatic with elevated free urine calcium, elevated parathyroid hormone (PTH) levels, and elevated serum calcium. She presented for surgical excision of a proposed hypersecreting adenoma. Reported cases of patients with recurrent laryngeal nerve palsy in patients without a past surgical history involving the neck is indicative of a more invasive lesion (1).

Case report

A 62-year-old Caucasian female presented to ambulatory surgery for a parathryoidectomy for hyperparathyroidism. The patient denied any neck masses or symptoms of throat tightness or dysphagia, and denied fatigue. No palpable neck mass was evident on physical examination. Her past medical history was significant for hypertension and Hepatitis C. Serum parathyroid hormone (PTH) level prior to surgery was 384.1 pg/mL and post-operative serum calcium level was 13.3 mg/dL. No other significant findings were evident on complete blood count, basic metabolic panel, or liver function testing.

A preoperative ultrasound revealed a 2 cm mass in the right lower pole of the parathyroid region. A follow-up sestamibi displayed increased radionucleotide uptake in same right location with the impression of a parathyroid adenoma. Upon surgical exploration, the parathyroid mass was found to be grossly fibrotic and irregular in comparison to adjacent tissue (*Figure 1*). This tissue was removed with adjacent thyroid tissue, along with two adjacent lymph nodes. Histopathological examination revealed parathyroid carcinoma with contained capsular invasion with thyroid and lymph node specimens negative for malignancy (*Figure 2*). Large pleomorphic cells with scattered mitoses and vascular invasion was also evident (*Figure 3*).

Discussion

The diagnosis of parathyroid carcinoma typically relies

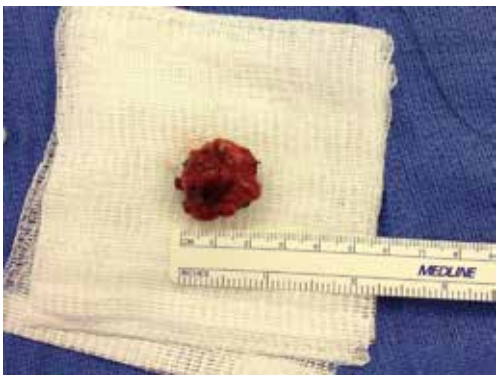

Figure 1 A 2 cm × 2.2 cm × 1.5 cm mass found in right inferior pole of the parathyroid gland. Noticeable fibrosis and gross morphology exhibits malignant features.

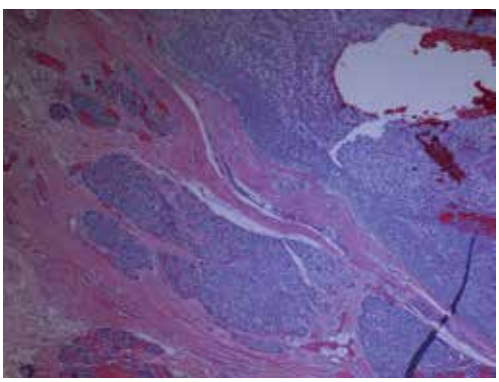

Figure 2 Hematoxylin and eosin (H&E) staining at 100× shows capsular invasion with malignant cells with fibrous tissue invasion of the parathyroid gland.

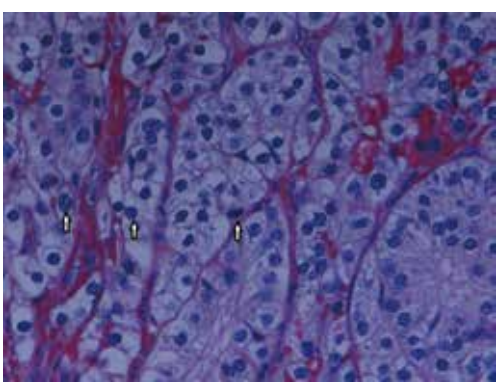

Figure 3 Hematoxylin and eosin (H&E) staining at 400× shows nests of large pleomorphic cells with scattered mitoses that are identified with arrows.

on the patient's clinical presentation, laboratory studies, imaging, and ultimately histopathology. In our case, the patient was absent of symptoms with only elevated serum calcium, elevated PTH level, elevated urinary calcium, and non-malignant imaging. Histopathological examination ultimately proved to be the final diagnosis. Ultrasound and Sestamibi scans are of additional benefit in localizing lesions and determining active *vs.* non-active lesions. The majority of parathyroid neoplasms are found in the inferior gland position, which is likely related to the different embryologic descent paths taken by the superior and inferior glands (5). Patients suspected of having parathyroid carcinoma should not undergo pre-operative biopsy procedures since the breaking away of cells in transit may serves as a nidus for ectopic dissemination of active parathyroid tissue (6,7). Measurement of intraoperative PTH level has been widely adopted to confirm removal of the hyperactive gland, and is considered satisfactory when the value is <50% of the pre-excision PTH level. However, the McGill University Thyroid Cancer Center has questioned this practice for adenomas localized preoperatively with two concordant imaging modalities, and instead recommends intraoperative PTH testing only if concordance between sestamibi scan, ultrasound and MRI cannot be established (8). In addition, intra-operative frozen section, although used frequently, has been shown to waste important tissue, and is therefore not recommended especially since tissue specimens are small and should be reserved for permanent section. However, in our case frozen sections allowed us to remove not just the mass but also adjacent tissue and lymph nodes to assess for local metastasis. Because of the difficulties in differentiating benign from malignant lesions, a set of standards set by Shantz and Castleman in 1973 has been adapted in ascertaining the diagnosis of a malignant parathyroid neoplasm. These include: mitoses within tumor parenchymal cells, vascular or capsular invasion by tumor cells, and a homogenous group of chief cells in a lobular pattern separated by thick fibrous septae (9,10). The parathyroid mass in our patient was grossly adhesed to the underlying thyroid tissue indicating heavy capsular invasion, the usual hallmark of parathyroid malignancy. In a large case series of 358 people, it was found that the most common sites of invasion, in descending order, were: ipsilateral thyroid gland, infrahyoid muscles, ipsilateral recurrent laryngeal nerve, esophagus, and trachea (3).

Molecular pathogenesis of parathyroid carcinoma has in part been revealed through studying Hyperparathyroidism-Jaw Tumor (HP-JT) syndrome. HP-JT is a rare autosomal

dominant disease in which patients develop ossifying bone tumors of the maxillary and/or mandibular regions in conjunction with primary hyperparathyroidism, renal masses, and uterine masses (11). About 15% of the parathyroid lesions causing hyperparathyroidism in HP-JT syndrome are parathyroid carcinomas (12). A study of 14 families with HP-JT syndrome revealed germline inactivating mutations in the *HRPT2/CDC73* tumor suppressor gene (13). The gene codes for a protein parafibromin which has been implicated in a variety of regulatory processes as well as histone methylation of promoter regions of various genes (14). Multiple studies have reported *HRPT2/CDC73* gene mutations even in sporadic parathyroid carcinomas, validating the role of this mutation in development of parathyroid malignancy (15,16). Supporting the malignant nature of this mutation, other studies examined benign parathyroid lesions including adenomas, and/or hyperplasias for evidence of the mutation, with no identifiable genetic aberrations (15,17). Although meta-analyses have indicated an incidence of less than 1% of the mutation in benign parathyroid lesions (17). This data supports the use of genetic testing in parathyroid lesions suspected for malignancy. Due to different histopathological approaches used to diagnose parathyroid carcinoma, identifying a *HPRT2/CDC73* mutation would be a definitive clue to a malignant parathyroid lesion. Case reports of histologically benign but metastatic parathyroid lesions have been reported that tested positive for the mutation further advocating the use of genetic testing in suspected parathyroid malignancy (18). In addition, it is recommended to test all parathyroid carcinoma confirmed patients for the mutation because up to one in five patients will have hidden HP-JT syndrome (16).

Multiple endocrine neoplasia (MEN)-1 syndrome is a rare autosomal dominant disease characterized primarily by a constellation of parathyroid adenomas, pituitary adenomas, and pancreatic tumors. The incidence of parathyroid carcinoma in MEN-1 patients is extremely rare; however, novel germline mutations in the *MEN-1* gene have been isolated which may validate genetic testing in select individuals presenting with parathyroid carcinoma for the MEN-1 syndrome (19).

Treatment of parathyroid carcinoma is dependent on the stage of diagnosis. An en-bloc resection of the ipsilateral thyroid tissue with associated parathyroid lesions is recommended to decrease rate of recurrence. In the same case series of 358 en bloc resections, results showed an 8% decrease in local recurrence as compared to a 51% rate of local recurrence in patients who received just removal of the involved parathyroid gland(s) (3). Although this is recommended, our diagnosis was hinted by intra-operative examination and confirmed by permanent section where no evidence of further invasion was evident; therefore, a conservative parathyroidectomy was performed. Cervical lymph node metastasis is rare with presence in less than one in five affected patients; however, it is advised that the tracheoesophageal groove with level VI nodes be explored and removed with further dissection only if gross metastatic changes to other chains of lymph nodes is present (1,20,21). When parathyroid carcinoma is metastatic or unresectable, the resulting hypercalcemia is typically treated with bisphosphonates and calcium receptor agonists; however, moderate success using dacarbazine and denosumab has been reported for those patients with a refractory response (22).

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References

1. Shane E. Clinical review 122: Parathyroid carcinoma. J Clin Endocrinol Metab 2001;86:485-93.
2. Dilli A, Gultekin SS, Ayaz UY, et al. Parathyroid carcinoma. JBR-BTR 2013;96:224-5.
3. Koea JB, Shaw JH. Parathyroid cancer: biology and management. Surg Oncol 1999;8:155-65.
4. Sharretts JM, Kebebew E, Simonds WF. Parathyroid cancer. Semin Oncol 2010;37:580-90.
5. Goldner B, Lee B, Stabile BE. The unequal distribution of parathyroid neoplasms in male patients. Am Surg 2013;79:1022-5.
6. Spinelli C, Bonadio AG, Berti P, et al. Cutaneous spreading of parathyroid carcinoma after fine needle aspiration cytology. J Endocrinol Invest 2000;23:255-7.
7. Kebebew E, Arici C, Duh QY, et al. Localization and reoperation results for persistent and recurrent parathyroid carcinoma. Arch Surg 2001;136:878-85.
8. Zawawi F, Mlynarek AM, Cantor A, et al. Intraoperative parathyroid hormone level in parathyroidectomy: which patients benefit from it? J Otolaryngol Head Neck Surg 2013;42:56.
9. Schantz A, Castleman B. Parathyroid carcinoma. A study of 70 cases. Cancer 1973;31:600-5.

10. Marcus S, Holley AC, Persad P, et al. Hypercalcemia in an elderly patient. JAMA Otolaryngol Head Neck Surg 2014;140:169-70.
11. Kutcher MR, Rigby MH, Bullock M, et al. Hyperparathyroidism-jaw tumor syndrome. Head Neck 2013;35:E175-7.
12. Carlson D. Parathyroid pathology: hyperparathyroidism and parathyroid tumors. Arch Pathol Lab Med 2010;134:1639-44.
13. Carpten JD, Robbins CM, Villablanca A, et al. HRPT2, encoding parafibromin, is mutated in hyperparathyroidism-jaw tumor syndrome. Nat Genet 2002;32:676-80.
14. Rozenblatt-Rosen O, Hughes CM, Nannepaga SJ, et al. The parafibromin tumor suppressor protein is part of a human Paf1 complex. Mol Cell Biol 2005;25:612-20.
15. Howell VM, Haven CJ, Kahnoski K, et al. HRPT2 mutations are associated with malignancy in sporadic parathyroid tumours. J Med Genet 2003;40:657-63.
16. Shattuck TM, Välimäki S, Obara T, et al. Somatic and germ-line mutations of the HRPT2 gene in sporadic parathyroid carcinoma. N Engl J Med 2003;349:1722-9.
17. Krebs LJ, Shattuck TM, Arnold A. HRPT2 mutational analysis of typical sporadic parathyroid adenomas. J Clin Endocrinol Metab 2005;90:5015-7.
18. Sarquis MS, Silveira LG, Pimenta FJ, et al. Familial hyperparathyroidism: surgical outcome after 30 years of follow-up in three families with germline HRPT2 mutations. Surgery 2008;143:630-40.
19. Juodelė L, Serapinas D, Sabaliauskas G, et al. Carcinoma of two parathyroid glands caused by a novel MEN1 gene mutation - a rare feature of the MEN 1 syndrome. Medicina (Kaunas) 2011;47:635-9.
20. Ricci G, Assenza M, Barreca M, et al. Parathyroid carcinoma: the importance of high clinical suspicion for a correct management. Int J Surg Oncol 2012;2012:649148.
21. Pelizzo MR, Piotto A, Bergamasco A, et al. Parathyroid carcinoma. Therapeutic strategies derived from 20 years of experience. Minerva Endocrinol 2001;26:23-9.
22. Vellanki P, Lange K, Elaraj D, et al. Denosumab for management of parathyroid carcinoma-mediated hypercalcemia. J Clin Endocrinol Metab 2014;99:387-90.

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The current status of intraoperative iPTH assay in surgery for primary hyperparathyroidism

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Abstract: Intraoperative intact parathyroid hormone (iPTH) monitoring has been accepted by many centers specializing in parathyroid surgery as a useful adjunct during surgery for primary hyperparathyroidism. This method can be utilized in three discreet modes of application: (I) to guide surgical decisions during parathyroidectomy in one of the following clinical contexts: (i) to confirm complete removal of all hyperfunctioning parathyroid tissue, which allows for termination of surgery with confidence that the hyperparathyroid state has been successfully corrected; (ii) to identify patients with additional hyperfunctioning parathyroid tissue following the incomplete removal of diseased parathyroid/s, which necessitates extended neck exploration in order to minimize the risk of operative failure; (II) to differentiate parathyroid from non-parathyroid tissue by iPTH measurement in the fine-needle aspiration washout; (III) to lateralize the side of the neck harboring hyperfunctioning parathyroid tissue by determination of jugular venous gradient in patients with negative or discordant preoperative imaging studies, in order to increase the number of patients eligible for unilateral neck exploration. There are many advantages of minimally invasive parathyroidectomy guided by intraoperative iPTH monitoring, including focused dissection in order to remove the image-indexed parathyroid adenoma with a similar or even higher operative success rate, lower prevalence of complications and shorter operative time when compared to conventional bilateral neck exploration. However, to achieve such excellent results, the surgeon needs to be aware of hormone dynamics during parathyroidectomy and carefully choose the protocol and interpretation criteria that best fit the individual practice. Understanding the nuances of intraoperative iPTH monitoring allows the surgeon for achieving intraoperative confidence in predicting operative success and preventing failure in cases of unsuspected multiglandular disease, while safely limiting neck exploration in the majority of patients with sporadic primary hyperparathyroidism. Thus, parathyroidectomy guided by intraoperative iPTH monitoring for the management of sporadic primary hyperparathyroidism is an ideal option for the treatment of this disease entity. However, the cost-benefit aspects of the standard application of this method still remain a matter of controversy.

Keywords: Primary hyperparathyroidism; intraoperative intact parathyroid hormone (iPTH) assay; a solitary parathyroid adenoma; multiglandular parathyroid disease

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Introduction

Since the time when the first parathyroidectomy was performed by Dr. Felix Mandl in 1925, the procedure of bilateral neck exploration done by an experienced parathyroid surgeon has been for many years the gold standard in parathyroid surgery, allowing for achieving cure rates exceeding 95% of patients with primary hyperparathyroidism (1,2). Nevertheless, the recently developed modern imaging techniques allowing for preoperative localization of diseased parathyroid gland, such as parathyroid scintigraphy or high-resolution ultrasonography, followed by developing a method of intraoperative quality control of surgical treatment based on intraoperative serum intact parathyroid hormone (iPTH) assay, became the milestones in forming the idea of minimally invasive parathyroidectomy, focusing on using a small incision to resect a solitary image-indexed parathyroid adenoma without a necessity of intraoperative identification and evaluation of the remaining parathyroids (3).

According to the literature published to date, minimally invasive parathyroidectomy has proven to be equally effective in restoring normocalcemia as bilateral neck exploration and is associated with a minimal risk of complications (4-6). A fundamental advantage of minimally invasive parathyroidectomy, in addition to better cosmetics effects and lesser pain is a significant decrease of the percentage of postoperative transient hypoparathyroidism to approximately 5% as compared to approximately 15-25% after bilateral neck exploration, as well as complete elimination of the risk of permanent hypoparathyroidism. This phenomenon is a consequence of preserving intact the blood supply of normal parathyroids, which have not been exposed in the course of minimally invasive parathyroidectomy. In turn, a lower rate of transient hypocalcemia after minimally invasive parathyroidectomy is associated with significantly decreased requirements for calcium and vitamin D3 preparations and a shorter hospitalization (7).

Historical perspective

In 1988, Nussbaum *et al*. modified the original immunoradiometric assay by increasing the temperature of incubation and employing a kinetic enhancer; the above changes decreased the turnover time to approximately 15 minutes (8). In this initial report, the first use of iPTH monitoring during parathyroidectomy was described, although the patients in this series underwent bilateral neck exploration and iPTH was measured postoperatively. Although the reporting of this experience appeared to be of clinical interest, it was not readily accepted as an alternative to the existing practice of highly successful conventional bilateral neck exploration. In 1990, Chapuis *et al*. from Paris reported in French their series of 13 patients in whom the iPTH dropped above 70% in 20 minutes after parathyroidectomy by using the immunoradiometric assay for intraoperative iPTH measurement (9). Utilizing a modification of the technique described by Nussbaum, Irvin was able to demonstrate a rapid decline in parathyroid hormone levels measured intraoperatively following removal of the second parathyroid adenoma. In 1991, Irvin *et al*. described for the first time a series of 21 patients who had their parathyroidectomy guided exclusively by intraoperative iPTH assay using an immunoradiometric method (10). With George Irvin's help, in 1996, this rapid assay method was developed further to an immunochemiluminescence method, and the "quick" iPTH assay became commercially available for intraoperative use, which is still the methodology used today (11). Currently, the majority of high-volume parathyroid surgeons utilize this technique to guide parathyroidectomy in patients with a sporadic primary hyperparathyroidism (12-18).

Areas of application of intraoperative iPTH monitoring

The intraoperative iPTH assay can be utilized in three discreet modes of application:

(I) To guide surgical decisions during parathyroidectomy in one of the following clinical contexts:
  (i) To confirm complete removal of all hyperfunctioning parathyroid tissue, which allows for termination of surgery with confidence that the hyperparathyroid state has been successfully corrected (12-16);
  (ii) To identify patients with additional hyperfunctioning parathyroid tissue following the incomplete removal of diseased parathyroid/s, which necessitates extended neck exploration in order to minimize the risk of operative failure (17,18);

(II) To differentiate parathyroid from non-parathyroid tissue by iPTH measurement in the fine-needle aspiration washout (19-21);

(III) To lateralize the side of the neck harboring hyperfunctioning parathyroid tissue by determination of jugular venous gradient in patients with negative or discordant preoperative imaging studies, in order to increase the number of patients eligible for unilateral neck exploration (22,23).

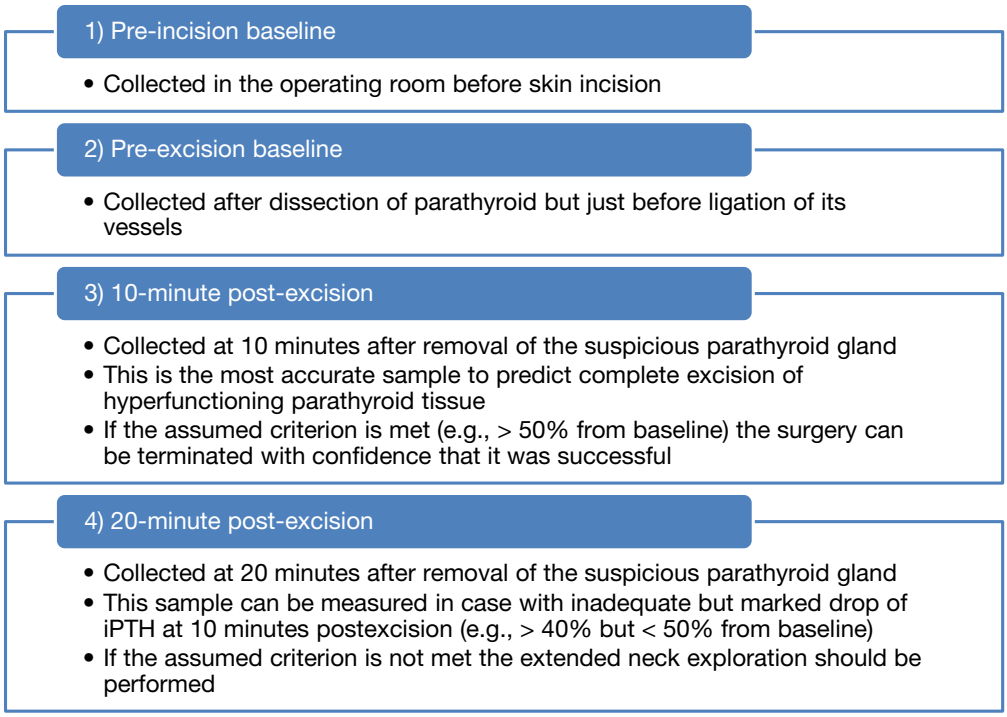

Figure 1 The recommended protocol of intraoperative iPTH assay sampling. iPTH, intact parathyroid hormone.

Protocol of intraoperative iPTH assay

A peripheral vein access is most commonly used for collection of blood samples. This access should be kept open with saline infusion throughout the procedure, and an intravenous extension is used to give the anesthesiologist access to the tubing for blood collection at times requested by the surgeon. It is extremely important to instruct the anesthesia team about discarding 10 mL of blood with saline to avoid sample dilution, potentially leading to falsely lower iPTH values. Totally 3 mL of blood are collected for iPTH measurement and are placed in an ethylenediaminetetraacetic acid (EDTA) coated tube at specific time-points and immediately centrifuged. To achieve reliable results, it is strongly recommended to follow the strict protocol of blood testing at specific time-points during parathyroidectomy, which allows for understanding the hormone dynamics during the operation. The following time-points of blood sampling for iPTH are most commonly used: (I) in the operating room before the skin incision is made (pre-incision baseline); (II) just before the blood supply to the suspicious parathyroid gland is ligated (pre-excision baseline); (III) at 10 minutes (10 minutes post-excision); and (IV) occasionally at 20 minutes after excision (20 minutes post-excision) of the suspected abnormal gland (*Figure 1*). An intraoperative iPTH drop of more than 50% from the highest either pre-incision or pre-excision baseline at 10 minutes post-excision is highly accurate in predicting postoperative normal or low serum calcium values (Miami criterion). The iPTH assay total turnaround time may vary from 8 to 15 minutes depending on the laboratory. During this waiting time, the surgeon can close the incision, but any manipulation of the remaining parathyroids should be avoided in order to minimize the chance of falsely elevating iPTH levels resulting in a delay in hormone drop. If the assumed criterion is not met at 10 minutes post-excision, the extended neck exploration is undertaken and the protocol for blood sampling is repeated for each additional excised suspicious parathyroid gland until all hypersecreting parathyroid tissue is removed, which is confirmed by meeting the criterion. In cases approaching but not meeting the assumed criterion of an iPTH drop at 10 minutes post-excision, some surgeons recommend obtaining an additional 20-minute post-excision sample for iPTH measurement in order to rule out the false negative result of the testing. However, such an approach is not uniformly agreed upon and some data suggest that extended neck exploration

Table 1 The most common intraoperative iPTH assay criteria used for prognostication of outcome of parathyroid surgery and their predictive values

Criterion	Definition for prediction of cure	PPV (%)	NPV (%)	Overall accuracy (%)
Halle	An iPTH decay into the low normal range (≤35 ng/L) within 15 minutes after removal of the hyperfunctioning parathyroid tissue (H. Dralle, personal communication, 2006)	100.0	14.2	65.0
Miami (29)	An iPTH drop of 50% or more from the highest of either preoperative baseline or pre-excision level at 10 minutes after excision of hyperfunctioning parathyroid gland(s)	99.6	70.0	97.3
Rome (31)	An iPTH decay greater than 50% from the highest pre-excision level, and/or iPTH concentration within the reference range at 20 minutes post-excision, and/or ≤7.5 ng/L lower than the value at 10 minutes post-excision	100.0	26.3	83.8
Vienna (30)	A decay of 50% or greater from the baseline (pre-incision) value within 10 minutes following resection	99.6	60.9	92.3

Validated among 260 patients with sporadic primary hyperparathyroidism and concordant results of both sestamibi scanning and ultrasound of the neck strongly suggestive for a solitary parathyroid adenoma, with multiglandular parathyroid disease encountered in nine patients (26). PPV, positive predictive value; NPV, negative predictive value; iPTH, intact parathyroid hormone.

should be rather attempted instead.

Intraoperative iPTH assay criteria for prognostication of success

The issue of appropriate patient selection plays a fundamental role in achieving a high success rate of minimally invasive parathyroidectomy approaching 100%. To achieve a high success rate of parathyroidectomy, the surgeon needs to be aware of intraoperative hormone dynamics during the case and carefully choose the protocol and interpretation criteria that best fit the individual practice. Understanding the nuances of intraoperative iPTH monitoring allows the surgeon for achieving intraoperative confidence in predicting operative success and preventing failure in cases of unsuspected multiglandular disease, while safely limiting neck exploration in the majority of patients with sporadic primary hyperparathyroidism. When concordant results of functional imaging (e.g., sestamibi scanning) and ultrasound performed by an experienced investigator are obtained, minimally invasive parathyroidectomy can be safely recommended (6,24-26). The prevalence of multiglandular parathyroid disease among patients with primary hyperparathyroidism and concordant imaging tests varies from 1% to 3.5% (26,27). Thus, when preoperative localization with sestamibi and ultrasound is concordant for single-gland disease, the use of intraoperative iPTH monitoring is of little value. However, if preoperative localization with sestamibi and ultrasound is not concordant and the surgeon wishes to perform a minimally invasive "selective" operation, the use of intraoperative iPTH monitoring is recommended, as the prevalence of multiglandular disease in this subgroup of patients with primary hyperparathyroidism approaches 17% (25,27,28). Similarly, the use of intraoperative iPTH monitoring is recommended for patients undergoing selective parathyroidectomy on the basis of a single preoperative localization study (27,28).

On the other hand, the accuracy of intraoperative iPTH monitoring in the detection of patients with multiglandular disease is highly dependent on the criteria applied. Few studies have shown that the Miami criterion followed by the Vienna criterion is the best balanced among other criteria, with the highest accuracy in intraoperative prediction of cure (26,29,30). However, the Rome criterion followed by the Halle criterion is most useful in intraoperative detection of multiglandular disease (26,30,31). Nevertheless, their application in patients qualified for minimally invasive parathyroidectomy with concordant results of sestamibi scanning and ultrasound of the neck would result in a significantly higher number of negative conversions to bilateral neck explorations and only a marginal improvement in the success rate of primary operations (26). Thus, the accuracy of intraoperative iPTH monitoring is highly dependent on the criteria used by the surgeon to predict the outcome of parathyroid surgery. The most common criteria used for prognostication of the outcome of parathyroid surgery and their predictive values are summarized in *Table 1* (26).

Value of intraoperative iPTH monitoring in predicting recurrence

Schneider *et al*. reported on long-term results of 1,368 parathyroid operations for primary hyperparathyroidism with intraoperative iPTH monitoring, including 1,006 minimally invasive parathyroidectomies and 380 conventional parathyroidectomies. There were no differences in recurrence between the minimally invasive and conventionally operated groups (2.5% *vs*. 2.1%; P=0.68), and the operative approach did not independently predict recurrent disease in the multivariate analysis. However, the percentage decrease in intraoperative iPTH was protective against recurrence for both the entire cohort (hazard ratio =0.96; 95% confidence interval, 0.93-0.99; P=0.03) and the minimally invasive subset. In addition, a higher postoperative iPTH levels also independently predicted disease recurrence. Thus, the percentage decrease in intraoperative iPTH is one of many adjuncts the surgeon can use to determine which patients are best served by bilateral exploration, whereas the postoperative iPTH can guide follow-up after parathyroidectomy (32).

Wachtel *et al*. analyzed 2,185 subjects undergoing parathyroidectomy with intraoperative iPTH monitoring and noted that 5.0% (n=110) experienced intraoperative failure (defined as failure to decrease iPTH intraoperatively by ≥50% and into the normal range). The intraoperative failure group had more multiglandular disease (35.2% *vs*. 16.6%, P<0.001) and smaller glands (13 *vs*. 15 mm, P=0.048) compared to the patients who experienced intraoperative success. On multivariate analysis, post-excision iPTH level was statistically, but not clinically, significantly associated with intraoperative failure (odds ratio =1.0; 95% confidence interval, 1.000-1.003). Persistent hyperparathyroidism was identified in 2.5% (n=15) of 592 patients with ≥6-month follow-up. Median intraoperative iPTH decrease was lower in patients with persistent hyperparathyroidism (67.1% *vs*. 85.8%, P<0.001). Thus, the authors concluded that intraoperative failure was associated with higher rates of multiglandular disease and smaller parathyroid glands. In addition, patients with persistent disease had significantly lower decreases in intraoperative iPTH values, but one-half of patients who experienced failure by intraoperative iPTH assay criterion were eucalcemic 6-month postoperatively (33). This observation was also confirmed by Wharry *et al*., who analyzed 1,108 initial parathyroid operations for sporadic primary hyperparathyroidism using intraoperative iPTH monitoring and reported that a final intraoperative iPTH level that was within the normal range and dropped by >50% from baseline was a strong predictor of operative success. Long-term recurrence was more likely in patients with a final intraoperative iPTH level of 41-65 pg/mL than with a level ≤40 pg/mL (1.2% *vs*. 0%; P=0.016). Hence, patients with a final intraoperative iPTH level between 41-65 pg/mL should be followed up beyond 6 months for long-term recurrence (34).

Cost-effectiveness of intraoperative iPTH monitoring

The added value of intraoperative iPTH monitoring remains controversial, because its ability to prevent failure of parathyroidectomy due to unrecognized multiple gland disease must be balanced against assay-related costs. Morris *et al*. performed a literature review focused on this issue and identified 17 studies involving 4,280 unique patients, permitting estimation of base case costs and probabilities using a decision tree and cost analysis model (35). The base case assumption was that in well-localized primary hyperparathyroidism, intraoperative iPTH monitoring would increase the success rate of minimally invasive parathyroidectomy from 96.3% to 98.8%. The cost of intraoperative iPTH varied with operating room time used. Intraoperative iPTH monitoring reduced overall treatment costs only when total assay-related costs fell below $110 per case. Inaccurate localization and high reoperation cost both independently increased the value of intraoperative iPTH monitoring. The intraoperative iPTH strategy was cost-saving when the rate of unrecognized multiglandular disease exceeded 6% or if the cost of reoperation exceeded $12,000 (compared with initial minimally invasive parathyroidectomy cost of $3,733). Setting the positive predictive value (PPV) of intraoperative iPTH monitoring at 100% and reducing the false-negative rate to 0% did not substantially alter these findings. The authors concluded that institution-specific factors influenced the value of intraoperative iPTH monitoring. In the analyzed model, intraoperative iPTH monitoring increased the cure rate marginally, while incurring approximately 4% of additional cost (35). One should also take into consideration that advantages and disadvantages of the variety of existing intraoperative iPTH monitoring success criteria are confusing and their assessment is often contradictory. Hence, particularly with respect to cost-benefit aspects, the standard application of this method of intraoperative quality control even in conventional open parathyroidectomy remains a matter of controversy (36). However, the use of intraoperative iPTH monitoring compensates for its cost by

shortening operative time and obviating the need for frozen sections. To decrease the cost of this intraoperative adjunct, some hospitals place the assay cart at the central laboratory, where the system can be used for other purposes and the technician does not need to be relocated to the operative room. This surgical adjunct is most helpful in reducing operative times when used as a point-of-care system in close proximity to the operating room, where PTH levels can be reported as soon as possible, allowing for real-time operative decisions based on iPTH dynamics (37).

The European Society of Endocrine Surgeons (ESES) recommended the use of intraoperative iPTH monitoring for patients undergoing "targeted" parathyroidectomy on the basis of a single preoperative localization study. If preoperative localization with sestamibi and ultrasound is not concordant and the surgeon wishes to perform a minimally invasive "targeted procedure", the use of intraoperative iPTH monitoring is recommended. When preoperative localization with sestamibi and ultrasound is concordant for single-gland disease, the use of this adjunct is of little value. In addition, the use of intraoperative iPTH can be recommended in reoperative parathyroidectomy to lateralize hyperfunctioning parathyroid tissue (internal jugular vein/s sampling) when preoperative localization is uncertain, or to predict cure and reduce the need for continued exploration in the scarred neck (28).

Other applications for intraoperative iPTH monitoring

Intraoperative iPTH assay can be utilized to differentiate between parathyroid and non-parathyroid tissue, such as thyroid nodules and lymph nodes, with a specificity of 100% by iPTH measurement in the fine-needle aspiration washout (19-21). The aspirated content in the needle is diluted with 1 mL of saline solution, centrifuged, and the supernatant is used for iPTH measurement. This technique is faster than frozen section if the quick assay is used as a point-of-care system, which can be very helpful when gland identification is difficult, e.g., in the case of an intrathyroidal parathyroid or a lesion that could be a thyroid nodule versus a subcapsular parathyroid gland (37).

In addition, intraoperative iPTH measurement can be used to lateralize the side of the neck harboring hyperfunctioning parathyroid tissue by determination of jugular venous gradient in patients with negative or discordant preoperative imaging studies, in order to increase the number of patients eligible for unilateral neck exploration (22,23). In this technique, which is positive in 70% to 81% of cases, 3 mL of whole blood is collected under ultrasound guidance from the most caudal portion in the neck of both internal jugular veins, just before skin incision. Intact PTH levels are then measured in both jugular vein samples, as well as in the initially collected sample from the peripheral access (37). The unilateral neck exploration is undertaken on the side of the neck indexed by the highest iPTH value and terminated after successful removal of a hyperfunctioning parathyroid gland using intraoperative iPTH monitoring to assure cure from hyperparathyroid state.

Conclusions

Minimally invasive parathyroidectomy guided by intraoperative PTH monitoring is widely accepted among parathyroid surgeons for the treatment of sporadic primary hyperparathyroidism. This intraoperative adjunct warrants the operation to be a safe, highly successful, less invasive procedure, and is associated with a lower prevalence of morbidity than bilateral neck exploration. Surgical awareness of hormone dynamics during parathyroidectomy and adherence to the sampling protocol and interpretation criteria that best fit the individual practice are crucial in achieving intraoperative confidence in predicting operative success and preventing failure in cases of unsuspected multiglandular disease, while safely limiting neck exploration in the majority of patients with sporadic primary hyperparathyroidism.

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References

1. Low RA, Katz AD. Parathyroidectomy via bilateral cervical exploration: a retrospective review of 866 cases. Head Neck 1998;20:583-7.
2. Allendorf J, DiGorgi M, Spanknebel K, et al. 1112 consecutive bilateral neck explorations for primary hyperparathyroidism. World J Surg 2007;31:2075-80.
3. Chen H, Mack E, Starling JR. A comprehensive evaluation of perioperative adjuncts during minimally invasive parathyroidectomy: which is most reliable? Ann Surg 2005;242:375-80; discussion 380-3.
4. Miccoli P, Berti P, Materazzi G, et al. Results of video-

assisted parathyroidectomy: single institution's six-year experience. World J Surg 2004;28:1216-8.
5. Udelsman R. Six hundred fifty-six consecutive explorations for primary hyperparathyroidism. Ann Surg 2002;235:665-70; discussion 670-2.
6. Barczyński M, Cichoń S, Konturek A, et al. Minimally invasive video-assisted parathyroidectomy versus open minimally invasive parathyroidectomy for a solitary parathyroid adenoma: a prospective, randomized, blinded trial. World J Surg 2006;30:721-31.
7. Bergenfelz A, Kanngiesser V, Zielke A, et al. Conventional bilateral cervical exploration versus open minimally invasive parathyroidectomy under local anaesthesia for primary hyperparathyroidism. Br J Surg 2005;92:190-7.
8. Nussbaum SR, Thompson AR, Hutcheson KA, et al. Intraoperative measurement of parathyroid hormone in the surgical management of hyperparathyroidism. Surgery 1988;104:1121-7.
9. Chapuis Y, Fulla Y, Icard P, et al. Peroperative assay of active parathormone 1-84 in surgery of primary hyperparathyroidism. Presse Med 1990;19:1461-2.
10. Irvin GL 3rd, Dembrow VD, Prudhomme DL. Operative monitoring of parathyroid gland hyperfunction. Am J Surg 1991;162:299-302.
11. Boggs JE, Irvin GL 3rd, Molinari AS, et al. Intraoperative parathyroid hormone monitoring as an adjunct to parathyroidectomy. Surgery 1996;120:954-8.
12. Irvin GL 3rd, Carneiro DM, Solorzano CC. Progress in the operative management of sporadic primary hyperparathyroidism over 34 years. Ann Surg 2004;239:704-8; discussion 708-11.
13. Irvin GL 3rd, Solorzano CC, Carneiro DM. Quick intraoperative parathyroid hormone assay: surgical adjunct to allow limited parathyroidectomy, improve success rate, and predict outcome. World J Surg 2004;28:1287-92.
14. Grant CS, Thompson G, Farley D, et al. Primary hyperparathyroidism surgical management since the introduction of minimally invasive parathyroidectomy: Mayo Clinic experience. Arch Surg 2005;140:472-8; discussion 478-9.
15. Westerdahl J, Bergenfelz A. Sestamibi scan-directed parathyroid surgery: potentially high failure rate without measurement of intraoperative parathyroid hormone. World J Surg 2004;28:1132-8.
16. Chen H, Pruhs Z, Starling JR, et al. Intraoperative parathyroid hormone testing improves cure rates in patients undergoing minimally invasive parathyroidectomy. Surgery 2005;138:583-7; discussion 587-90.
17. Cayo AK, Sippel RS, Schaefer S, et al. Utility of intraoperative PTH for primary hyperparathyroidism due to multigland disease. Ann Surg Oncol 2009;16:3450-4.
18. Hughes DT, Miller BS, Doherty GM, et al. Intraoperative parathyroid hormone monitoring in patients with recognized multiglandular primary hyperparathyroidism. World J Surg 2011;35:336-41.
19. Chan RK, Ibrahim SI, Pil P, et al. Validation of a method to replace frozen section during parathyroid exploration by using the rapid parathyroid hormone assay on parathyroid aspirates. Arch Surg 2005;140:371-3.
20. Barczynski M, Golkowski F, Konturek A, et al. Technetium-99m-sestamibi subtraction scintigraphy vs. ultrasonography combined with a rapid parathyroid hormone assay in parathyroid aspirates in preoperative localization of parathyroid adenomas and in directing surgical approach. Clin Endocrinol (Oxf) 2006;65:106-13.
21. James BC, Nagar S, Tracy M, et al. A novel, ultrarapid parathyroid hormone assay to distinguish parathyroid from nonparathyroid tissue. Surgery 2014;156:1638-43.
22. Lew JI, Solorzano CC, Montano RE, et al. Role of intraoperative parathormone monitoring during parathyroidectomy in patients with discordant localization studies. Surgery 2008;144:299-306.
23. Barczynski M, Konturek A, Hubalewska-Dydejczyk A, et al. Utility of intraoperative bilateral internal jugular venous sampling with rapid parathyroid hormone testing in guiding patients with a negative sestamibi scan for minimally invasive parathyroidectomy--a randomized controlled trial. Langenbecks Arch Surg 2009;394:827-35.
24. Mihai R, Barczynski M, Iacobone M, et al. Surgical strategy for sporadic primary hyperparathyroidism an evidence-based approach to surgical strategy, patient selection, surgical access, and reoperations. Langenbecks Arch Surg 2009;394:785-98.
25. Bergenfelz AO, Hellman P, Harrison B, et al. Positional statement of the European Society of Endocrine Surgeons (ESES) on modern techniques in pHPT surgery. Langenbecks Arch Surg 2009;394:761-4.
26. Barczynski M, Konturek A, Hubalewska-Dydejczyk A, et al. Evaluation of Halle, Miami, Rome, and Vienna intraoperative iPTH assay criteria in guiding minimally invasive parathyroidectomy. Langenbecks Arch Surg 2009;394:843-9.
27. Barczynski M, Konturek A, Cichon S, et al. Intraoperative parathyroid hormone assay improves outcomes of minimally invasive parathyroidectomy mainly in patients with a presumed solitary parathyroid adenoma and missing

concordance of preoperative imaging. Clin Endocrinol (Oxf) 2007;66:878-85.
28. Harrison BJ, Triponez F. Intraoperative adjuncts in surgery for primary hyperparathyroidism. Langenbecks Arch Surg 2009;394:799-809.
29. Carneiro DM, Solorzano CC, Nader MC, et al. Comparison of intraoperative iPTH assay (QPTH) criteria in guiding parathyroidectomy: which criterion is the most accurate? Surgery 2003;134:973-9; discussion 979-81.
30. Riss P, Kaczirek K, Heinz G, et al. A "defined baseline" in PTH monitoring increases surgical success in patients with multiple gland disease. Surgery 2007;142:398-404.
31. Lombardi CP, Raffaelli M, Traini E, et al. Intraoperative PTH monitoring during parathyroidectomy: the need for stricter criteria to detect multiglandular disease. Langenbecks Arch Surg 2008;393:639-45.
32. Schneider DF, Mazeh H, Chen H, et al. Predictors of recurrence in primary hyperparathyroidism: an analysis of 1386 cases. Ann Surg 2014;259:563-8.
33. Wachtel H, Cerullo I, Bartlett EK, et al. What Can We Learn from Intraoperative Parathyroid Hormone Levels that Do Not Drop Appropriately? Ann Surg Oncol 2014. [Epub ahead of print].
34. Wharry LI, Yip L, Armstrong MJ, et al. The final intraoperative parathyroid hormone level: how low should it go? World J Surg 2014;38:558-63.
35. Morris LF, Zanocco K, Ituarte PH, et al. The value of intraoperative parathyroid hormone monitoring in localized primary hyperparathyroidism: a cost analysis. Ann Surg Oncol 2010;17:679-85.
36. Lorenz K, Dralle H. Intraoperative parathyroid hormone determination for primary hyperparathyroidism. Chirurg 2010;81:636, 638-42.
37. Carneiro-Pla D, Pellitteri PK. Intraoperative PTH monitoring during parathyroid surgery. In: Randolph GW. eds. Surgery of the thyroid and parathyroid glands, 2nd ed. Philadelphia: Elsevier Saunders, 2013:605-12.

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Minimally invasive parathyroid surgery

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Abstract: Traditionally, bilateral cervical exploration for localization of all four parathyroid glands and removal of any that are grossly enlarged has been the standard surgical treatment for primary hyperparathyroidism (PHPT). With the advances in preoperative localization studies and greater public demand for less invasive procedures, novel targeted, minimally invasive techniques to the parathyroid glands have been described and practiced over the past 2 decades. Minimally invasive parathyroidectomy (MIP) can be done either through the standard Kocher incision, a smaller midline incision, with video assistance (purely endoscopic and video-assisted techniques), or through an ectopically placed, extracervical, incision. In current practice, once PHPT is diagnosed, preoperative evaluation using high-resolution radiographic imaging to localize the offending parathyroid gland is essential if MIP is to be considered. The imaging study results suggest where the surgeon should begin the focused procedure and serve as a road map to allow tailoring of an efficient, imaging-guided dissection while eliminating the unnecessary dissection of multiple glands or a bilateral exploration. Intraoperative parathyroid hormone (IOPTH) levels may be measured during the procedure, or a gamma probe used during radioguided parathyroidectomy, to ascertain that the correct gland has been excised and that no other hyperfunctional tissue is present. MIP has many advantages over the traditional bilateral, four-gland exploration. MIP can be performed using local anesthesia, requires less operative time, results in fewer complications, and offers an improved cosmetic result and greater patient satisfaction. Additional advantages of MIP are earlier hospital discharge and decreased overall associated costs. This article aims to address the considerations for accomplishing MIP, including the role of preoperative imaging studies, intraoperative adjuncts, and surgical techniques.

Keywords: Primary hyperparathyroidism; hypercalcemia; parathyroid adenoma; parathyroidectomy; minimally invasive; focused; unilateral; parathyroid surgery; video-assisted; robotic

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Background

Historically, until the 1990s, bilateral cervical exploration for localization of all four parathyroid glands and removal of any that were grossly enlarged had been the standard surgical treatment for primary hyperparathyroidism (PHPT). Challenges with intraoperative adenoma localization and damage to surrounding structures have long hindered utilizing less invasive approaches for parathyroidectomy. In the past two decades however, significant improvements in the accuracy and reliability of preoperative localization studies have facilitated further advances in surgical management, allowing a more targeted, minimally invasive surgical approach. Minimally invasive parathyroidectomy (MIP) is defined as any focused surgical approach that preoperatively aims to identify and remove a single enlarged parathyroid gland (focused or targeted parathyroidectomy) and may in certain circumstances allow examination of the ipsilateral gland as well (unilateral parathyroidectomy). Because 80-90% of patients with PHPT have a solitary parathyroid adenoma, resection of one gland leads to cure (normocalcemia for 6 months

Table 1 The Fourth International Workshop from the 2014 National Institutes of Health recommendations on the management of asymptomatic PHPT (5). If any one of these criteria is met, the patient is considered to be a candidate for parathyroid surgery

Guidelines for parathyroidectomy
Serum calcium is greater than 1 mg/dL (0.25 mmol/L) above the upper limit of normal
Creatinine clearance below 60 mL/min/1.73 m^2
Patients are younger than 50 years of age
Bone mineral density measurement is reduced >2.5 standard deviations at spine, hip, or radius, or presence of vertebral fracture
24-h urine for calcium >400 mg/d (10 mmol/d) and increased stone risk by biochemical stone risk analysis
Presence of nephrolithiasis or nephrocalcinosis
Patient requests surgery, or patient is unsuitable for long-term surveillance

following surgery) in most cases while eliminating the unnecessary dissection of multiple glands or a bilateral exploration.

The first unilateral approach for solitary parathyroid adenomas was reported in 1982. The procedure involved the removal of both a parathyroid adenoma and ipsilateral normal parathyroid gland (1). Since then, several minimally invasive techniques have been described, including radio-guided parathyroidectomy, endoscopic parathyroidectomy with gas insufflation, and video-assisted parathyroidectomy without gas insufflation. The confluence of improved adenoma localization using different preoperative localization studies and the concomitant advent of minimally invasive approaches have led to fewer complications, shorter operative time, shorter hospitalization, a more rapid postoperative recovery, an improved cosmetic result, and greater patient satisfaction (2,3). Minimally invasive parathyroidectomy has become the preferred procedure over bilateral neck exploration for PHPT by most endocrine surgeons. Nonetheless, a prospective randomized controlled trial, conducted by a large volume center with significant experience comparing unilateral to bilateral neck exploration showed no statistical differences between complication rates, costs, and operative time between the two groups (4). If this experience is not available, MIP is recommended when a parathyroid adenoma is localized preoperatively, as it can be removed without visualizing the other glands, and the rapid intraoperative parathyroid hormone (IOPTH) assay is employed to confirm an adequate resection. Minimal access techniques have therefore replaced a bilateral neck exploration in patients with localized disease, although a traditional cervical incision with bilateral neck exploration remains the indicated approach for non-localized disease.

Candidates for minimally invasive parathyroidectomy

Patients being evaluated for MIP should undergo a comprehensive history and physical examination in addition to routine laboratory testing to establish the diagnosis of PHPT. While most patients with PHPT are asymptomatic, this does not negate the need for eliciting pertinent symptoms related to a history of renal calculi, renal failure, pathologic fractures, and a family history of multiple endocrine neoplasia (MEN). In addition to this, a history of prior neck surgery should be obtained. A physical examination should be performed and should include palpation for existing thyroid nodules or lymphadenopathy. The next step in the workup of a patient with a presumed hyperfunctioning parathyroid gland should include efforts to definitely localize the gland, which entails the use of high-resolution radiographic imaging and nuclear medicine modalities.

The indications for MIP are the same as those for traditional cervical exploration, that is, symptomatic patients or those with asymptomatic PHPT fulfilling the criteria established by the most recent National Institutes of Health consensus meeting (*Table 1*) (5). Consideration should be given to the differential diagnosis of benign familial hypocalciuric hypercalcemia and vitamin D deficiency based on past medical history and interpretation of biochemical values. A MIP technique can be successfully performed for patients with persistent or recurrent disease. However, MIP is rarely employed when preoperative localization of the hyperfunctioning parathyroid gland is not performed, is negative, discordant on multiple imaging studies, or is consistent with multiglandular enlargement. A conventional, 4-gland exploration approach should be performed in these cases and is usually accomplished through a small cervical

Table 2 Contraindications to minimally invasive parathyroidectomy

Absolute contraindications	Relative contraindications
Previous neck irradiation therapy	Previous neck surgery
Equivocal localization studies	Anticoagulation therapy
Suspected multiglandular disease	Known contralateral recurrent laryngeal nerve injury
Parathyroid carcinoma	Chronic renal failure
Family history of MEN	Morbid obesity
Concomitant thyroid pathology	

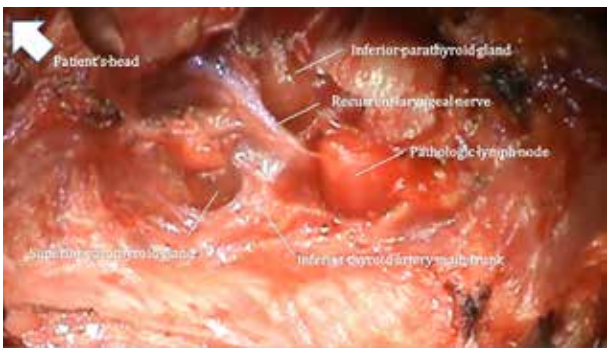

Figure 1 Anatomic location of the right superior and inferior parathyroid glands in relation to the right recurrent laryngeal nerve. The inferior parathyroid glands are consistently anterior (ventral) to the recurrent laryngeal nerve, whereas the pedicle to the superior parathyroid gland is always posterior (dorsal) to the recurrent laryngeal nerve. Image obtained during right thyroid lobectomy.

incision. A comprehensive list of contraindications to MIP is presented in *Table 2*.

The informed consent process should include discussion with the patient on the possibility of conversion to a traditional incision or 4-gland exploration around 7% of the time based on data from large-volume centers, in addition to the usual risks of parathyroid surgery.

Anatomic considerations

The focused approach of MIP requires an intimate familiarity with the location of normal and aberrant parathyroid glands and their relationship to surrounding landmarks within the neck. The location of the parathyroid gland follows definite embryonically influenced patterns. Superior parathyroid glands are embryologically derived from the 4th branchial pouch while the inferior parathyroid glands originate from the 3rd branchial pouch. As superior parathyroid glands have a shorter distance of migration, their location tends to be more consistent compared to that of the inferior parathyroid glands. A systematic approach should be adopted in obtaining adequate exposure for visualization of the parathyroid bearing regions which often entails ligation of the middle thyroid vein to allow for medial retraction of the thyroid lobe, identification of the prevertebral fascial plane (also known as the viscerovertebral angle) between the thyroid lobe and carotid artery and the tracheoesophageal groove. Following medial retraction of the thyroid lobe, the superior parathyroid glands are usually located within the tracheoesophageal groove and have a posterior-lateral relationship to the recurrent laryngeal nerve. Aberrant superior parathyroid glands may however lie within the posterior superior mediastinum or in a retroesophageal location. The inferior parathyroid artery commonly courses anteriorly to the gland. Inferior parathyroid adenomas usually lie in an antero-inferior location to the thyroid lobe within a fatty envelope, which is often contiguous with the thyrothymic ligament. The recurrent laryngeal nerve conventionally has a posterior relation to the inferior parathyroid gland and once identified, dissection of the gland proceeds first along its lateral and posterior aspect to allow for progressive medial retraction and eventual ligation of medial vessels close to the thyroid gland (*Figure 1*). The absence of an inferior parathyroid gland in its normal location should prompt exploration in a perithymic location or superior anterior mediastinum. A summary of anatomic pearls for MIP is presented in *Table 3*.

Preoperative localizing imaging studies

Although preoperative localizing studies were historically considered not necessary for patients undergoing initial bilateral neck exploration, current trends toward minimally

Table 3 Anatomic pearls in minimally invasive parathyroidectomy

Superior parathyroid glands can be inferior to the inferior gland, yet still retain their normal position dorsal to the recurrent laryngeal nerve
The vast majority of superior parathyroid glands are within 1 cm of the junction of the inferior thyroidal artery main trunk and recurrent laryngeal nerve
The recurrent laryngeal nerve is more oblique (extending from lateral to medial) on the right side than the left, which ascends in a more strictly caudal-to-cranial direction
When located within the thyroid capsule, enlarged parathyroid glands expand but remain within the confines of the surgical capsule of the thyroid
When located external to the thyroid capsule, enlarged parathyroid glands become displaced posteriorly behind the gland in the tracheoesophageal region.

invasive surgery with limited exploration of the neck are only made possible by preoperative localization studies. Parathyroid localizing studies have evolved since their inception in the late 1960s. Today, the role of preoperative localization studies is to assist the surgeon in identifying the precise anatomic location of a hyperfunctioning parathyroid gland and its relationship to adjacent structures, thus enabling a more focused exploration. Imaging studies have no role in the diagnosis PHPT or in the decision to proceed with surgery. Preoperative localization studies should only be obtained after a diagnosis of PHPT is made. Presently a variety of noninvasive and invasive imaging studies are available. Usually, preoperative imaging studies include ultrasound, nuclear medicine (specifically the sestamibi scan), or computed tomography examinations, either alone or in combination. Ideally, preoperative localization studies should include a nuclear medicine imaging study to provide information of gland function in combination with an anatomic imaging study, to provide useful information about surrounding structures and regional anatomy. This information, gathered by combination of both imaging modalities, allows for optimization of preoperative planning and surgery.

The quality, sensitivity, and specificity of these imaging studies depend on the skill and experience of the person performing and interpreting them, therefore, it is necessary to secure the services of a dedicated team of imaging professionals with experience and an interest in parathyroid disease. The surgeon should direct the selection and order of the preoperative images to be obtained in order to tailor the most efficient and effective surgical intervention.

Table 4 Factors that limit the accuracy of ultrasound imaging

Operator skill and experience
Obesity
Smaller gland size
Concurrent thyroid pathology (i.e., thyroiditis, multinodular goiter)
Reoperative cases or previous neck surgery
Retrotracheal, retroesophageal, and mediastinal glands
Multiglandular disease

Noninvasive methods

High-resolution ultrasound

Of all the imaging modalities, ultrasound is the least expensive and least invasive; it does not involve radiation and is readily accessible. It is performed using a high-frequency linear transducer ideally in the range of 12-15 mHz. Parathyroid glands appear as well-circumscribed and oval, hypoechoic, and usually solid nodules. *Table 4* summarizes the factors that limit the accuracy of ultrasound imaging. The surgeon must always keep in mind the possibility of an intrathyroidal parathyroid adenoma, which can present in up to 5% of cases, thus requiring proper patient counseling for a possible thyroid lobectomy. The sensitivity of ultrasound detection of parathyroid adenomas ranges from 27-95%, with a specificity of 92-97%. It is the operator experience that has the greatest effect on the ability to detect diseased parathyroid glands and likely accounts for the wide range of reported sensitivity.

US-guided fine-needle aspiration (FNA) can be considered to confirm intrathyroidal parathyroid adenomas or in selected cases of persistent or recurrent PHPT after failed exploration. An elevated PTH washout concentration from the FNA can help identify parathyroid gland lesions. With the PTH washout technique, MIP can be implemented even with negative cytology, thus allowing success of a targeted surgical approach in difficult reoperative cases.

Nuclear medicine sestamibi scan

Technetium (Tc-99m) sestamibi scan detects mitochondrial uptake of the radionuclide tracer in areas

Table 5 Positive predictive values of various preoperative localization studies

Ultrasound	Sestamibi	CT	MRI	PET
60-92%	78-100%	36-100%	51-100%	70-74%

Abbreviations: PET, positron emission tomography; CT, computed tomogra-phy; MRI, magnetic resonance imaging.

of hyperfunctioning tissue. The injected tracer is initially concentrated in normal thyroid and abnormal parathyroid tissues. The concentration in normal thyroid tissue decreases rapidly, leaving behind foci of relatively enhanced uptake of the tracer in abnormal thyroid and parathyroid tissues. After injection of the radiotracer, one set of images is taken within 15 minutes and then a delayed set is taken at 2 hours. Asymmetry of uptake can be noted on early images, but usually, the delayed images are necessary to locate the focus of radiotracer, which characterizes hyperfunctioning parathyroid. A lack of retention of the tracer does not exclude the diagnosis of PHPT, as sestamibi imaging can miss small parathyroid adenomas and hyperplasia. The combination of ultrasound and sestamibi scintigraphy to localize hyperfunctioning parathyroid glands preoperatively increases the sensitivity to 95% because each modality contributes complementary data to help determine the offending gland(s) location (*Table 5*) (6).

Multiphase computed tomography (CT)

This is an imaging modality that is similar to CT angiography. The name is derived from 3-dimensional CT scanning with an added dimension from the changes in perfusion of contrast over time. Multiphase CT generates exquisitely detailed, multilane images of the neck and allows the visualization of differences in the perfusion characteristics of hyperfunctioning parathyroid glands (i.e., rapid uptake and washout), compared with normal parathyroid glands and other structures in the neck. The images that are generated by multiphase CT provide both anatomic information and functional information in a single study that the operating surgeon can interpret easily and may serve an important role in localization before both initial and reoperative parathyroid procedures.

Magnetic resonance imaging (MRI)

MRI may be selectively applied for parathyroid imaging. Hyperfunctional parathyroid glands tend to be isointense to low signal intensity on T1-weighted images, high signal intensity on T2-weighted images, and with intense enhancement after intravenous gadolinium administration. MRI evaluation of parathyroid localization may be more applicable for ectopic adenomas located in the mediastinum. Limitations of the use of MRI include cost and patient compliance with reference to a sense of close confinement during examination.

Invasive methods

Fine-needle aspiration (FNA) biopsy

It may be applied with either CT or ultrasound guidance for correct needle placement in suspected abnormal parathyroid tissue during localization in preparation for reoperative surgery, where radiographic findings are otherwise equivocal. Cytologic evaluation of tissue samples obtained by FNA biopsy is less sensitive than measuring washout PTH levels of the aspirate material, because follicular thyroid tumors may be misinterpreted as parathyroid tissue under cytologic review. PTH washout is an accurate way to localize culprit lesions in patients with findings indicating parathyroid lesions on neck ultrasound.

Selective arteriography

Selective angiographic injection of the inferior thyroid arteries will demonstrate a vascular blush that may be present in up to 25-70% of parathyroid adenomas. Significant complications attributable to this technique have been reported and include central nervous system embolic infarction and potential quadriplegia. As a consequence of these potential risks and because of improvements in noninvasive imaging studies, selective parathyroid arteriography is rarely performed currently. A more selective arteriographic modality is that of super selective digital subtraction angiography. This is a highly sensitive method for localization of ectopic parathyroid tissue and has an indication for patients with recurrent or persistent PHPT in whom previous noninvasive testing has failed to identify the adenoma in a usual or utopic location.

Selective venous sampling

This modality is performed by catheterization of veins draining the neck and mediastinum. By obtaining blood samples and comparing PTH levels obtained from sampling of the iliac veins with those obtained from thyroid veins (superior, middle and inferior), vertebral veins, and the thymic vein, the anticipated location of the adenoma will be within the area where venous PTH levels are at least twice

as high as the systemic levels. Selective venous sampling has been shown to be more accurate than large vein sampling, with accuracy of 83% as contrasted to 29%, respectively. This modality became significantly more accurate with the utilization of improved intact PTH assays, which increased the sensitivity of venous sampling to 87-95% in some investigations. Selective venous sampling should be reserved for patients requiring reoperation and in whom noninvasive studies are negative, equivocal, or conflicting. This modality is technically challenging and its success depends on an experienced interventional radiologist.

Intraoperative adjuncts

Intraoperative ultrasound

The availability of high-resolution ultrasound has led some surgeons to further utilize it in their operating room. Intraoperative ultrasound may be useful in a number of operative settings. Using this adjunct will allow the surgeon to scan the neck and, where possible, correlate structures with preoperative images just prior to surgery. This achieves accurate visualization of the ultimate position of both the parathyroid lesion and other structures in the neck, in particular the relation to the internal jugular vein and carotid artery. This technique may also assist in precisely localizing the incision once the patient is in the neck extension position, for an ideal access for removal of parathyroid tissue. Ultrasound can be combined with FNA for PTH to interrogate hypoechoic structures identified in the thyroid or neck intraoperatively.

Frozen section analysis

The histological identification of parathyroid tissue relies on the identification of three types of cells that comprise the parathyroid tissue; chief, oxyphil, and water clear cells. Chief cells can be similar to thyroid follicular cells and oxyphil cells are indistinguishable from thyroid Hurthle cells, thus the distinction of parathyroid from thyroid tissue is more challenging. However, follicles and colloid like material are uncommon in parathyroid specimens. Frozen section is an unreliable method for distinguishing between multiglandular disease and adenomas. The distinction between hyperplasia and adenoma is not based on pathologic criteria, rather on the operative findings. If the pathologist receives a biopsy from a single parathyroid gland for frozen section interpretation, the possible diagnosis would be, hypercellular parathyroid tissue. An adenoma can be diagnosed with confidence if only one gland of the four glands is enlarged and hypercellular. Therefore, without biopsies from all four glands, the pathologist is unable to determine the cellularity of the remaining parathyroid glands. Nevertheless, the use of frozen section to distinguish parathyroid tissue from non-parathyroid tissue has an accuracy of 99.2% (7).

Intraoperative PTH assay

To further improve the surgical success of MIP and to minimize the possibility of persistent or recurrent PHPT after surgery, some have advocated the use of surgical adjuncts such as IOPTH monitoring. IOPTH is useful in assessing the adequacy of resection by functional means without the need to expose all the parathyroid glands. Before exiting the operating room, the surgeon can confirm that the patient will be eucalcemic by demonstrating an appropriate reduction in IOPTH levels after excision of all hyperfunctioning parathyroid tissue. The ability to confirm complete removal of all hypersecreting glands and predict operative success minimizes operative time, diminishes the need for bilateral neck exploration, and improves cure rates (8). IOPTH is based on the short half-life of circulating PTH. PTH is cleared from the blood in an early rapid phase with a half-life variably reported as 1.5-21.5 minutes in patients with normal renal function. PTH levels are measured preoperatively and at set post-excision times. Due to the different IOPTH decrease criteria for a successful operation, several studies aimed to identify the optimal criteria and its predictive cure rate. A decline of >50% in iPTH level from the highest pre-incision or pre-excision level is associated with predictive cure in 94-97% of cases (9,10). We prefer a PTH drop of at least 50% and into the normal range before concluding the procedure. The single criterion of PTH drop into the normal range is somewhat problematic as some patients have a normal or slightly elevated baseline levels and thus some institutions adjusted their criteria and required a 50% PTH drop with and/or normalization of PTH levels. Different criteria may be utilized with similar accuracy rates (*Table 6*) (11). When used correctly, we believe that IOPTH is the most accurate adjunct available to the surgeon performing parathyroid surgery. Nonetheless, when there are concordant Sestamibi scans and US localization, IOPTH appears to add little benefit to the cure rate (12).

Of note, there is a distinct entity of parathyroid disease that manifests normal PTH levels and can therefore be referred to as normohormonal PHPT. Interestingly, a normohormonal parathyroid disorder may occur with iPTH

Table 6 Different available criteria for successful parathyroidectomy using intraoperative PTH monitoring

Institute	And/Or	Minute	Drop	Compared to	PTH levels
Miami		10	≥50%	Pre-incision	
				Pre-excision	
Vienna		10	≥50%	Pre-incision	
Rotterdam	Or	10	>70%		And PTH 100-200 ng/L
		10	>80%		And PTH >200 ng/L
Ann Arbor	And		50%	Baseline	
		5 or 10			12-75 pg/mL
Wisconsin		5, 10, or 15	≥50%	Pre-incision, T5 if higher	

Abbreviation: PTH, parathyroid hormone.

levels as low as 5-15 pg/mL, which is at the lowest reference point of most iPTH assays or below the detectable range. Awareness of this unusual phenotype may facilitate earlier diagnosis and surgery. Nonetheless, it is particularly difficult to apply this intraoperative adjunct to decide the surgical cure of the patient when the serum PTH level is within the normal range. Very few studies have focused on this issue, and we believe the utility of IOPTH monitoring in this subset of patients needs to be further studied.

Surgical technique

Minimally invasive parathyroidectomy encompasses a number of different techniques, including open approaches using "mini-incisions", minimally invasive radio-guided parathyroidectomy, video-assisted parathyroidectomy, and purely endoscopic parathyroidectomy with or without robotic assistance. Nonetheless, the term minimally invasive should be reserved for procedures that allow parathyroidectomy through access that minimizes trauma of the surgical exposure and dissection. Minimally invasive parathyroidectomy should obtain at least the same cure outcome of traditional 4-gland exploration, with the main advantage of reducing the skin incision and, consequently, allowing better cosmetic results. Other advantages are decreased postoperative pain, which should be mainly related to less extensive surgical dissection.

Open minimally invasive parathyroidectomy

This approach represents the most widespread minimally invasive technique, performed through a small, 1-2 inch central, or a lateral (over the adenoma location, overlying the anterior border of the sternocleidomastoid muscle) incision, guided by preoperative localization studies and IOPTH. This approach is straightforward, can be reproduced in different surgical settings, and can be performed under locoregional anesthesia, with reduced operative time and as a short-stay procedure (13).

Using a central or midline incision allows access to virtually all localized inferior glands and many non-ectopic superior parathyroid glands. The lateral approach is classically used for re-operative parathyroid surgery. Some advocate this approach for superior parathyroid adenomas that are deep or lateral in their position. Regardless of the type of approach, general surgical principles similar to that of traditional parathyroidectomy are of great importance, given the narrow working space. These include meticulous hemostasis with clips or diathermy, adequate exposure of the prevertebral fascia between the thyroid lobe and carotid artery, and the identification and preservation of the recurrent laryngeal nerve. Once the parathyroid tumor is identified, it is highly critical to handle the tumor gently to avoid rupture of the capsule with ensuing spillage and bleeding.

The main limitation of this technique resides in the potential poor visualization of the neck structures, because of the small size of the skin incision or, conversely, the need for a larger skin incision when compared with video-assisted or endoscopic techniques. An advantage is quick conversion to a bilateral neck exploration if need be, sometimes even without enlargement of the skin incision.

Video-assisted parathyroidectomy

This approach was first described by Miccoli *et al.* (14). Early after its first description, this technique encountered worldwide acceptance, as it is easy to reproduce in different surgical settings. This method requires two assistants, one

for holding retraction and the other for endoscope placement in addition to the primary surgeon, with monitors placed on either side of the assistants for optimal visualization of the surgical field. A 1.5 cm transverse incision is carried out 2 cm above the sternal notch, followed by dissection to the level of the midline raphe. The midline raphe is divided in a superior to inferior direction by 4 cm, followed by retraction of the strap muscles ipsilateral to the localized adenoma. A second retractor is utilized to perform medial reflection of the ipsilateral thyroid lobe. Insertion of a 30° 5 mm endoscope through the insertion follows. Exploration commences on the ipsilateral side of the anticipated location of the parathyroid adenoma based on preoperative imaging. The middle thyroid vein is divided, followed by the use of a dissecting spatula to expose the carotid artery laterally, pre-vertebral plane posteriorly and groove between the thyroid and trachea using spatulated instruments before surgical exploration of the parathyroid adenoma commences. Effort is made to identify the location and course of the recurrent laryngeal nerve before any vessel ligation around the vicinity of the parathyroid adenoma is performed. The hyperfunctioning parathyroid gland is then removed and retrieved through the incision followed by measurement of IOPTH prior to closure of the incision site.

The main advantages of these approaches are the direct access to the gland and small neck incisions. To date, all published series reported less operative pain, better cosmesis, shorter hospital stay, and ability to perform these surgeries on an outpatient basis. However, since incisions are made in the neck, for some they remain visible and prone to hypertrophy and keloid formation. Furthermore, some surgeons would argue that given the strict selection criteria used, such as nodule size ≤3 cm in diameter, thyroid volume ≤30 mL, previous conventional neck surgery, recurrent or persistent PHPT, an open approach using a similar incision is also possible. This partly led some surgeons to pursue the indirect/extracervical, remote approaches. Nonetheless, with increasing experience, selection criteria for minimally invasive video-assisted parathyroidectomy have been refined and widened.

Radio-guided Tc-99m sestamibi

Tc-99m sestamibi uptake by parathyroid tissue is a function of metabolic activity. This forms the basis for utilizing sestamibi scans to localize hyperfunctioning parathyroid glands in patients with PHPT. Patients are injected with a Tc-99m sestamibi isotope on the day of surgery, usually within approximately 2 hours of the operation. A hand-held gamma probe is used to direct the incision site and to localize the abnormal parathyroid glands. The initial scan provides information regarding localization of presumed adenomas and the presence of delayed uptake of nuclear material within the thyroid gland. After identification and removal of the abnormal parathyroid gland, the gamma probe may be used to confirm high metabolic activity within the resected tissue as compared with the radioactivity of the surgical bed, thus validating that no additional hyperactive glands remain behind. Potential advantages of radioguided parathyroid identification include facilitation of targeted parathyroidectomy, shorter operating time and verification of successful surgery. Absolute contraindications for radioguided parathyroidectomy include pregnancy and allergy or sensitivity to Tc-99m sestamibi. The Twenty percent rule, published by Murphy and Norman, which suggests that any excised tissue containing >20% of background radioactivity in a patient with a positive Sestamibi scan, results in finding a solitary parathyroid adenoma (15). This protocol, however, has limited ability to exclude non parathyroid tissue or multiglandular disease, and that the signal is proportional to the gland size.

The overall accuracy of radioguided parathyroidectomy is 83% with a conversion rate to bilateral neck exploration of 10% for single gland disease, 50% for multiglandular disease and 50% for hyperplasia. The gamma probe is considered unhelpful in up to 48% of cases. The limitations include logistic difficulties with timing isotope injection, equipment problems, confusing counts, and easily identified abnormal glands. Therefore, most parathyroid surgeons will only consider intraoperative radioguided parathyroidectomy in patients with an ectopic parathyroid adenoma or previous thyroidectomy where confusing background counts are not a concern.

Endoscopic parathyroidectomy

Procedures that utilize the endoscope take advantage not only of a targeted approach but also of the endoscopic magnification with optimal visualization of the neck structures, such as the recurrent laryngeal nerve and parathyroid glands. These procedures require dedicated surgical instrumentation, and an adequate and relatively prolonged learning curve.

Anterior endoscopic approach

Gagner first described this totally endoscopic approach

in 1996 (16). It is carried out entirely under steady gas flow, using a 5 mm endoscope introduced through a central trocar, and two or three additional trocars for the instruments. The dissection is first performed beneath the platysma to obtain a good working space. The midline is then opened and the strap muscles retracted to expose the thyroid lobe and explore the parathyroid glands after dissecting the thyroid from the fascia.

These procedures provide an optimal cosmetic result because of the small, distant scars, but they are difficult to reproduce, especially by surgeons who do not have endoscopic experience. In addition, the risks related to CO_2 absorption are not completely eliminated.

Lateral endoscopic approach

This approach was first described by Henry *et al*. (17), characterized by a 12 mm skin incision on the anterior border of the sternocleidomastoid muscle, 3 to 4 cm above the sternal notch on the side of the affected parathyroid gland. Through this incision the tissue is dissected with an open technique in order to reach the prevertebral fascia. Once enough space has been created, two 2.5-mm trocars are inserted on the line of the anterior border of the sternocleidomastoid muscle 3 to 4 cm above and below the first incision through which a 10-mm trocar for the endoscope (10 mm, 0 degrees) is inserted. Dissection is carried out with 8 mmHg carbon dioxide insufflation during the whole procedure. The main technical limitation of the technique is the unilateral approach that prevents the possibility of accomplishing a bilateral exploration when necessary without conversion to an open conventional procedure.

Extracervical/remote access approaches

These approaches involve placing incisions outside the neck, requiring extensive dissection under the skin. The operating space is maintained by either CO_2 insufflation or external retraction by specially designed skin retractors. Recently, the application of robotic technology to further assist the surgeon in accomplishing these techniques facilitated remote access parathyroid surgery and helped avoid the need for insufflation (18). The addition of the da Vinci Si surgical system (Intuitive Surgical, Sunnyvale, CA, USA) could make some of the extracervical approaches technically less challenging but certainly adds cost to the procedure. Moreover, it should be emphasized that the remote access approach is not considered "minimally invasive", as it actually requires much more dissection than the traditional endoscopic parathyroidectomy. A robotic-assisted thoracoscopic approach, an alternative to conventional invasive sternotomy, has also been reported for parathyroid adenomas located within the mediastinum (19).

Summary

The success of MIP has been established by several studies displaying cure and complication rates that are at a minimum equivalent to those achieved by conventional 4-gland exploration. In contrast to bilateral exploration, MIP has been shown to be associated with significantly reduced complications (1.2% *vs*. 3.1%), enhanced cure rates (99.4% *vs*. 97.1%), an approximate 50% reduction in operating time (1.3 *vs*. 2.4 hours), a sevenfold reduction in length of hospital stay (0.24 *vs*. 1.64 days), and a mean savings of $2,700 per procedure (2,3). A prospective randomized controlled trial comparing unilateral to bilateral neck exploration showed no statistical differences between complication rates, costs, and operative time between the two groups (4).

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References

1. Tibblin S, Bondeson AG, Ljungberg O. Unilateral parathyroidectomy in hyperparathyroidism due to single adenoma. Ann Surg 1982;195:245-52.
2. Udelsman R. Six hundred fifty-six consecutive explorations for primary hyperparathyroidism. Ann Surg 2002;235:665-70; discussion 670-2.
3. Udelsman R, Lin Z, Donovan P. The superiority of minimally invasive parathyroidectomy based on 1650 consecutive patients with primary hyperparathyroidism. Ann Surg 2011;253:585-91.
4. Bergenfelz A, Lindblom P, Tibblin S, et al. Unilateral versus bilateral neck exploration for primary hyperparathyroidism: a prospective randomized controlled trial. Ann Surg 2002;236:543-51.
5. Bilezikian JP, Brandi ML, Eastell R, et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. J Clin Endocrinol Metab 2014;99:3561-9.
6. Ruda JM, Hollenbeak CS, Stack BC Jr. A systematic review of the diagnosis and treatment of primary

hyperparathyroidism from 1995 to 2003. Otolaryngol Head Neck Surg 2005;132:359-72.
7. Westra WH, Pritchett DD, Udelsman R. Intraoperative confirmation of parathyroid tissue during parathyroid exploration: a retrospective evaluation of the frozen section. Am J Surg Pathol 1998;22:538-44.
8. Chen H, Pruhs Z, Starling JR, et al. Intraoperative parathyroid hormone testing improves cure rates in patients undergoing minimally invasive parathyroidectomy. Surgery 2005;138:583-7; discussion 587-90.
9. Irvin GL 3rd, Solorzano CC, Carneiro DM. Quick intraoperative parathyroid hormone assay: surgical adjunct to allow limited parathyroidectomy, improve success rate, and predict outcome. World J Surg 2004;28:1287-92.
10. Chiu B, Sturgeon C, Angelos P. Which intraoperative parathyroid hormone assay criterion best predicts operative success? A study of 352 consecutive patients. Arch Surg 2006;141:483-7; discussion 487-8.
11. Mazeh H, Chen H. Intraoperative adjuncts for parathyroid surgery. Expert Rev Endocrinol Metab 2011;6:245-53.
12. Gawande AA, Monchik JM, Abbruzzese TA, et al. Reassessment of parathyroid hormone monitoring during parathyroidectomy for primary hyperparathyroidism after 2 preoperative localization studies. Arch Surg 2006;141:381-4; discussion 384.
13. Lee JA, Inabnet WB 3rd. The surgeon's armamentarium to the surgical treatment of primary hyperparathyroidism. J Surg Oncol 2005;89:130-5.
14. Miccoli P, Pinchera A, Cecchini G, et al. Minimally invasive, video-assisted parathyroid surgery for primary hyperparathyroidism. J Endocrinol Invest 1997;20:429-30.
15. Murphy C, Norman J. The 20% rule: a simple, instantaneous radioactivity measurement defines cure and allows elimination of frozen sections and hormone assays during parathyroidectomy. Surgery 1999;126:1023-8; discussion 1028-9.
16. Gagner M. Endoscopic subtotal parathyroidectomy in patients with primary hyperparathyroidism. Br J Surg 1996;83:875.
17. Henry JF, Defechereux T, Gramatica L, et al. Minimally invasive videoscopic parathyroidectomy by lateral approach. Langenbecks Arch Surg 1999;384:298-301.
18. Noureldine SI, Lewing N, Tufano RP, et al. The role of the robotic-assisted transaxillary gasless approach for the removal of parathyroid adenomas. ORL J Otorhinolaryngol Relat Spec 2014;76:19-24.
19. Bodner J, Profanter C, Prommegger R, et al. Mediastinal parathyroidectomy with the da Vinci robot: presentation of a new technique. J Thorac Cardiovasc Surg 2004;127:1831-2.

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Undescended parathyroid adenomas as cause of persistent hyperparathyroidism

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Background: Undescended glands are a rare cause of primary and secondary hyperparathyroidism (HPT), but they are more common, however, among patients with recurrent HPT or those who have undergone a failed initial cervical exploration. The currently development of more precise noninvasive imaging techniques has improved the results of preoperative diagnosis of these ectopic lesions.

Methods: The operative reports of patients undergoing parathyroidectomy at our institution were reviewed to identify patients with an undescended parathyroid gland adenomas. Demographic, clinical, imaging and surgical variables were recorded.

Results: Three patients were included: 2/598 parathyroidectomies performed for primary HPT and 1/93 performed for secondary HPT. One case is presented as jaw tumor syndrome (JTS). All the patients had undergone at least one operation before the definitive focused surgery and represented 6% of our parathyroid reoperations. No significant complications and no recurrences were observed in the long-term follow up.

Conclusions: Accurate preoperative localization of these lesions was possible with noninvasive studies. High cure rate is possible through selective approach when accurate preoperative localization. Thorough knowledge of parathyroid embryology and meticulous surgical technique are essential, particularly in patients with previous unsuccessful explorations.

Keywords: Undescended parathyroid adenoma (UPA); persistent hyperparathyroidism (HPT); selective surgical approach; parathymus

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Introduction

Undescended parathyroid adenomas (UPA) are very uncommon cause of primary and secondary hyperparathyroidism (HPT). They are far more represented in series of parathyroid reoperations for recurrent or persistent HPT after a failed initial cervical exploration. If an inferior gland has not been identified at the initial operation in an orthotopic or low thymic location, an undescended parathyroid gland should be suspected.

Ectopic parathyroid glands can be located anywhere along the trajectory of their embryological descent. Inferior parathyroid glands are more suitable to descend to abnormal ectopic locations like the mediastinum or to descend incompletely and stand at the carotid sheath. This is likely related to their longer embryologic migration tract (1).

Historically, Hellstrom (2) reported that the term of "parathyroid" might be the reason why surgeons only explored the area around the thyroid gland. Weller (3) named the inferior parathyroid gland as parathymus, due to its vicinity to the thymus during embryologic development and its final position. This term is a reminder that surgeons should be aware of occasional need to explore a wider area of the thymus embryologic descent.

In the past preoperative invasive studies such as arteriography or selective venous sampling were often required to identify UPAs (4). Current development of noninvasive imaging techniques such as single photon

Table 1 Demographic data, presentation, lab tests and previous operations

Patient (n)	Age	Gender	Type of HPT	Symptoms	Serum calcium (mg/dL)	Serum PTH (pg/mL)	Previous procedures (N)	Time to recurrence (months)
1	61	F	pHPT	Kidney stones	11.8	351	1	4
2	42	M	sHPT	Fatigue	10.4	1,405	1	8
3	23	F	HPT-JTS	Kidney stones; osteoporosis	10.6	98	5	68

HPT, hyperparathyroidism; F, female; M, male; sHTP, secondary HPT; pHPT, primary HPT; HPT-JTS, HPT-jaw tumor syndrome.

emission computed tomography (SPECT) has improved the preoperative localization of UPAs and increased the surgical successful rate (5).

Materials and methods

We reviewed the database of patients evaluated and treated in our centre for persistent or recurrent primary and secondary HPT. Operative reports were reviewed to identify patients with an UPA. This was defined as a parathyroid adenoma found >1 cm above the upper pole of the thyroid gland in the vicinity of the common carotid artery bifurcation. Persistent or recurrent HPT was documented in all the patients by elevated serum calcium (>10.2 mg/dL) and PTH >55 pg/mL.

All the patients underwent localizing studies at our institution. Noninvasive studies consisted in ultrasonography, computed tomography, magnetic resonance imaging, technetium 99m sestamibi scintigraphy and single-photon emission computed tomography.

The operative strategy for each patient was determined on the basis of records from the initial exploration and the preoperative localization studies. A selective surgical approach was used in all cases. Intraoperative biopsy was performed to confirm the parathyroid nature of the lesion. Intraoperative PTH determination was used in two cases.

Results

Two patients with UPA were identified from a database of 598 parathyroidectomies for primary HPT (case 1) and 93 for secondary HPT (case 2) initially performed at our institution. A third case (case 3) was referred from another institution for persistent primary HPT-jaw tumor syndrome (JTS) with mutation in germ-line of HRPT2 (CDC73 type). No patient reported a previous family history. Clinical details of these three patients are shown in *Table 1*.

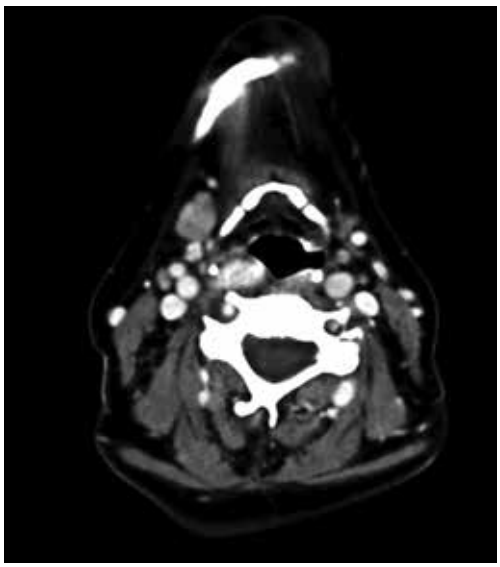

Figure 1 CT scan showing a right parapharyngeal tumor blush in the typical location of an UPA (case 1). CT, computed tomography; UPA, undescended parathyroid adenoma.

Case 1 underwent a bilateral neck exploration (BNE) for a thyroid nodule and primary HPT. A right thyroid lobectomy and left inferior parathyroidectomy were performed, with the pathological findings of benign thyroid nodule and parathyroid adenoma. Three normal parathyroid glands were identified. Hypercalcemia persisted and a both scintigraphy and a CT scan revealed a second undescended adenoma sitting on a fifth gland (*Figure 1*) that was confirmed at reoperation. Intraoperative PTH showed a curative descent from 239 to 69 pg/mL. The patient has remained normocalcemic for five years.

In case 2, a BNE was performed for secondary HPT with the identification and excision of three hyperplasic glands; the left inferior parathyroid gland was not found. A repeat parathyroid scintigraphy with an oblique

projection disclosed a left UPA (*Figure 2*) that was excised at reoperation. An autotransplantation to the forearm was performed. He later received a kidney transplant.

Case 3 was a young woman whose mother had been exposed to radiation in the Chernobyl disaster during her fourth month of pregnancy. As a child she underwent three thyroid and parathyroid explorations in her country of origin. A fourth procedure was performed in a referral Spanish unit and included a right inferior parathyroidectomy, reported as parathyroid carcinoma. Persistent HPT led to a fifth surgical procedure with excision of a cystic parathyroid gland and left thyroid lobectomy. At the time, a mutation in germ-line HRPT-2 was identified and was referred to us with the presumed diagnosis of parathyroid carcinoma with lymph node metastasis in the right lateral compartment II. A SPECT and a neck ultrasound (US) disclosed a hypoechoic nodule close to the carotid bifurcation (*Figure 3*). A right UPA consisting in two separate parathyroid adenomas was found and resected. Intraoperative PTH showed a curative descent from 180 to 21 pg/mL. The patient required calcium and vitamin supplementation for six months. At four years she is normocalcemic and her PTH is 20 pg/mL.

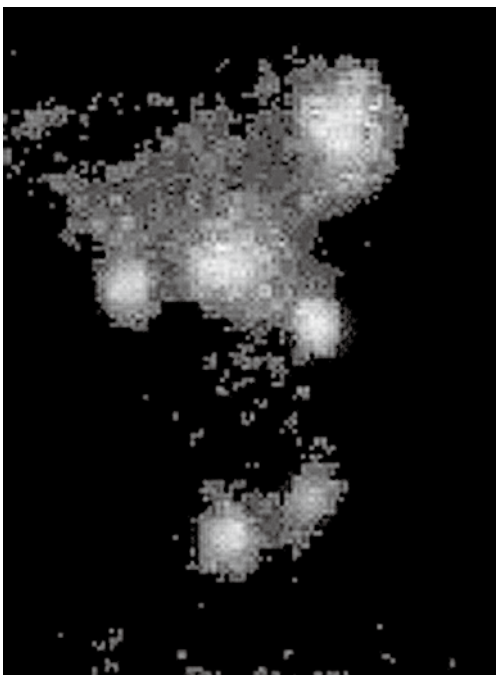

Figure 2 An oblique sestamibi projection clearly showing a left UPA (case 2). UPA, undescended parathyroid adenoma.

Preoperative localizing studies and operative approach are described in *Table 2*. A fine needle aspirate (FNA) was performed on case 3 to rule lymph nodes metastasis. All patients went on to have a successful focused procedure (*Figures 4* and *5*) through a high transverse lateral incision (*Figure 6*). In all cases the location of the UPAs was medial to the carotid bifurcation. The mean operative time was 76 minutes. Autotransplantation was performed in case 2, since three hyperplasic glands had been previously resected. The mean weight of UPAs was 1.6 grs. And two glands were excised in case 3.

Discussion

In the fifth week of the embryogenesis the parathyroid glands arise from endodermal epithelial cells. The superior parathyroid glands derive from the fourth and the inferior

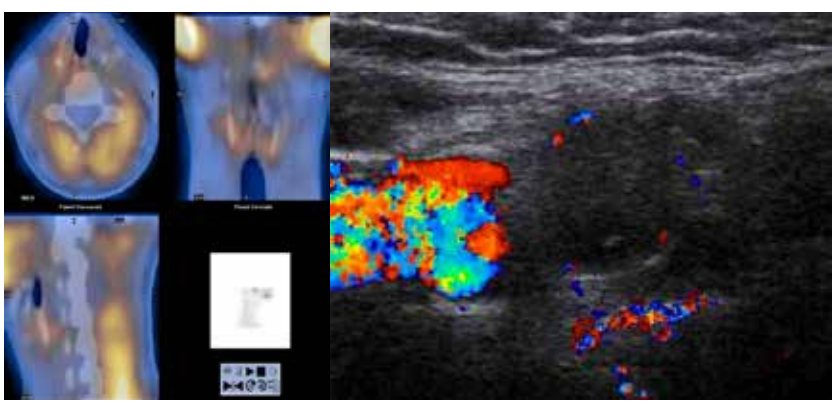

Figure 3 SPECT and Doppler ultrasound of a right upper UPA in case 3 showing a large hypoechoic nodule in the vicinity of the carotid bifurcation. SPECT, single photon emission computed tomography; UPA, undescended parathyroid adenoma.

Table 2 Preoperative localizing studies and operative approach

Patient (n)	US	FNA	MIBI	CT	SPECT	Procedure	Location	Time (min)	Gland weight (mg)	ioPTH
1	+	No	+	+	+	SP	MCB right	90	2,360	Yes
2	+	No	+	+	Not done	SP + AT	MCB left	60	2,950	No
3	+	+	+	+	+	SP	MCB right	80	1,129	Yes

US, ultrasound; FNA, fine needle aspirate; CT, computed tomography; SPECT, single photon emission CT; ioPTH, intraoperative PTH; SP, selective parathyroidectomy; MCB, medial to carotid bifurcation; AT, autotransplant.

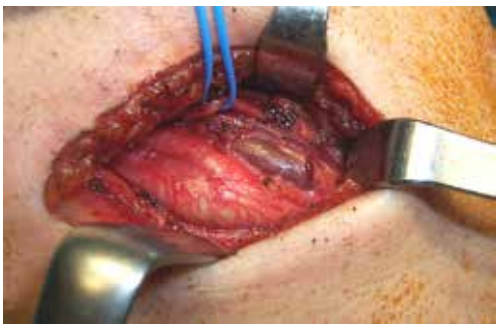

Figure 4 An UPA (case 1) medial to the carotid bifurcation in the usual position of undescended arathymus. UPA, undescended parathyroid adenoma.

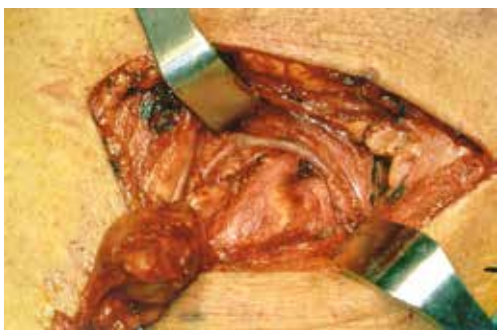

Figure 5 Surgical field after removal of a left upper UPA in case 2. UPA, undescended parathyroid adenoma.

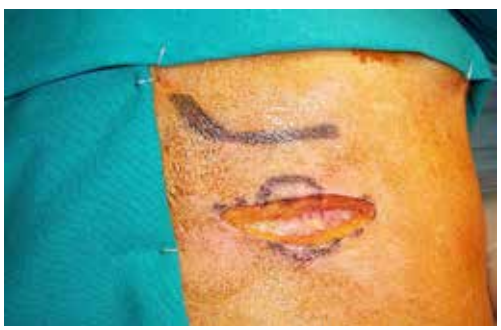

Figure 6 Recommended high lateral transverse incision to approach an UPA. UPA, undescended parathyroid adenoma.

glands from the third branchial pouch, the latter closely associated with the thymus. Therefore the inferior parathyroid glands have a longer route of embryologic descent and its final location at or around the lower pole of the thyroid lobe are variable. An inferior gland that fails to descend with the thymus remains at its embryologic origin close to the carotid bifurcation usually embedded in an ectopic thymic remnant (6,7).

From careful anatomic studies of 312 inferior parathyroid glands, Wang (8) concluded that UPAs occur in up to 2% of necks. In clinical series of previously unoperated primary cases, the incidence of UPAs is <1% (9). In the present report, only one UPA, case 1, was diagnosed (as second adenoma) in series of almost 600 parathyroidectomies; a 0.15% prevalence. UPAs were described by Simeone *et al.* (10) as an exceptional finding in five patients from a series of 3,000 patients (0.08%).

The incidence of UPAs in reoperative cases is higher, particularly in multiglandular HPT, as shown by cases reported here: one with a double adenoma and two with four gland diseases. In 1979, Edis *et al.* (1) reported seven UPAs in primary HPT patients: 1/414 found at initial operations (0.25%) and 6/27 at reoperation (22%). In a series of Fraker *et al.* (5) from 145 patients with persistent or recurrent HPT, nine (6.2%) had an UPA. A similar prevalence was reported by Shen *et al.* (11); from 102 patients who required reoperation, nine (8.8%) had an UPA. Billingsley *et al.* (12) reported 17 UPAs from series of 255 failed cervical explorations. These figures are similar to those reported in the present series.

UPAs localized by preoperative imaging studies are best removed by a focused approach through a high transverse lateral incision in the neck, one fingerbreadth below the mandible (*Figure 6*) (5,6). This avoids going through previously operated cervical structures and distorted surgical planes (13,14).

Two or more concordant preoperative imaging studies detect hyperfunctional parathyroid tissue in 60% to 70%

of reoperative cases (15). The success rate of revision parathyroidectomy without preoperative localization is only 60%. Several observational studies, however, have reported success rate of 95% when a preoperative localization is possible (16,17). Localization studies identify multiple gland disease, in almost 20% of recurrent HPT (18).

In a recent study by Lee *et al.* (19) UPAs were identified in 16/5,241 patients who underwent parathyroidectomy at three referral centres (0.3% prevalence). Seven patients underwent selective approach (44%) while nine underwent bilateral exploration. Fourteen cases (87%) were primary operations thanks to a proper preoperative localization and two (12%) were revision cases. Cure rate was achieved in all patients and success rate of selective approach was best when there was a second concordant imaging study in addition to scintigraphy. This study differs from previously published reports in that most cases were first-time surgeries, suggesting that currently, the diagnosis of UPA is made before the initial neck exploration in specialized referral centres.

Studies on UPA in persistent multiglandular HPT are less common although recurrence is more likely in this setting. In the present review all three cases were related with some type of multiglandular disease. Secondary HPT involving an UPA is uncommon. Matsuoka *et al.* (20) presented a series parathyroidectomies for secondary HPT, where the prevalence of UPAs was 16/1,750 (0.9%). However, the rate of UPA in the reoperated patients is increased to 3.2%.

Case 3 is a good example of multiglandular genetic disease involving ectopic parathyroid tissue. HPT-JTS is a rare autosomal disease caused by inactivated germline mutations of *HRPT-2* gene with subsequent loss of parafibromin expression. Some 20% to 30% of mutations develop spontaneously or may be radiation induced. Most patients with HRPT-2 mutation present with metachronous multiglandular involvement causing recurrence after selective parathyroidectomy (SP). HPT-JTS shows an increased risk of parathyroid carcinoma in 10-40% (21). Thus in these patients ectopic parathyroid adenomas, especially UPAs, can be misdiagnosed as metastatic lymph nodes. The more contemporary series of Mehta *et al.* (22) showed 20% of recurrent disease, 31% multiglandular involvement and 37.5% developed parathyroid carcinoma. Given the risk of malignancy and multiglandular involvement in this cohort, bilateral exploration is recommended and en bloc resection of parathyroid tumors suspicious for cancer, as well as life-long postoperatively follow-up.

Conclusions

UPAs were the cause of failed cervical exploration in 3 of 52 patients (5.6%) reoperated at our unit. All occurred in patients with multiple gland disease. Accurate preoperative localization of these lesions was possible with noninvasive studies and focused approach was performed successfully in all cases.

Although UPAs are exceptional as a cause of primary HPT (<1%), they are not uncommon among patients who require reoperation. Surgeons must take into account the possibility of an undescended gland both before the initial operation and, particularly, at revision surgery, when parathyroid adenomas cannot be found in orthotopic position.

Acknowledgements

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References

1. Edis AJ, Purnell DC, van Heerden JA. The undescended "parathymus". An occasional cause of failed neck exploration for hyperparathyroidism. Ann Surg 1979;190:64-8.
2. Hellstrom J. The causes of unsuccessful or inadequate parathyroidectomy in hyperparathyroidism. Acta Chir Scand 1957;112:79-91.
3. Weller GL. Development of the thyroid, parathyroid and thymus glands in man. Contrib Embryo 1933;24:93-139.
4. Edis AJ, Sheedy PF, Beahrs OH, et al. Results of reoperation for hyperparathyroidism, with evaluation of preoperative localization studies. Surgery 1978;84:384-93.
5. Fraker DL, Doppman JL, Shawker TH, et al. Undescended parathyroid adenoma: an important etiology for failed operations for primary hyperparathyroidism. World J Surg 1990;14:342-8.
6. Bliss RD, Gauger PG, Delbridge LW. Surgeon's approach to the thyroid gland: surgical anatomy and the importance of technique. World J Surg 2000;24:891-7.
7. Akerström G, Malmaeus J, Bergström R. Surgical anatomy of human parathyroid glands. Surgery 1984;95:14-21.
8. Wang C. The anatomic basis of parathyroid surgery. Ann Surg 1976;183:271-5.
9. Akerström G, Rudberg C, Grimelius L, et al. Causes of failed primary exploration and technical aspects of re-operation in primary hyperparathyroidism. World J Surg

1992;16:562-8; discussion 568-9.
10. Simeone DM, Sandelin K, Thompson NW. Undescended superior parathyroid gland: a potential cause of failed cervical exploration for hyperparathyroidism. Surgery 1995;118:949-56.
11. Shen W, Düren M, Morita E, et al. Reoperation for persistent or recurrent primary hyperparathyroidism. Arch Surg 1996;131:861-7; discussion 867-9.
12. Billingsley KG, Fraker DL, Doppman JL, et al. Localization and operative management of undescended parathyroid adenomas in patients with persistent primary hyperparathyroidism. Surgery 1994;116:982-9; discussion 989-90.
13. Chan TJ, Libutti SK, McCart JA, et al. Persistent primary hyperparathyroidism caused by adenomas identified in pharyngeal or adjacent structures. World J Surg 2003;27:675-9.
14. Brennan MF, Norton JA. Reoperation for persistent and recurrent hyperparathyroidism. Ann Surg 1985;201:40-4.
15. Feingold DL, Alexander HR, Chen CC, et al. Ultrasound and sestamibi scan as the only preoperative imaging tests in reoperation for parathyroid adenomas. Surgery 2000;128:1103-9; discussion 1109-10.
16. Gough I. Reoperative parathyroid surgery: the importance of ectopic location and multigland disease. ANZ J Surg 2006;76:1048-50.
17. Yen TW, Wang TS, Doffek KM, et al. Reoperative parathyroidectomy: an algorithm for imaging and monitoring of intraoperative parathyroid hormone levels that results in a successful focused approach. Surgery 2008;144:611-9; discussion 619-21.
18. Jaskowiak N, Norton JA, Alexander HR, et al. A prospective trial evaluating a standard approach to reoperation for missed parathyroid adenoma. Ann Surg 1996;224:308-20; discussion 320-1.
19. Lee JC, Mazeh H, Serpell J, et al. Adenomas of cervical maldescended parathyroid glands: pearls and pitfalls. ANZ J Surg 2012. [Epub ahead of print].
20. Matsuoka S, Tominaga Y, Uno N, et al. Surgical significance of undescended parathyroid gland in renal hyperparathyroidism. Surgery 2006;139:815-20.
21. Iacobone M, Masi G, Barzon L, et al. Hyperparathyroidism-jaw tumor syndrome: a report of three large kindred. Langenbecks Arch Surg 2009;394:817-25.
22. Mehta A, Patel D, Rosenberg A, et al. Hyperparathyroidism-jaw tumor syndrome: Results of operative management. Surgery 2014;156:1315-24; discussion 1324-5.

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Technical hints and potential pitfalls in modified radical neck dissection for thyroid cancer

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Abstract: Modified radical neck dissection (MRND) is often performed in conjunction with total thyroidectomy for the management of thyroid cancer. Prevention of postoperative sequelae after MRND is closely dependent on the avoidance of technical mistakes that may lead to significant complications and long-term morbidity. A thorough technical discussion with emphasis on potential pitfalls is made of the most relevant steps of MRND using the extrafascial approach: fascial dissection, approach to the accessory nerve, posterior limits, upper internal jugular vein (IJV), transverse cervical vessels, thoracic duct and compartment V dissection. Some anatomical hints are emphasized to help the novice surgeon to develop a refined surgical technique, the key to an uneventful postoperative course.

Keywords: Neck dissection; papillary cancer; pitfalls; landmarks

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Introduction

Appropriate surgical management has become the mainstay treatment of differentiated thyroid cancer (1). Total thyroidectomy, central neck dissection and, when indicated, lateral neck dissection have now been implemented in most referral centers as the standard of surgical care whereas the use of radioiodine is whithering, largely because it rests on controversial evidence built in the 70's and 80's when inappropriate surgical was common worldwide (2). Despite the biased ATA guidelines still recommend routine RAI ablation and the repeated use of stimulated Tg values, in the real world, well-operated differentiated low risk thyroid cancers—which represent 75-85% of all thyroid cancers are being increasingly followed-up with low intensity protocols due to the high efficacy of appropriate surgery to prevent recurrence and in rendering patients thyroglobulin-negative.

With the increased awareness of the relevance of lateral neck nodal disease in papillary cancer, modified radical neck dissection (MRND) is now more often performed, either synchronously with thyroidectomy or metachronously if recurrence is detected during follow-up. In our unit, 30-40% of patients with papillary cancer >1 cm will eventually require a MRND. Lateral neck dissection is also well-established for the initial treatment of many, if not all, medullary thyroid carcinomas. MRND implies the careful skeletonization of many relevant anatomical structures and should only be performed by appropriately trained surgeons. This article deals with the most important steps of MRND and the pitfalls that the surgeon may face in each of them. Its purpose is not to describe in detail the surgical technique of MRND, but to warn the trainee and the less experienced surgeon dealing with this procedure about the origin and causes of technical complications and pitfalls during lymph node neck dissection.

The surgeon must be aware that nodal clearance for thyroid cancer should be comprehensive, thorough and compartment-oriented. There is no role for node picking or single compartment dissection. Recurrences after MRND range from 10% to 50% (3) and are usually linked to an incomplete initial surgical procedure, particularly in patients

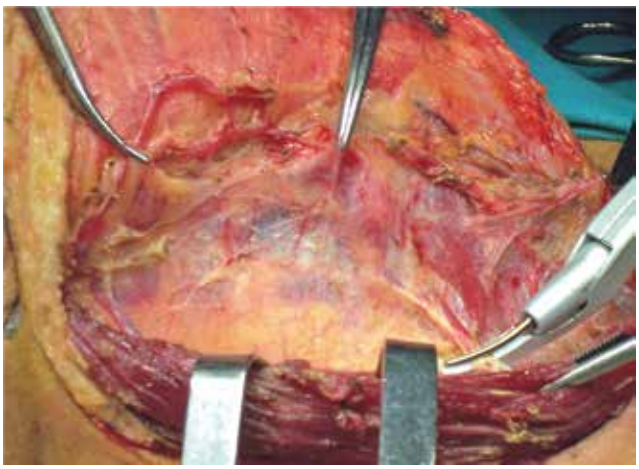

Figure 1 Elevation of the SCM fascia all along the lateral and internal surfaces of the muscle. Perforating vessels are dealt with (right side).

over 55 years of age with large (>3 cm) nodal metastasis (4). The most commonly performed lymph node dissection for thyroid cancer involves a selective approach with clearance of compartments IIa, III and IV (5,6). The most common variant is to enlarge the dissection field to compartments IIb and V in cases of massive lymphatic involvement. Resection of the sternocleidomastoid muscle (SCM) and the accessory nerve is only exceptionally performed in neck dissections for thyroid cancer, but the internal jugular vein (IJV) is often resected due to its infiltration by large nodal metastasis. Unilateral excision of the IJV does not carry additional morbidity nor neck deformities as happens with muscular or accessory nerve resections.

Surgical technique at our institution

Our technical approach to MRND (or functional neck dissection) follows the steps thoroughly described and illustrated by Gavilán *et al*. (7) of the Osvaldo Suárez School. This approach puts particular emphasis on the complete removal of the cervical lymphatic nodes by encasing them within the middle cervical fascia, and on the preservation of the SCM, the IJV and the accessory nerve. When combined with total thyroidectomy, we do first the lateral neck dissection, second the same side thyroid resection and third the contralateral thyroidectomy.

Briefly, a long transverse collar incision at the level of the cricoid cartilage is performed. J-shaped prolongation is rarely needed unless the patient has a long neck with massive involvement of compartments IIa and IIb. The SCM fascia is raised around the anterior and internal border of the muscle, the accessory nerve and the craneal end of the IJV are identified and a downwards dissection is performed to clear compartments IIa and III preserving the deep prevertebral fascia and as many branches as possible of the deep cervical plexus. Then the omohyoid muscle is cut or retracted and the dissection is carried out downwards preserving the transverse cervical vessels. The compartment IV is then cleared. At this stage, the more internal part of compartment V may be pulled from below the SCM and included in the specimen. The vagus nerve, the phrenic nerve and the brachial plexus are routinely identified and preserved. In the left side care is taken not to injure the thoracic duct. The specimen is then rotated medially, the carotid-middle cervical facia incised and the IJV unwrapped along its entire length.

The prevalence of postoperative hypocalcemia and permanent hypoparathyroidism are higher after total thyroidectomy and nodal dissection for thyroid cancer than after total thyroidectomy for benign conditions (8). For this reason, the surgeon must be particularly careful and skilled to adequately identify, dissect and preserve the parathyroid glands, particularly if a central neck dissection is also performed as we do routinely (9).

How to proceed?

The middle cervical fascia

When performing the collar incision, care is taken not to cut through the SCM fascia. Once the skin flaps have been raised, the segment of the external jugular vein overlying the SCM is excised and the SCM fascia is elevated (*Figure 1*) to unwrap de SCM and enter the neck vascular space externally, through the middle fascial plane. The SCM fascia continues with the fascia enveloping the IJV and the carotid artery and is used as a reference landmark all over the procedure. The raised fascia will be used as an envelope containing all the lymphonodal tissue around the IJV. Failure to do so will hamper the complete removal of nodes in compartments IIa-IV. Some perforating vessels are dealt with during this step (*Figure 1*). When transecting the external jugular vein at the level of the posterior border of the SCM, care should be taken not to injure a branch that, occasionally, communicates this vein with the IJV running below the muscle. This can lead to troublesome bleeding coming from the IJV, still hidden by the SCM.

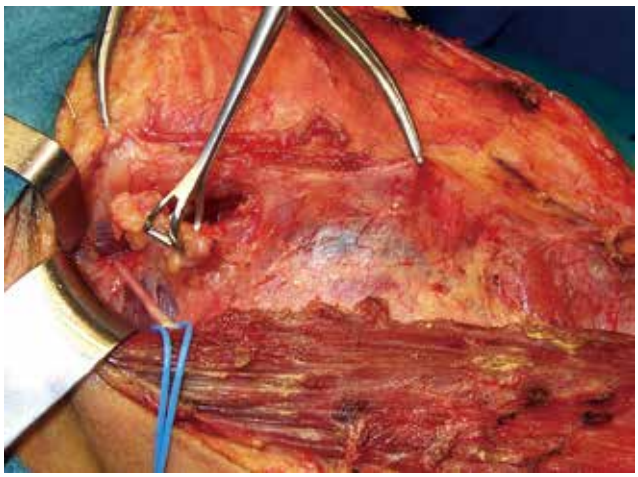

Figure 2 The accessory nerve is dissected between the SCM and the IJV and the compartment IIa cleared (right side).

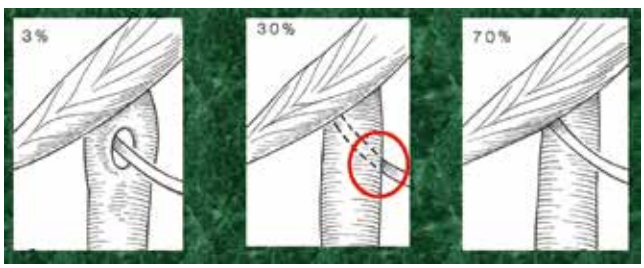

Figure 3 Relationship between the posterior belly of the digastric muscle, the IJV and the accessory nerve (left side). The red circle points the site where vein injury may result during accessory nerve dissection. From www2.utmb.edu/otoref/grnds/Neck-Dissection-020116/Neck-Dissection-020116-slides.pdf.

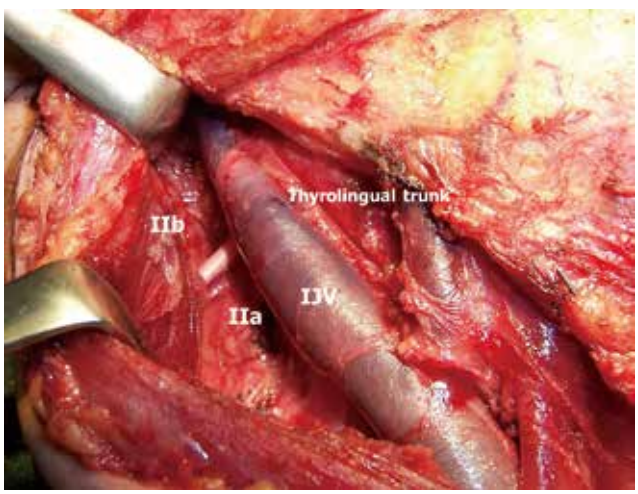

Figure 4 Clearance of compartments IIa and IIb (right side). Notice the less common anterior position of the internal jugular vein to the accessory nerve.

The spinal accessory nerve

Once the SCM fascia has been dissected off the muscle from the mastoid to the clavicle over its inner and deeper surfaces, the accessory nerve is identified high in the surgical field. A low approach may miss the segment of the accessory nerve running between the SCM and the IJV (*Figure 2*) and the surgeon will encounter the deep cervical plexus, a thick branch of which may be mistaken for the accessory nerve. Careful use of cautery will stimulate the nerve (and produce a contraction of the trapezius muscle) prior to actually identifying it. Once identified, the accessory nerve is looped and dissected from the SCM internal border to the IJV which lies either anterior (30%) or posterior (70%) to the nerve (*Figure 3*). An anterior course of the IJV facilitates the unintentional damage to its lateral side during accessory nerve dissection. The IIa compartment is cleared and the floor of the surgical field is bluntly dissected without entering the deep cervical facia. A too deep dissection will mislead the surgeon into the splenius and *levator scapulae* muscles eventually transecting the phrenic nerve it its most superior course. If the compartment IIa is obviously involved, the IIb nodes—above and posterior to the accessory nerve—have to be dissected (10,11). This can be done by careful upwards lifting of the nerve and gentle pulling of the IIb nodes below the nerve (*Figure 4*). This is the only extrafascial lymph node group of the whole neck dissection.

The deep cervical fascia and the floor of MRND

Once compartment II has been cleared, the deep fascia appears exposed as the "floor" of the surgical field, just caudal and posterior to the accessory nerve. Staying superficial to the deep fascia along the whole procedure is crucial to avoid damaging the brachial plexus and the phrenic nerve. The dissection then proceeds downwards and the surgeon will now encounter the deep cervical plexus running over the deep fascia and below the SCM to innervate the skin around the shoulder and the high chest area (*Figure 5*). In most cases all or most of the branches of the cervical plexus can be preserved thus preventing or alleviating shoulder pain, a common sequel of MRND. Furthermore, some of the branches of the deep plexus anastomose with the accessory nerve contributing with some motor fibers. The dissection then proceeds downwards uncovering the *levator scapulae* muscle externally and the anterior and middle scalene muscles medially.

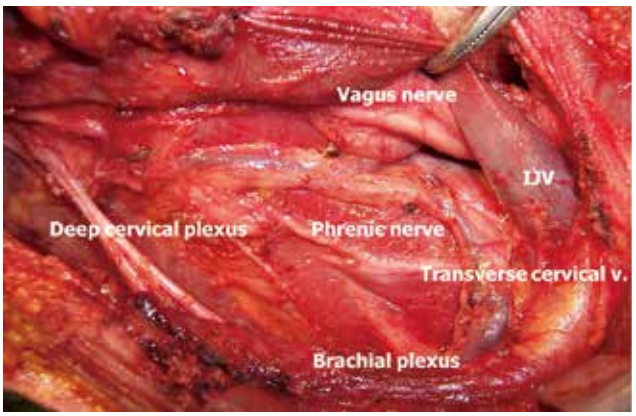

Figure 5 Anatomical structures on the floor of the surgical field covered by the deep cervical fascia (right side).

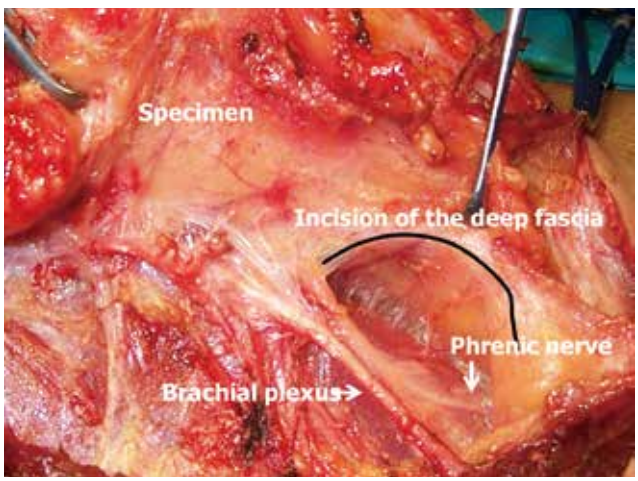

Figure 6 Too deep dissection below the deep fascia overexposing the brachial plexus, the phrenic nerve and the nude anterior surface of the anterior scalene muscle (right side).

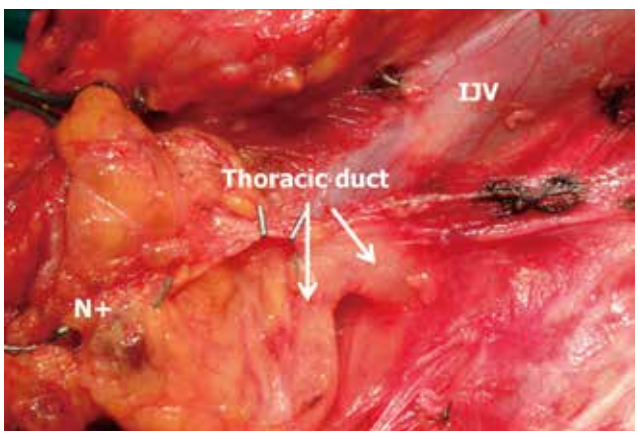

Figure 7 Identification of the thoracic duct. Notice its intimate anatomical relationship to the metastatic compartment IV nodes (N+) and the lower end of the internal jugular vein.

The transverse cervical vessels

The specimen is now rotated medially down to the crossing of the omohyoid muscle. The muscle can be preserved or cut according to the patient's anatomy and the extension of the nodal involvement. At this stage the transverse cervical vessels are identified lying anterior to the deep fascia and are preferably left *in situ*. The distal transection of these vessels implies its inclusion in the specimen and that they should be ligated again close to the subclavian vessels. Injurying the transverse vessels at their origin may cause troublesome hemorrhage deep in the neck close to the midline. Leaving the transverse cervical vessels *in situ* provides a good landmark to preserve the deep fascia overlying the scalene muscles and the phrenic nerve. If these vessels are transected distally and lifted up with the specimen, the surgeon risks entering the plane below the deep fascia where the brachial plexus and the phrenic nerve may be injured (*Figures 5,6*). There are numerous variations of the branching of the transverse cervical vessels and the thyrocervical trunk that should make the surgeons cautious at this stage of the operation (7).

The proximal end of the jugular vein

Compartments III and IV are the most commonly involved in thyroid cancer. Thus, dissection around the proximal end of the IJV, close to its junction with the subclavian vein, becomes an important step in MRND. The surgeon must take care not leaving behind involved nodes that may hide dorsally to the IJV or that may extend laterally towards compartment V. At this point, medial traction of the specimen by the assistant to facilitate the dissection, results in the vein folding and becoming vulnerable to sharp dissection. Torsion of the proximal end of the IJV attenuates or completely blocks blood flow and the surgeon loses sight of the vein walls that may be then inadvertently punctured with the scalpel blade or the scissors.

The thoracic duct

Large metastatic nodes in the left IV compartment pose a threat to the integrity of the thoracic duct since it usually lies deep close to the enlarged nodes. Extremely cautious dissection should be done around the distal segment of the left IJV, particularly when it joins the left subclavian vein. The thoracic duct is usually identified as a thin-walled conduct filled with whitish fluid (*Figure* 7). If it is

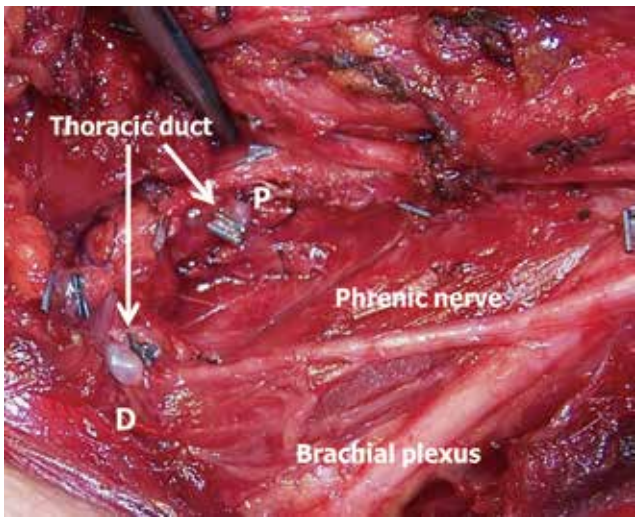

Figure 8 The IJV has been removed together with large metastatic nodes in the left IV compartment. The thoracic duct was transected and the proximal (P) and distal (D) ends clipped. Notice the characteristic withish fluid within the duct ends.

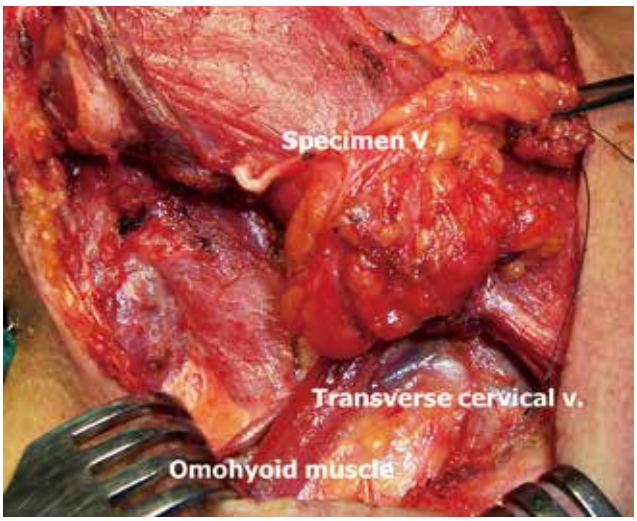

Figure 9 The comparment V has been dissected and the specimen is now ready to be pulled below the SCM. The omohyoid muscle and the transverse cervical vessels have been preserved.

injured, lymph usually flows out and is easily detected by the experienced surgeon. If the thoracic duct has been damaged, both ends should be identified and ligated or clipped (*Figure 8*). Failure to do so will lead to a chyle leak in the immediate postoperative period with its attendant morbidity (12). Independently of whether or not a major lymph duct injury has occurred, meticulous lymphostasis around the proxymal end of both IJVs is a must to prevent lymphatic fistulas and seromas. A Valsalva maneuver may help to identify lymphatic leakage.

The compartment V

Dissection of the supraclavicular fossa in thyroid cancer remains a controversial issue. The prevalence of node metastasis in this compartment varies from 15% to 50%. Level V lymphadenectomy may lead to spinal accessory nerve injury and increases shoulder pain. Most authors follow a selective approach to level V lymphadenectomy which may be only indicated in patients with lymph node metastasis in the ipsilateral lateral neck with macroscopic extranodal extension (13). In most cases, part of the level V compartment is excised in continuity with level IV dissection, by pulling the supraclavicular fibrofatty tissue from below the SCM.

If formal compartment V dissection is warranted, we usually start the MRND by clearing the supraclavicular fossa and by first identifying the accessory nerve deep to Erb's point. Some branches of the deep cervical plexus follow a similar course than the accessory nerve and may mislead the novice surgeon. This is the most demanding part of compartment V dissection. The fibrofatty tissue of the supraclavicular fossa is then pulled downwards around the omohyoid muscle, preserving the most lateral segment of the transverse cervical vessels that can be identified overlying the fascia of the *elevator scapula* muscle (*Figure 9*). Dissection proceeds down to the subclavian vein and close to compartment IV. We then leave the compartment V specimen *in situ* and proceed to clear compartments II and III. Then, the compartment V specimen is pulled to the midline below the SCM and the compartment IV dissection is performed.

Conclusions

If properly done, MRND is not a too invasive surgical procedure and patients can be discharged from the hospital on the second to fourth postoperative day. For a smooth postoperative course, the following advices seem pertinent to avoid pitfalls during MRND for thyroid cancer and are a good summary of the text above:

I. Start by appropriately elevating the SCM fascia;
II. Do not miss the accessory nerve;
III. Do not go deep below the deep cervical fascia;

IV. Preserve the deep cervical plexus;
V. Preserve the transverse cervical vessels;
VI. Identify the brachial plexus, the phrenic nerve and the vagus nerve;
VII. Beware of IJV torsion when dissecting the compartment IV;
VIII. Identify and clip all lymphatic leaks after dissecting left and/or right IV compartments;
IX. Dissect selectively compartments IIb and V according to cancer extension.

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References

1. Grant CS, Stulak JM, Thompson GB, et al. Risks and adequacy of an optimized surgical approach to the primary surgical management of papillary thyroid carcinoma treated during 1999-2006. World J Surg 2010;34:1239-46.
2. Hay ID. Selective use of radioactive iodine in the postoperative management of patients with papillary and follicular thyroid carcinoma. J Surg Oncol 2006;94:692-700.
3. de Meer SG, Dauwan M, de Keizer B, et al. Not the number but the location of lymph nodes matters for recurrence rate and disease-free survival in patients with differentiated thyroid cancer. World J Surg 2012;36:1262-7.
4. Ito Y, Kudo T, Takamura Y, et al. Lymph node recurrence in patients with N1b papillary thyroid carcinoma who underwent unilateral therapeutic modified radical neck dissection. World J Surg 2012;36:593-7.
5. Caron NR, Tan YY, Ogilvie JB, et al. Selective modified radical neck dissection for papillary thyroid cancer-is level I, II and V dissection always necessary? World J Surg 2006;30:833-40.
6. Lee J, Sung TY, Nam KH, et al. Is level IIb lymph node dissection always necessary in N1b papillary thyroid carcinoma patients? World J Surg 2008;32:716-21.
7. Gavilán J, Herranza J, DeSanto LW, et al. Functional and selective neck dissection. New York: Thieme Medical Publishers, Inc. 2002.
8. Sitges-Serra A, Ruiz S, Girvent M, et al. Outcome of protracted hypoparathyroidism after total thyroidectomy. Br J Surg 2010;97:1687-95.
9. Pereira JA, Jimeno J, Miquel J, et al. Nodal yield, morbidity, and recurrence after central neck dissection for papillary thyroid carcinoma. Surgery 2005;138:1095-100, discussion 1100-1.
10. Lee BJ, Wang SG, Lee JC, et al. Level IIb lymph node metastasis in neck dissection for papillary thyroid carcinoma. Arch Otolaryngol Head Neck Surg 2007;133:1028-30.
11. Farrag T, Lin F, Brownlee N, et al. Is routine dissection of level II-B and V-A necessary in patients with papillary thyroid cancer undergoing lateral neck dissection for FNA-confirmed metastases in other levels. World J Surg 2009;33:1680-3.
12. Nussenbaum B, Liu JH, Sinard RJ. Systematic management of chyle fistula: the Southwestern experience and review of the literature. Otolaryngol Head Neck Surg 2000;122:31-8.
13. Shim MJ, Roh JL, Gong G, et al. Preoperative detection and predictors of level V lymph node metastasis in patients with papillary thyroid carcinoma. Br J Surg 2013;100:497-503.

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The effect of neck dissection on quality of life in patients with differentiated thyroid cancer

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Abstract: Cervical lymph node metastases are very common in patients with differentiated thyroid cancer (DTC). The overall long term survival rate in patients with DTC is higher than 90%, with variations in subsets of groups. Despite that DTC has an excellent prognosis, lymphatic spread is associated with increased risk of loco-regional recurrence, which significantly impairs quality-of-life (QOL) and can alter prognosis of the patient. As a result, a rapid shift in patient care from a focus on overall survival to a focus on recurrence-free survival has recently noted. The appropriate lymph node dissection is of great importance in order to achieve this goal. This surgical strategy will prevent disease recurrence, which may require an additional and more morbid surgery. Traditionally, the main outcome measure in oncology patients has been survival, based on tumor control, but recently it has been increasingly recognized that the diagnosis and management of cancer can have a major effect on every aspect of the QOL of a patient. The aims of cancer treatment became not only to increase survival but also to preserve QOL, and measuring these changes has been considered to be of paramount importance.

Keywords: Differentiated thyroid cancer (DTC); lymph node dissection; quality of life (QOL)

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Patients with differentiated thyroid cancer (DTC) have an excellent survival rate. As a general they also have a good prognosis. Cervical lymph node metastases occur in 30% to 80% of these and are associated with a significant probability for loco-regional recurrence of the disease, even in low-risk patients. This reflects in a rapid shift in patient care from a focus on overall survival to a focus on recurrence-free survival (1-3).

Tumor free survival has been the most important measure outcome recently, but nowdays it has been realized that the diagnosis and management of cancer can alter every aspect of the quality of life (QOL) of a patient. The main goal of cancer treatment became not only to increase survival but also to preserve QOL, which is considered to be of paramount importance (1,4,5).

Thus the effect of neck dissection on QOL in patients with DTC is a matter of question that has to be reviewed in two aspects.

(I) The first one is about the indications and extent of neck dissection in patients with DTC;

(II) The second is about the definition and measurement of QOL in these patients.

According to The American Thyroid Association (ATA) 2009 guidelines the aims of surgical treatment of DTC patients are as follows:

(I) To remove the primary tumor, disease that has extended beyond the thyroid capsule, and involved cervical lymph nodes. Completeness of surgical resection is an important determinant of outcome, while residual metastatic lymph nodes represent the most common site of disease persistence recurrence;

(II) To minimize treatment-related morbidity. The extent of surgery and the experience of the surgeon both play important roles in determining the risk of surgical complications;

(III) To permit accurate staging of the disease. Because

disease staging can assist with initial prognostication, disease management, and follow-up strategies, accurate postoperative staging is a crucial element in the management of patients with DTC;

(IV) To facilitate postoperative treatment with radioactive iodine, where appropriate. For patients undergoing RAI remnant ablation, or RAI treatment of residual or metastatic disease, removal of all normal thyroid tissue is an important element of initial surgery. Near total or total thyroidectomy also may reduce the risk for recurrence within the contralateral lobe;

(V) To permit accurate long-term surveillance for disease recurrence. Both RAI whole-body scanning (WBS) and measurement of serum Tg are affected by residual normal thyroid tissue. Where these approaches are utilized for long-term monitoring, near-total or total thyroidectomy is required;

(VI) To minimize the risk of disease recurrence and metastatic spread. Adequate surgery is the most important treatment variable influencing prognosis, while radioactive iodine treatment, TSH suppression, and external beam irradiation each play adjunctive roles in at least some patients (6).

As a part of adequate surgery, neck dissection play important role for definitive treatment of the cancer. In 1991 a standardized classification of Academy's Committee for Head and Neck Surgery and Oncology was published by Robbins *et al*. and was worldwide accepted (7).

This system is based on four concepts:

(I) Radical neck dissection (RND) is the standard basic procedure for cervical lymphadenectomy against which all other modifications are compared;

(II) Modifications of the RND which include preservation of any non-lymphatic structures are referred to as modified radical neck dissection (MRND);

(III) Any neck dissection that preserves one or more groups or levels of lymph nodes is referred to as a selective neck dissection (SND);

(IV) An extended neck dissection refers to the removal of additional lymph node groups or non-lymphatic structures relative to the RND.

As a result of this conceptual approach is the Academy's classification:

(I) RND;

(II) MRND;

- MRND Type I: excision of all lymph nodes routinely removed by radical neck dissection with preservation of the SAN;
- MRND Type II: excision of all lymph nodes routinely removed by radical neck dissection with preservation of the SAN and IJV;
- MRND Type III (functional or comprehensive neck dissection): excision of all lymph nodes routinely removed by radical neck dissection with preservation of the SAN, IJV and SCM.

(III) SND;

- Supra-omohyoid type;
- Lateral type;
- Posterolateral type;
- Anterior compartment type.

(IV) Extended radical neck dissection.

Due to location of thyroid gland and its lymphatic drainage the first affected lymph nodes are situated in the anterior compartment. In some cases various groups of nodes could be involved.

On *Figure 1* is presented division of regional neck nodes according to Memorial Sloan-Kettering Cancer Center. It is well visible that anterior compartment and level VI represent the same anatomical region.

But what is the definition of anterior compartment dissection? Which are the anatomic boundaries of anterior compartment? By the Academy's Committee for Head and Neck Surgery and Oncology the definition of SND Anterior Compartment is: En bloc removal of lymph structures in Level VI including:

- Perithyroidal nodes;
- Pretracheal nodes;
- Precricoid nodes (Delphian);
- Paratracheal nodes along recurrent nerves.

Gradoni *et al.* emphasize on the location of the thyroid gland which is low in the neck near the thoracic inlet, the lymphatic drainage is contiguous with the anterior superior mediastinum that is accessible via a cervical approach. As a result, the inferior border of the central compartment is defined as the innominate artery on the right and the corresponding axial plane on the left. In terms of Robbins levels, it means that the central neck dissection (CND) should include the VI and VII levels (8).

So the SND anterior compartment type including level VI, VII is equal to so called CND.

In order to better understand complicated terminology in indications of neck dissection I will clarify some of the names most frequently met in the literature. Routine, elective or prophylactic neck dissection. All the terms mean the same—a neck dissection implies that nodal metastasis is not detected clinically or by imaging (clinically N0)

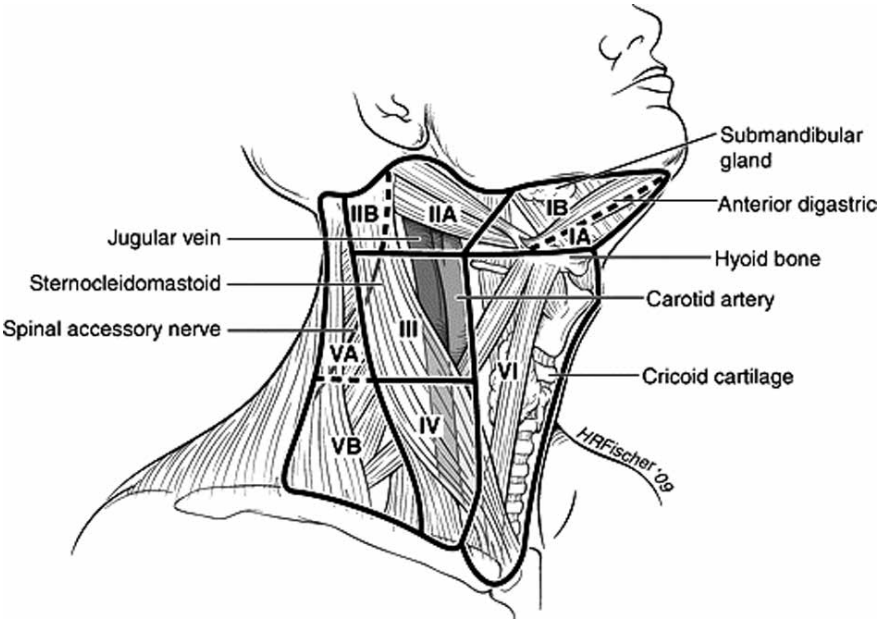

Figure 1 Division of neck nodes according to Memorial Sloan-Kettering Cancer Center (6). Reproduced from American Thyroid Association Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, *et al.* Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167-214.

pND. Therapeutic neck dissection—a therapeutic neck dissection implies that nodal metastasis is apparent clinically (preoperatively or intraoperatively) or by imaging (clinically N1a) tND (9).

What the guidelines say about the indications and extent of neck dissection in DTC patients?

The ATA guidelines [2009] state that tCND should be offered to clinical N+ patients. In patients with clinically uninvolved lymph nodes, ipsilateral or bilateral pCND may be performed, especially for advanced primary tumours (T3 or T4). It is recognized that for patients with small, noninvasive tumors, the balance of risk and benefit may favour simple near-total thyroidectomy with close inspection of the central compartement with compartmental dissection only in the presence of obviously involved lymph nodes. The level of this recommendation is an expert opinion based one.

Lymph nodes in the lateral neck (compartments II-IV) and posterior triangle (compartment V) may also be involved by DTC. For those patients in whom nodal disease is evident clinically, on preoperative ultrasound, or at the time of surgery, surgical resection may reduce the risk of recurrence and possibly mortality. Functional compartmental en-bloc dissection is favored over selective dissection (berry picking) with limited data suggesting improved mortality. Lateral neck compartmental lymph node dissection should be performed for patients with biopsy-proven metastatic cervical lymphadenopathy detected clinically or by imaging, especially when they are likely to fail radioactive iodine treatment based on lymph node size, number, or other factors, such as aggressive histology of the primary tumor. The recommendation is based on fair evidence that the service or intervention can improve important health outcomes (6).

According to the National Comprehensive Cancer Network guidelines (NCCN v.1.2010) compartment oriented neck dissection has to be performed when lymph nodes are palpable or biopsy positive. If the nodes are negative, prophylactic CND can be considered but is not required in all cases. Features that could call for prophylactic CND are: age <15 and >45; radiation history; known distant metastasis; extrathyroidal extension; tumour >4 cm in diameter and aggressive hystological variant. The recommendation expressed is based on lower-level evidence and there is nonuniform NCCN consensus but no major disagreement (10).

In the British Thyroid Association guidelines (BTA, 2007) is said that in patients with clinically uninvolved nodes but who are deemed high risk (i.e., they have any of the following features: male sex, age >45 years, tumours greater than 4 cm in diameter, extracapsular or extrathyroidal disease), pCND should be performed.

Palpable disease in level VI nodes discovered at surgery is treated by a tCND. When suspicious/clinically involved nodes are apparent pre-operatively or are encountered at surgery in the lateral neck, and confirmed by needle biopsy or frozen section, then a therapeutic SND (levels IIa-Vb) is recommended, preserving the accessory nerve, sternocleidomastoid muscle and internal jugular vein. The recommendation is based on evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities (11).

The European consensus for the management of differentiated thyroid carcinoma endorsed by the European Thyroid Association in 2006 state that lymph nodes dissections should be performed in patients with pre-operative or intra-operative diagnosis of lymph nodes metastases. The benefits of prophylactic CND is deemed controversial. According to this task force, there is no evidence that the prophylactic CND improves recurrence or mortality rates, but it allows an accurate staging of the disease that may guide subsequent treatment and follow-up (12).

According to Latin American Thyroid Society recommendations, pCND should be considered only for those patients with T3 or T4 and is not warranted in all patients. If at the time of surgery there is obvious metastatic disease in the jugular chain or lateral neck, modified neck dissection with removal of the lymph nodes at levels II, III, IV, and V is generally recommended. Modified neck dissection for thyroid carcinoma preserves all the important structures, such as the sternomastoid muscle, internal jugular vein, and accessory nerve, along with the submandibular salivary gland. The panel does not recommend the pCND in all patients with diagnosis of papillary thyroid cancer; however, it is deserved for any patient with a T3 or T4 (13).

There is no definitive clear statement about the indication and extent of neck dissection in patients with DTC. Summarizing published guidelines I can say that clinically evident lymph nodes metastasis require CND or MRND IIa-Vb—both therapeutic. Prophylactic MRND is definitely not recommended, till prophylactic CND is preserved for T3, T4 patients with perineural, extracapsular invasion and it is yet deemed controversial. Hence we have to look for the effect of CND or MRND on QOL of the patients.

The second aspect of review is to clarify the definition and measurement of the QOL

Definition given by WHO—QOL 1993 designate QOL as the perceptions of an individual regarding his or her position in life in the context of the culture and value systems in which he or she lives and in relation to his or her goals, expectations, standards, and concerns (14).

Health related quality of life (HR-QOL) has some specifics and it refers to a multidimensional concept that encompasses perception of negative and positive aspects of physical, emotional, social, and cognitive functions, which could be affected by the disease or its treatment (15).

There are increasing number of studies measured QOL as an end point in the evaluation of the effect of the disease and its treatment on the daily life of the patient (5).

However, there have been relatively few HR-QOL studies looking specifically at patients with thyroid cancer (4,5,15) and only one specifically looking for the effect of neck dissection in such a patients (16).

How the neck dissection could affect the QOL of patients and how it could be measured?

Neck dissection could directly affect the QOL of patients by means of postoperative morbidity. There are several structures in the neck put in risk of damage during the procedure. Even in experienced hands neck dissection is associated with increasing incidence of major complications. The complication rate increases as the cervical LND range become more radical (17).

Complications most frequently met in both type of dissection are as follows: hypoparathyroidism, recurrent laryngeal nerves palsy, thoracic duct injury, spinal accessory nerve damage, transection of cervical rootlets, seroma, and wound infection.

Postoperative hypoparathyroidism

Transient hypoparathyroidism is the complication most frequently met after total thyroidectomy and neck dissection. Its incidence could rise up to 24% of the cases especially in bilateral procedures (18).

Roh *et al.* demonstrated no difference in incidental

parathyroidectomy in patients with or without neck dissection after total thyroidectomy, but postoperative hypoparathyroidism was significantly higher in the neck dissection group than those with no dissection (19).

Their study found that increased hypoparathyroidism appeared not to be associated with incidental removal of the parathyroid glands or the number of parathyroid glands preserved during surgery. In addition, selective parathyroid autotransplantation did not appear to solve this problem since, despite more frequent use of this procedure in the node dissection group, a lot of patients experienced permanent hypocalcemia (19).

There is no significant difference between complication in CND or MRND (20). Prevention of permanent hypoparathyroidism is based on parathyroid autotransplantation in sternocleidomastoid muscle. Autotransplantation is a procedure deserved for any devascularized gland. Confirmation of parathyroid gland nature by frozen section is of great importance due to its potential misidentification with metastatic lymph node. Total thyroidectomy and neck dissection include considerable dissection in the paratracheal area, especially along the recurrent laryngeal nerve. This has a direct implication in a higher incidence of nerve injury and injury to the parathyroid glands, leading to temporary or permanent hypoparathyroidism (21).

Recurrent laryngeal nerve palsy

Injury of the recurrent laryngeal nerves is a severe complication that requires artificial airway secure in bilateral cases. The nerves are at risk in both CND and MRND. Although RLN palsy could be met it total thyroidectomy alone, authors reported as much incidence of this complication as more surgery is performed (20,22).

In the study of Malgorzata Wierzbicka *et al.* investigating morbidity of secondary neck dissections in thyroid cancer metastases, in 15.7 % of the cases permanent vocal cord paresis was observed; in 5.9 % tracheotomy had to be maintained (23).

On the other hand in article of Henry *et al.* concerning recurrent laryngeal nerve palsies in patients with total thyroidectomy alone and with pCND in one stage, there was no difference between the two groups of patients. This has been reported in other series and it confirms that the dissection of the nerve is no more dangerous during a total thyroidectomy associated with pCND than during a total thyroidectomy alone (24).

Prevention is generally associated with anatomical identification and confirmation of functional integrity of the nerves by the help of magnifying glasses and intraoperative neuromonitoring (25,26).

Thoracic duct injury

Thoracic duct, usually runs into the posterior mediastinum, generally opens up at the junction of the left jugular vein and subclavian vein. Cleaning of nodal metastasis at level IV in thyroid carcinoma may lead to injury of the lymphatic structures. This is manifested by chyle leak. Sometimes, it may be manifested postoperatively as large amount of chylous fluid into the drainage system. In these cases, a conservative approach with observation, pressure dressings, a fat free diet or potentially total parenteral nutrition is successful in most patients. Injection of tetracycline or other sclerosing agents has been proposed by some authors, but may lead to considerable scarring and fibrosis, inflammatory reaction, and pain (27).

If a chyle leak is identified at the time of surgery, it should be corrected by ligation of nonabsorbable ties, silk or prolene, or with hemoclips (28).

Neck anesthesia/neuropathic pain/decreased shoulder mobility

Yatrogenic damage of the cervical rootlets or injury of the spinal accessory nerve during neck dissection may lead to neck sensory abnormality (anesthesia, numbness, and/or neuropathic pain), edema and limitation of neck/shoulder movement, decline in speech and eating abilities. These complications usually are observed following MRND and may alter daily activities, social function, and professional performance. Varying degrees of dysfunction of the spinal accessory nerve are common after level V dissection even with nerve preservation. Indeed, even after complete nerve preservation, shoulder pain has been observed in 79% of patients after radical neck dissection, 65% of patients after MRND and 52% of patients after SND (29,30).

This is due to neuropraxia, caused by excessive traction, extensive dissection and skeletonization, devascularization and ischemia, thermal injury, blunt trauma during dissection, leading to degeneration of the upper trapezius and sternocleidomastoid muscles (31).

Instruments used to measure HR-QOL in patients with DTC are the same as these used in patients with head and neck cancer. Interesting is the fact that investigators of HR-QOL in head and neck cancer patients exclude from theirs research, patients with DTC because of its biologic

behavior and specific treatment.

There are limited numbers of data in the literature about the measurement of HR-QOL in DTC patients with neck dissection. The paucity of specific instruments to assess the QOL of patients with thyroid cancer associated with low mortality and morbidity rates of the treatment can explain why there are so few studies in this field.

Validated instruments most widely used for finding clinical predictors of QOL in such a patient are Neck Dissection Impairment Index (NDII), Constant Shoulder Scale, and University of Washington Quality of Life questionnaire (UW-QOL).

NDII was developed and validated by Rodney J. Taylor *et al.* in 2002 in order to identify the factors that affect QOL following neck dissection due to head and neck cancer (32).

Reliability of the index was evaluated with test-retest correlation and internal consistency using the Cronbach α coefficient. Convergent validity was assessed using the 36-Item Short-Form Health Survey (SF-36) and the Constant Shoulder Scale, a shoulder function test. They used multiple variable regressions to determine variables that most affected QOL following neck dissection.

There is recent survey of Lee J *et al.* that compare oncological outcomes and QOL after robotic versus conventional open thyroidectomy with MRND in patients with papillary thyroid carcinoma and lateral neck node metastases (16).

They used arm abduction tests and questions from NDII and concluded that the robot technique was associated with improved QOL, including excellent cosmetic results and reductions in neck sensory changes and swallowing discomfort after surgery (16).

UW-QOL questionnaire is a validated, accurate, and internationally accepted survey instrument. In the original description, Hassan and Weymuller stated that 'the advantages of the UW-QOL head and neck questionnaire are that (I) it is brief and self-administered; (II) it is multi-factorial, allowing sufficient detail to identify subtle change; (III) it provides questions specific to head and neck cancer; and (IV) it allows no input from the health provider, thus reflecting the QOL as indicated by the patient (33).

The current version 4 of the UW-QOL questionnaire consists of 12 single question domains, these having between three and six response options that are scaled evenly from 0 (worst) to 100 (best) according to the hierarchy of response. The domains are pain, appearance, activity, recreation, swallowing, chewing, speech, shoulder, taste, saliva, mood and anxiety. Another question asks patients to choose up to three of these domains that have been the most important to them. There are also three global questions, one about how patients feel relative to before they developed their cancer, one about their health-related QOL and one about their overall QOL. In regard to their overall QOL patients are asked to consider not only physical & mental health, but also many other factors, such as family, friends, spirituality or personal leisure activities that were important to their enjoyment of life.

In the study of Almeida J *et al.* there is some data about the clinical predictors of HR-QOL in DTC patients. According to their investigation the main factor that affects QOL of patients is RIT treatment. There is no significant data about the neck dissection as a clinical predictor (34).

Another study that evaluated the results of the adverse effects of surgery and RIT on such patients is a work of Dagan T *et al.* (35).

This study used an UW-QOL questionnaire that was adapted but not validated. The authors evaluated 20 patients with thyroid cancer and reported that those older than 45 years had worse general health, appearance, and chewing scores but did not show an association of RIT or neck dissection with any domain.

As a conclusion I would say that neck dissection affect the QOL of patients with DTC on two ways: positive and negative.

The positive way is correlated with appropriate neck dissection as a procedure of great importance to achieve the main goals of surgical therapy in patients with DTC.

The negative way is associated with higher risk and greater incidence of postoperative complications as main clinical predictors of impaired QOL of such a patient. Due to limited number of studies and lack of statistically correct data about the effect of neck dissection on QOL of patient with DTC, I recommend following the instructions of worldwide accepted guidelines (ATA, ETA, BTA, and LATG) regarding the indications and extent of neck dissection in DTC patients.

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References

1. Tan LG, Nan L, Thumboo J, et al. Health-related quality of life in thyroid cancer survivors. Laryngoscope 2007;117:507-10.

2. Myers EN. eds. Cancer of the head and neck, 4th ed. Philadelphia, PA: Saunders, 2003:850.
3. Cooper DS, Doherty GM, Haugen BR, et al. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2006;16:109-42.
4. Huang SM, Lee CH, Chien LY, et al. Postoperative quality of life among patients with thyroid cancer. J Adv Nurs 2004;47:492-9.
5. Vartanian JG, Carvalho AL, Yueh B, et al. Long-term quality-of-life evaluation after head and neck cancer treatment in a developing country. Arch Otolaryngol Head Neck Surg 2004;130:1209-13.
6. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167-214.
7. Robbins KT, Medina JE, Wolfe GT, et al. Standardizing neck dissection terminology. Official report of the Academy's Committee for Head and Neck Surgery and Oncology. Arch Otolaryngol Head Neck Surg 1991;117:601-5.
8. Gradoni P, Giordano D, Oretti G, et al. Prophylactic central neck dissection for papillary thyroid carcinoma: the terms of the debate. Acta Biomed 2011;82:14-9.
9. American Thyroid Association Surgery Working Group, American Association of Endocrine Surgeons, American Academy of Otolaryngology-Head and Neck Surgery, et al. Consensus statement on the terminology and classification of central neck dissection for thyroid cancer. Thyroid 2009;19:1153-8.
10. Available online: www.nccn.org
11. British Thyroid Association, Royal College of Physicians. Guidelines for the management of thyroid cancer. Perros P, ed. 2nd edition. Report of the Thyroid Cancer Guidelines Update Group. London: Royal College of Physicians, 2007.
12. Pacini F, Schlumberger M, Dralle H, et al. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol 2006;154:787-803.
13. Pitoia F, Ward L, Wohllk N, et al. Recommendations of the Latin American Thyroid Society on diagnosis and management of differentiated thyroid cancer. Arq Bras Endocrinol Metabol 2009;53:884-7.
14. Study protocol for the World Health Organization project to develop a Quality of Life assessment instrument (WHOQOL). Qual Life Res 1993;2:153-9.
15. Crevenna R, Zettinig G, Keilani M, et al. Quality of Life in patients with non-metastatic differentiated thyroid Cancer under thyroxine supplementation therapy. Support Care Cancer 2003;11:597-603.
16. Lee J, Kwon IS, Bae EH, et al. Comparative analysis of oncological outcomes and quality of life after robotic versus conventional open thyroidectomy with modified radical neck dissection in patients with papillary thyroid carcinoma and lateral neck node metastases. J Clin Endocrinol Metab 2013;98:2701-8.
17. Sakorafas GH, Sampanis D, Safioleas M. Cervical lymph node dissection in papillary thyroid Cancer: current trends, persisting controversies, and unclarified uncertainties. Surg Oncol 2010;19:e57-70.
18. Cheah WK, Arici C, Ituarte PH, et al. Complications of neck dissection for thyroid cancer. World J Surg 2002;26:1013-6.
19. Roh JL, Park JY, Park CI. Total thyroidectomy plus neck dissection in differentiated papillary thyroid carcinoma patients: pattern of nodal metastasis, morbidity, recurrence, and postoperative levels of serum parathyroid hormone. Ann Surg 2007;245:604-10.
20. Palestini N, Borasi A, Cestino L, et al. Is central neck dissection a safe procedure in the treatment of papillary thyroid cancer? Our experience. Langenbecks Arch Surg 2008;393:693-8.
21. Shaha AR. Complications of neck dissection for thyroid cancer. Ann Surg Oncol 2008;15:397-9.
22. Mazzaferri EL, Doherty GM, Steward DL. The pros and cons of prophylactic central compartment lymph node dissection for papillary thyroid carcinoma. Thyroid 2009;19:683-9.
23. Wierzbicka M, Gurgul E, Wasniewska-Okupniak E, et al. The feasibility and efficacy of secondary neck dissections in thyroid cancer metastases. Eur Arch Otorhinolaryngol 2013. [Epub ahead of print].
24. Henry JF, Gramatica L, Denizot A, et al. Morbidity of prophylactic lymph node dissection in the central neck area in patients with papillary thyroid carcinoma. Langenbecks Arch Surg 1998;383:167-9.
25. Kim MK, Mandel SH, Baloch Z, et al. Morbidity following central compartment reoperation for recurrent or persistent thyroid cancer. Arch Otolaryngol Head Neck Surg 2004;130:1214-6.
26. Dimov RS, Deenichin GP, Damianliev RA, et al. Safety and efficacy of modified radical lymph nodes dissection in patients with papillary thyroid cancer and clinically evident lymph nodes metastasis. Folia Med (Plovdiv) 2006;48:17-22.

27. Shaha AR. Complications of neck dissection for thyroid cancer. Ann Surg Oncol 2008;15:397-9.
28. Roh JL, Kim DH, Park CI. Prospective identification of chyle leakage in patients undergoing lateral neck dissection for metastatic thyroid cancer. Ann Surg Oncol 2008;15:424-9.
29. Dijkstra PU, van Wilgen PC, Buijs RP, et al. Incidence of shoulder pain after neck dissection: a clinical explorative study for risk factors. Head Neck 2001;23:947-53.
30. Cheng PT, Hao SP, Lin YH, et al. Objective comparison of shoulder dysfunction after three neck dissection techniques. Ann Otol Rhinol Laryngol 2000;109:761-6.
31. Kupferman ME, Weinstock YE, Santillan AA, et al. Predictors of level V metastasis in well-differentiated thyroid cancer. Head Neck 2008;30:1469-74.
32. Taylor RJ, Chepeha JC, Teknos TN, et al. Development and validation of the neck dissection impairment index: a quality of life measure. Arch Otolaryngol Head Neck Surg 2002;128:44-9.
33. Hassan SJ, Weymuller EA Jr. Assessment of quality of life in head and neck cancer patients. Head Neck 1993;15:485-96.
34. Almeida JP, Vartanian JG, Kowalski LP. Clinical predictors of quality of life in patients with initial differentiated thyroid cancers. Arch Otolaryngol Head Neck Surg 2009;135:342-6.
35. Dagan T, Bedrin L, Horowitz Z, et al. Quality of Life of well-differentiated thyroid carcinoma patients. J Laryngol Otol 2004;118:537-42.

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The pros and cons of routine central compartment neck dissection for clinically nodal negative (cN0) papillary thyroid cancer

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Abstract: Metastatic disease to regional lymph nodes (LNs) is common in papillary thyroid carcinoma (PTC). LN dissection is increasingly performed as part of the surgical management of PTC. The role of prophylactic central neck dissection (pCND) in PTC is unclear. There is limited evidence to support a routine pCND in clinical setting for nodal negative (cN0) PTC. The aim of this review was to examine the pros and cons of prophylactic neck dissection in cN0 PTC. In summary, the advantages of pCND are: removal of the central LNs that potentially harbor micro-metastases, more accurate staging of disease in order to plan more individualized management, reducing the need for re-operation to remove the metastatic LNs which have developed later and possible improvement in overall survival. The disadvantages are: an extensive surgery but lack of evidence of survival benefit, higher incidence of complications with little impact on local recurrence rate, possibility of over treating in cN0 patients and it does not sound like a cost effective approach in the management of small thyroid cancer. Considering low frequency of permanent morbidity, some authors believe that prophylactic neck dissection is safe in experienced hands even though its prognostic benefit has yet to be demonstrated.

Keywords: Central compartment neck dissection; nodal negative papillary thyroid cancer; prophylactic central neck dissection (pCND)

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Introduction

Although thyroid cancers represent approximately 1% of all new cancer diagnoses in the United States each year, it is the most common endocrine related cancer (1). The American Cancer Society estimated that approximately 44,670 new cases of thyroid cancer would be diagnosed in 2010. The overall incidence has risen from 1.3/100,000 for women and 4.6/100,000 for men in the year 1935 to 16.3/100,000 for women and 5.6/100,000 for men in 2008 (2). The age & gender adjusted incidence has increased faster than that of any other malignancy in the recent years, with the majority of this increase belonging to small papillary thyroid carcinoma (PTC) (3).

Epidemiology

Thyroid cancers are divided into PTCs (80%), follicular thyroid carcinomas (FTCs) (10%), medullary thyroid carcinomas (5-10%) and anaplastic thyroid carcinomas (1-2%). Primary lymphomas and sarcomas are rare (1). PTC and FTC make up the well-differentiated thyroid carcinomas. The prognosis of the differentiated thyroid carcinomas (DTC) is generally excellent. Ten-year relative survival rates in a large cohort of United States patients with papillary and follicular cancer were, respectively, 93% and 85% (4). In one cohort study, 40 years recurrence rates were about 35%, two thirds of which occurred within the first decade after initial therapy. Thirty years cancer mortality rates were about 12% with local recurrence and 43% with distant recurrence (5).

DTC

PTC is the most common type of differentiated thyroid

carcinoma. It is well known as a lymphotropic type of cancer and thus has high tendency to metastasize to regional lymph nodes (LNs) (6). Clinically evident nodal disease is present in approximately 5 to 10 percent of patients with PTC and a preoperative neck ultrasound can detect LN disease in up to 30 percent of patients (7-10). In contrast, less than five percent of patients with FTC develop nodal metastatic disease; the hematogenous rather than the lymphatic route is the primary pathway for metastasis (11). The prognosis of FTC is related to the age on presentation and the degree of capsular with or without vascular invasion. The diagnosis of FTC cannot always be made at the time of initial surgery. Prophylactic central neck dissection (pCND) during the first operation is of no value in FTC because the diagnosis of cancer is not established at that moment and also it tends not to spread via the lymphatic route.

Central neck dissection (CND) for PTC at the time of total thyroidectomy (TT)

The availability of non-invasive ultrasound and fine needle aspiration has led to detection of PTC in early stage. Higher incidence of small thyroid nodule with unknown cervical LNs status has posed a new management challenge to clinicians. Despite the excellent prognosis, many patients with PTC will develop nodal metastases in the central neck (level VI) or lateral neck (levels II, III, and IV) at the time of presentation or during the course of follow-up.

The guideline from the National Comprehensive Cancer Network recommends CND only in the presence of clinically nodal disease. Similarly, the current standard of care for thyroid cancer based on the consensus guideline from American Thyroid Association (ATA), includes TT and a "therapeutic" LN dissection for patients with clinical evidence of nodal disease or a "prophylactic" CND in patients with a tumor more than 4 cm (T3 or T4 tumor) even in the absence of clinical evidence of nodal involvement (3). Most endocrine surgeons agree that compartment-based nodal dissection is appropriate for enlarged LNs that are identified on preoperative or during intraoperative inspection and palpation. However, substantial controversy still exists regarding the role of "prophylactic" neck dissection for patients with PTC.

The neck dissection is defined by ATA as compartment oriented removal of all the lymphatic tissue with the fibroadipose tissue en bloc within the neck while preserving critical structures. A pCND is defined as resection of level VI LNs that appear normal in preoperative imaging and intra-operative assessment. Anatomical neck level VI or central compartment of the neck refers to the LNs that located between the carotid arteries from the innominate artery to the hyoid bone, includes the pretracheal, prelaryngeal and parartracheal LNs (3).

In general, cervical nodal metastasis tends to spread in a stepwise fashion from the thyroid to the ipsi-lateral central (level VI), then to the lateral compartment (level II to V) and/or contra-lateral central compartment. Therefore, the central compartment is considered to be the first echelon of nodal metastasis in thyroid cancer. Theoretically, removal of central LNs may alter the prognosis of thyroid cancer especially in PTC. Many endocrine surgeons have advocated pCND in their patient without clinical or radiographic evidence of LN involvement at the time of TT (12). The actual role of pCND in thyroid cancer remains a major topic of debate. This article aimed to review the arguments for and against pCND in PTC.

Arguments for pCND in clinically nodal negative (cN0) PTC

(I) Metastatic disease to central compartment LNs is frequently identified in patients with PTC. Nodal disease is an important issue in managing patients with thyroid cancer. According to ATA, LN metastasis is present in up to 20-50% of the patients undergoing an elective node dissection for PTC and up to 90 percent of patients will have microscopic metastatic disease (13,14). Sergio Zuniga *et al.* demonstrated that in 136 patients who underwent pCND, 82.3% (112 patients) had metastatic LNs (15). Similar conclusion was drawn by Roh *et al.* in which 51 (62.2%) out of 82 patients with neck dissection had LN metastases in the central neck compartment (16). Therefore, there were significant numbers of patients undergoing TT for cN0 PTC without pCND are likely to have occult nodal disease left behind in the neck.

(II) Some studies have raised the possibility that failure to remove tumour bearing cervical LN could be detrimental in patient with PTC. Cervical LN metastasis is associated with higher risk of disease recurrence and cancer mortality. This is supported by the following studies:

(i) In a retrospective review by Wada *et al.*, among 134 patients with papillary thyroid cancer undergoing TT with neck dissection, 17 patients (12.7%) developed local recurrence in cervical LNs. Recurrence rate was significantly higher for patients undergoing a therapeutic neck dissection

Table 1 A comparison of local regional recurrence rates between those underwent total thyroidectomy with prophylactic neck dissection (TT + CND) and those underwent total thyroidectomy (TT) alone

Author	Follow up period	No of patients		Local regional recurrence rate (%)		P-value
		TT + CND	TT	TT + CND	TT	
So *et al.* 2012 (20)	44.7 months (CND); 45.4 months (TT)	119	113	1.7	3.5	Not significant
Lang *et al.* 2011 (21)	Median: 26 months	82	103	3.7	2.9	1.0
Moo *et al.* 2012 (22)	3.1 years	45	36	4.4	16.7	0.13
Costa *et al.* 2009 (23)	Mean: 47 months (CND); 64 months (TT)	126	118	6.3	7.7	0.83
Gemsenjager *et al.* 2003 (24)	Median: 6.5 years	29	88	3	2	Not reported
Wada *et al.* 2003 (25)	Mean: 52 months	235	155	0.43	0.65	Not significant
Syawak *et al.* 2006 (26)	Median: 24.5 months (CND); 70 months (TT)	56	391	3.6	5.6	Not reported
Roh *et al.* 2007 (16)	Mean: 52 months	82 (PCND: 40)	73	0	2.6	0.37
Bardet *et al.* 2008 (27)	15 months	181 (with lateral neck dissection)	161	2.8	3.7	Not reported

Abbreviations: TT, total thyroidectomy; CND, central neck dissection.

for suspicious lymphadenopathy (n=42) when compared to patients undergoing an elective neck dissection (END) with no lymphadenopathy [23.8% (10 patients) versus 7.6% (7 patients)]. Microscopic disease was identified in 62 of 92 patients (67.4%) undergoing an END. Of the 62 patients with microscopic nodal disease, the local recurrence rate was 11.3%. Of the 30 patients with histologically negative nodes, there were no local recurrences. Of the 104 patients with histologically positive nodes, the local recurrence rate was 16.3%. Thus, he concluded that lymphadenopathy and microscopic nodal status were significantly associated with recurrences and disease free survival rates (17).

(ii) In a Cox regression model, studied of 1,355 patients with 30 years of follow-up, the likelihood of cancer death was increased by regional lymph-node metastases in patients without distant metastases (18).

(iii) Additional data from Surveillance Epidemiology and End Results database comprising 19,918 patients showed that for those with LN metastasis, the 14-year survival rate was 79% and was 82% in non-metastatic patients (P<0.05) (19).

Based on the above findings, there are potential benefits of lower recurrence in those who underwent pCND. *Table 1* summarizes the local regional recurrence rates between those underwent TT with prophylactic neck dissection and those who underwent TT alone.

In contrast, a recent meta-analysis by Zetoune *et al.*, comprising five retrospective comparative studies (n=1,264), found that there was an "insignificant" trend toward lower overall recurrence rate in the group who underwent either unilateral or bilateral pCND when compared to those who had TT only (2.02% versus 3.92%, odds ratio =1.05, 95% CI, 0.48-2.31) (28). Furthermore, people may argue that the subclinical LN metastasis could be ablated by radioactive iodine post operation. But, it is worth noting that not all tumours will respond to RAI ablation.

(III) Ultrasound neck and aspiration cytology are currently the preferred investigation tools for evaluation of the thyroid and cervical LN. However, detection of central compartment LN metastasis using ultrasound remains difficult even in expert hand because the abnormal central LNs are often small in size and frequently located deep inside the neck or just posterior to the sternum (29-31), where the overlying thyroid gland often hinders adequate visualization (32).

Kim *et al.* found that preoperative ultrasound has an accuracy of 77% only in detection of LN metastasis. Despite the fact that ultrasound has high specificity of

92% and positive predictive value of 81%, the sensitivity is only 51% and the negative predictive value is 76% (33,34). Other sophisticated imaging modalities such as computer tomography and magnetic resonance imaging have not shown any additional advantage, they are more beneficial in patients with extensive nodal involvement. Because of the lymphadenopathy cannot be reliably assessed by imaging studies, pCND has been advocated. Prophylactic CND allows histology examination of LNs and more accurate pathological staging.

Wang *et al.* reviewed 49 patients (48%) who were cN0 PTC and found that pCND resulted in detection of unsuspected metastasis lymphadenopathy in 20 (41%) of patients and changed RAI recommendation in 14 (33%) of patients (35). Similarly, in a study performed in our hospital, of 82 patients underwent pCND, 17.1% were upstaged from stage I/II to stage III due to detection of nodal metastasis after surgery (21).

(IV) A detectable post-operation Thyroglobulin (Tg) level is a surrogate marker of persistent or recurrent thyroid cancer after TT and RAI ablation. Prophylactic CND results in a higher rate of stimulated athyroglobulinemia after surgery. Hence, it could facilitate follow up and cancer surveillance of the neck. The relation between pCND and Tg was illustrated by the following studies:

(i) Sywak *et al.* examined 447 patients with clinically node-negative PTC. 56 patients underwent TT plus pCND. There was a significantly lower level of stimulated Tg at six months after RAI ablation (mean: 0.4 versus 9.3 mg/L, P<0.02) and higher proportion of athyroglobulinemia (72% versus 43%; P<0.001) (26).

(ii) In a study compared serum Tg level in 113 patients underwent TT alone with 119 patients underwent TT in conjunction with pCND bilaterally: the post-operative Tg was significantly less in pCND group (1.07 *vs.* 2.24 ng/mL respectively; P=0.022). However, the two groups became similar after low dose radioactive iodine treatment (0.44 *vs.* 0.69 ng/mL respectively; P=0.341). There was also no significant difference in three years local-regional control rate in both the studied groups (98.35% *vs.* 96.5%; P=0.368). Thus, he concluded that pCND lower the serum Tg level but is not helpful in decreasing short term recurrence in patient with cN0 PTC (20).

(iii) Lang *et al.* analysed 185 patients with PTC retrospectively. In this study, 82 (44.3%) patients underwent unilateral TT with pCND and found that this group of patient has lower median pre-ablative-stimulated Tg level (<0.5 versus 6.7 μg/L, P<0.001) and achieved a higher rate of pre-ablative athyroglobulinemia (51.2% versus 22.3%, P=0.024) than those who underwent a TT only. However, these differences were not observed six months after ablation (31). The most likely explanation for this difference was that the residual microscopic disease was ablated by RAI ablation subsequently. Thus, the group without pCND achieved similar stimulated Tg levels and similar rate of athyroglobulinemia six months after ablation (36).

Unlike the above studies, no difference was found by Raffaelli M *et al.* concerning mean post-operative basal and stimulated Tg after a prospective evaluation of total 186 patients with cN0 underwent TT with or without; ipsi- or bilateral CND (37). Similarly, Hughes *et al.* also found that there was no difference in post-ablation median-stimulated Tg level or rate of athyroglobulinemia between patients underwent TT with or without bilateral pCND (38).

(V) Thyroid cancer patients without pCND are at higher risk of neck recurrence which may require second operation. Re-operation is associated with a higher morbidity than pCND when done at the time of initial TT. Complications such as iatrogenic injuries of the nerve and parathyroid gland would be higher in re-operative central lymph node dissection (CLND) because of the scarring in the operative field and distorted anatomy in the central neck after TT. For example, Segal *et al.* who had reviewed 503 patients retrospectively found that reoperation had a significantly higher complication rate of permanent recurrent nerve injury (25% versus 5.8%) and hypoparathyroidism (8.3% versus 5.0%) compared with primary operation (39). Other studies also revealed similar outcomes (40-43). It is reasonable to dissect LNs in the central compartment routinely, because subsequent surgery for node metastases in this area poses more difficulties. On the other hand, Shen *et al.* argued that neck reoperation could also be performed as safely as first operation by an "experienced" surgeon. In his study, the initial and re-operative CLND had similar complication and recurrence rates (44).

Arguments against pCND in cN0 PTC

(I) The most frequently quoted data arguing against the need for routine pCND is increased risk of transient hypoparathyroidism. Risk of transient hypocalcemia has been consistently shown in many studies (*Table 2*).

Table 2 A comparison of the rate of hypoparathyroidism (hypocalcemia) between total thyroidectomy (TT) alone and total thyroidectomy with central neck dissection (TT + CND)

Author	No of patients		Transient hypocalcaemia/ hypoparathyroidism (%)		P-value	Permanent hypocalcaemia/ hypoparathyroidism (%)		P-value
	TT + CND	TT alone	TT + CND	TT alone		TT + CND	TT alone	
Moo *et al*. 2010 (22)	45	35	31	5	0.001	0.0	5.0	0.41
So *et al*. 2012 (20)	119	113	41.2	33.6	0.235	5.9	1.8	0.105
Lang *et al*. 2011 (21)	82	103	18.3	8.7	0.017	2.4	1.0	1.000
Shindo *et al*. 2010 (45)	122	134	13.1	25.4	0.02	0.8	0.7	0.99
Palestini *et al*. 2008 (46)	93	148	26.9	12.8	0.003	0.0	2.7	0.2
Roh *et al*. 2007 (16)	82	73	30.5	9.6	0.001	4.9	0.0	0.056
Sywak *et al*. 2006 (26)	56	391	18	8	0.02	1.8	0.5	0.27
Giordano *et al*. 2012 (47)	385 (unilateral), 308 (bilateral)	394	36.1 (unilateral), 51.9 (bilateral)	27.7	0.014 (unilateral), 0.001 (bilateral)	7.0 (unilateral), 16.2 (bilateral)	6.3	0.818 (unilateral), <0.001 (bilateral)

Abbreviations: TT, total thyroidectomy; CND, central neck dissection.

(i) Moo *et al*. found that the rates of temporary hypocalcemia were higher in CND group compared to no neck dissection group (31% versus 5 %; P=0.01). Interestingly, the rate of permanent hypocalcemia were the same (5% versus 0%; P=0.41) (22).

(ii) A meta-analysis found that patients with pCND were almost 2.5 times more likely to have temporary hypocalcemia than those who underwent TT alone (26.0% *vs.* 10.8%; OR=2.56; 95% CI: 1.75-2.57) (48).

(iii) So *et al*. reviewed 232 patients who underwent surgery for clinically node negative papillary thyroid micro-carcinoma from 1999 to 2006, reported that the frequency of permanent hypocalcemia was approximately 3 times greater in TT with pCND (5.9%) than TT only (1.8%) although this finding did not reach statistical significance (20).

(iv) A recent systematic review of five retrospective studies, evaluated the morbidity of pCND and found that there was one extra case of transient hypocalcaemia for every eight pCNDs performed (49). However, there was no increased risk of permanent hypocalcaemia and recurrent laryngeal nerve injury. The higher rate of temporary hypoparathyroidism could be explained by the higher chance of unintentional removal or devascularisation of parathyroid glands during dissection.

Prophylactic CND also contributes to the higher rate of temporary recurrent laryngeal nerve injury in a study by Shindo *et al*. (45) (*Table 3*). Palestini *et al*. reported four times higher rate of transient recurrent laryngeal nerve injury in patients underwent TT plus bilateral neck dissection (1.4% versus 5.4%, P=0.059), although it was not statistically significant (46). To date, no studies have shown an increase risk of "permanent" recurrent laryngeal nerve injury in patient underwent pCND. A good example was a study by Giordano *et al*. as shown in *Table 3* (47).

In general, surgical morbidity correlates with the extent of surgical dissection and the operation skill of surgeons. Since the risks of transient complications are high, especially when performed by low volume surgeons (fewer than 50 cases/year), a selective approach should be considered by determine which patients are likely required pCND pre-operatively and the experience of the surgeon (51).

Several studies described the risk factors that associated with LN metastasis in PTC but the results were inconsistent (46,52,53). In a study by So *et al*., the male gender, tumour multi-focality and extra-thyroidal extension were independently predictive of subclinical central LN

Table 3 Recurrent laryngeal nerve or vocal cord injuries in the total thyroidectomy with and without central neck dissection

Author	No of patients		Transient vocal cord palsy (%)		P-value	Permanent vocal cord palsy (%)		P-value
	TT + CND	TT alone	TT + CND	TT alone		TT + CND	TT alone	
So *et al.* 2012 (20)	119	113	3.4	3.5	0.941	0.8	1.8	0.531
Giordano *et al.* 2012 (47)	385 (unilateral), 308 (bilateral)	394	3.9 (unilateral), 5.5 (bilateral)	3.6	0.404	0.5 (unilateral), 2.3 (bilateral)	1.0	0.099
Lang *et al.* 2011 (21)	82	103	1.8	0.0	0.324	0.6	0.5	0.443
Shindo *et al.* 2010 (45)	122	134	0.0	4.5	0.03	0.0	0.0	–
Sadowski *et al.* 2009 (50)	169	130	8.9	4.6	0.18	2.4	3.1	1.0
Palestini *et al.* 2008 (46)	93	148	5.4	1.4	0.059	0.0	1.4	0.344
Roh *et al.* 2007 (16)	82	73	7.3	4.1	0.394	3.6	2.7	0.747
Sywak *et al.* 2006 (26)	56	391	1.8	1.0	0.62	0.0	1.0	0.45

Abbreviations: TT, total thyroidectomy; CND, central neck dissection.

metastasis. It was recommended that patient with these features should be considered for pCND (52). However, realistically only male sex is known preoperatively. Some researchers also believed that large tumour size, patients who have decreased capacity for RAI and those with *BRAF* mutation should be undergoing pCND at the time of TT (36). Alternatively, suspected LN that found intra-operatively may be confirmed by frozen section examination before proceeding to neck dissection.

(II) LN involvement in papillary thyroid cancer can be macroscopic (identified on preoperative imaging or intraoperative inspection) or microscopic (identified on pathologic review only). Macroscopic LN involvement is associated with a significant higher rate of local recurrence (10-42%) (54,55). It is unknown what the natural history is, in PTC with only microscopic LN involvement/subclinical nodal metastasis.

Studies have shown that only subclinical metastatic LNs would be identified at the time of pCND for small PTC (56). Wada *et al.* studied microscopic regional LN status in 92 patients with PTC underwent pCND and found that only few nodes (mean 2.7 nodes/17.8%) were involved pathologically when there was no lymphadenopathy clinically (31). Besides, Vergez *et al.* also found in their study that most of these pathologically involved LN were subclinical and less that 5 mm in size (66%) (57). With the advances of radio-active iodine ablation, these micrometastasis wouldn't ultimately result in poorer prognosis. Additionally, it is doubtful that this subclinical occult LN metastasis would eventually develop into clinically significant recurrences in the future.

(i) In another data presented by Wada *et al.* on 259 patients with papillary microcarcinoma of thyroid, of mean 53 months follow up, LN metastasis was frequent in the pCND group (60.9%) for central compartment and 39.5% for ipsilateral lateral compartment. While, only 0.43% patient underwent prophylactic neck dissection developed recurrence despite high microscopic LN involvement (25). The nodal recurrence did not differ between the pCND group and the no-dissection group (0.43% *vs.* 0.65%).

(ii) Gemsenjäger *et al.* reported a similar finding in their study of 159 patients with PTC and concluded that the rate of occult nodal disease was relatively low and it did not frequently progress to clinical recurrent disease (24).

In summary, for patients harbouring central neck compartment "micrometastasis", pCND dissection may only provide a limited benefit in terms of reducing recurrence. Routine CND targeted at subclinical LN metastasis has little prognostic benefit. Unnecessary CND will prolong

Table 4 Mean doses of radioactive iodine ablative therapy

Author	No of patients		Mean dose of I-131 per treatment		P-value
	TT + CND	TT alone	TT + CND	TT alone	
Moo *et al*. 2010 (22)	45	36	102.7 mCi	66.3 mCi	0.002
Hughes *et al*. 2010 (38)	78	65	150.0 mCi	30.0 mCi	0.01
Sywak *et al*. 2006 (26)	56	391	5.2 GBq	4.8 GBq	0.2

Abbreviations: TT, total thyroidectomy; CND, central neck dissection.

operation time and increase surgical complications.

(III) There is also little evidence to show that pCND improves cancer-specific survivals in "cN0 PTC".

(i) A survical benefit for pCND in DTC was suggested in a study carried out by Tisell *et al*. (58). They evaluated 175 patients who underwent TT with CND and compared with contemporaneous controls from two other studies conducted on patients in Norway and Finland (59,60). They showed that patients who underwent TT with pCND had a higher survival rate (1.6% versus 8.4-11.1%). However, this study was limited by lack of statistical comparison between the studies.

(ii) In the retrospective review of 244 patients by Costa *et al*., found that central neck metastasis was predictive of disease recurrent but not influencing the prognosis. The overall recurrence rate in his paper was 6.35 % (8/126; mean follow-up of 47 months) in TT plus pCND group and 7.7% (9/118; mean follow-up of 64 months) in TT alone group (P=0.83). Of those underwent pCND, 47% were diagnosed pN1a but there was no difference in survival rate statistically (23).

(iii) Additional finding came from a cohort analysis of 266 patients with 6.3 years mean follow up and the study reported that the 5-year disease-free survival was comparable; 88.2% in the CND group versus 85.6% in the group that did not undergo CND (P=0.72) (15). Absented of survival benefit with more extensive surgery and longer operation time have limited the routine application of pCND (24).

(IV) The number of positive cervical LNs could affect the disease stage. Prophylactic CND provides more accurate pathological staging and hence, greater incidence of N1a is found. In a study conducted by our hospital demonstrated that 17.1% of 82 patients were upstage from stage I/II to III after pCND (21). Basically, the pathological staging of the tumour for patients aged more than 45 years old are changed to higher stage III (AJCC/UICC TNM staging system) even without any extra-thyroidal extension or other poor prognostic factors (61,62). The outcome of stage migration will be reflected in the overall cancer-specific survival rate. Confusion may occur as they would be classified as stage III with lower 10-year survival (85-90%) while those patients younger than 45 would still remain as stage I with 10-year survival rates of more than 95% (31,61-64).

(V) Because of upstaging, more patients would receive RAI ablation and higher doses of RAI, which might not be necessary in certain patients. In a retrospective study, Hughes *et al*. had observed that patients in the TT plus pCND group received significantly higher dose of RAI than those in the TT group (150 *vs.* 30 mCi, P=0.01). Despite a higher dose of RAI, there was no difference in central neck recurrence between TT plus pCND and TT alone group. The author concluded that pCND allows stratification of patient to receive higher doses of RAI but not affected the local recurrence rate (38). *Table 4* revealed the published series of doses of I-131 used during RAI ablation. pCND increased LN positivity and has encouraged higher usage of RAI. This is foreseeable that increase of health care costs will be one of the major concerns in the future.

Although the treatments with 131-I are generally safe and well-tolerated, patients would still be subjected to potential short- and long-term side-effect of RAI. RAI is contraindicated in patients who are pregnant or breastfeeding. Men who receive RAI treatment for thyroid cancer may have decreased sperm counts and temporary infertility for a period of roughly two years (65,66). Furthermore, Lee *et al*. found that nausea, vomiting, ageusia (loss of taste), salivary gland swelling, sialoadenitis associated xerostomia, dental caries, pulmonary fibrosis, naso-lacrimal outflow obstruction, and, more importantly, increased risk of second primary malignancies are associated with radioiodine therapy (67,68). I-131 is preferentially taken up by normal and malignant thyroid follicular cells, but it is also accumulated in the stomach, salivary glands, colon, and bladder; salivary glands and breast tissue contain sodium iodide transporters. The risk of salivary gland,

breast, bladder and gastrointestinal cancers can theoretically increase in thyroid cancer patients treated with radioiodine. The risk is typically more prominent between two and ten years after therapy with a prevalence of about 0.5% (65,66).

Conclusions

The extent of dissection in the neck is a balance between the greater morbidity of a more extensive neck dissection and the possibility of leaving residual untreated metastatic LN. There is little good evidence (level II or better) to justify pCND in all cN0 PTC. Our review has summarized the conflicting recommendations in which the applicability to clinical practice remains questionable. Further studies in this controversial subject are much needed.

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References

1. Sharma PK. Thyroid cancer. Medscape Medical News [serial online]. Sep 9, 2013; Accessed August 1, 2013. Available online: http://emedicine.medscape.com/article/851968
2. Michael TR. Overview of papillary thyroid cancer. UpToDate [serial online]. May 24, 2013; Accessed August 1, 2013. Available online: http://www.uptodate.com/contents/overview+of+papillary+thyroid+cancer
3. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167-214.
4. Hundahl SA, Fleming ID, Fremgen AM, et al. A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985-1995 [see commetns]. Cancer 1998;83:2638-48.
5. Mazzaferri EL, Kloos RT. Clinical review 128: Current approaches to primary therapy for papillary and follicular thyroid cancer. J Clin Endocrinol Metab 2001;86:1447-63.
6. Sippel RS. Central and lateral compartment lymphadenectomy (neck dissection) for differentiated thyroid cancer. UpToDate [serial online]. March 21, 2013; Accessed August 1, 2013. Available online: http://www.uptodate.com/contents/central-and-lateral-compartment-lymphadenectomy-neck-dissection-for-differentiated-thyroid-cancer
7. Grubbs EG, Evans DB. Role of lymph node dissection in primary surgery for thyroid cancer. J Natl Compr Canc Netw 2007;5:623-30.
8. Ito Y, Uruno T, Nakano K, et al. An observation trial without surgical treatment in patients with papillary microcarcinoma of the thyroid. Thyroid 2003;13:381-7.
9. Kim E, Park JS, Son KR, et al. Preoperative diagnosis of cervical metastatic lymph nodes in papillary thyroid carcinoma: comparison of ultrasound, computed tomography, and combined ultrasound with computed tomography. Thyroid 2008;18:411-8.
10. Stulak JM, Grant CS, Farley DR, et al. Value of preoperative ultrasonography in the surgical management of initial and reoperative papillary thyroid cancer. Arch Surg 2006;141:489-94; discussion 494-6.
11. Zaydfudim V, Feurer ID, Griffin MR, et al. The impact of lymph node involvement on survival in patients with papillary and follicular thyroid carcinoma. Surgery 2008;144:1070-7; discussion 1077-8.
12. Pisello F, Geraci G, Lo Nigro C, et al. Neck node dissection in thyroid cancer. A review. G Chir 2010;31:112-8.
13. Arturi F, Russo D, Giuffrida D, et al. Early diagnosis by genetic analysis of differentiated thyroid cancer metastases in small lymph nodes. J Clin Endocrinol Metab 1997;82:1638-41.
14. Cooper DS, Doherty GM, Haugen BR, et al. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2006;16:109-42.
15. Zuniga S, Sanabria A. Prophylactic central neck dissection in stage N0 papillary thyroid carcinoma. Arch Otolaryngol Head Neck Surg 2009;135:1087-91.
16. Roh JL, Park JY, Park CI. Total thyroidectomy plus neck dissection in differentiated papillary thyroid carcinoma patients: pattern of nodal metastasis, morbidity, recurrence, and postoperative levels of serum parathyroid hormone. Ann Surg 2007;245:604-10.
17. Wada N, Suganuma N, Nakayama H, et al. Microscopic regional lymph node status in papillary thyroid carcinoma with and without lymphadenopathy and its relation to outcomes. Langenbecks Arch Surg 2007;392:417-22.
18. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med 1994;97:418-28.
19. Podnos YD, Smith D, Wagman LD, et al. The implication of lymph node metastasis on survival in patients with well-differentiated thyroid cancer. Am Surg 2005;71:731-4.
20. So YK, Seo MY, Son YI. Prophylactic central lymph node dissection for clinically node-negative papillary thyroid

microcarcinoma: influence on serum thyroglobulin level, recurrence rate, and postoperative complications. Surgery 2012;151:192-8.
21. Lang BH, Wong KP, Wan KY, et al. Impact of routine unilateral central neck dissection on preablative and postablative stimulated thyroglobulin levels after total thyroidectomy in papillary thyroid carcinoma. Ann Surg Oncol 2012;19:60-7.
22. Moo TA, McGill J, Allendorf J, et al. Impact of prophylactic central neck lymph node dissection on early recurrence in papillary thyroid carcinoma. World J Surg 2010;34:1187-91.
23. Costa S, Giugliano G, Santoro L, et al. Role of prophylactic central neck dissection in cN0 papillary thyroid cancer. Acta Otorhinolaryngol Ital 2009;29:61-9.
24. Gemsenjäger E, Perren A, Seifert B, et al. Lymph node surgery in papillary thyroid carcinoma. J Am Coll Surg 2003;197:182-90.
25. Wada N, Duh QY, Sugino K, et al. Lymph node metastasis from 259 papillary thyroid microcarcinomas: frequency, pattern of occurrence and recurrence, and optimal strategy for neck dissection. Ann Surg 2003;237:399-407.
26. Sywak M, Cornford L, Roach P, et al. Routine ipsilateral level VI lymphadenectomy reduces postoperative thyroglobulin levels in papillary thyroid cancer. Surgery 2006;140:1000-5; discussion 1005-7.
27. Bardet S, Malville E, Rame JP, et al. Macroscopic lymph-node involvement and neck dissection predict lymph-node recurrence in papillary thyroid carcinoma. Eur J Endocrinol 2008;158:551-60.
28. Zetoune T, Keutgen X, Buitrago D, et al. Prophylactic central neck dissection and local recurrence in papillary thyroid cancer: a meta-analysis. Ann Surg Oncol 2010;17:3287-93.
29. Marshall CL, Lee JE, Xing Y, et al. Routine pre-operative ultrasonography for papillary thyroid cancer: effects on cervical recurrence. Surgery 2009;146:1063-72.
30. Hwang HS, Orloff LA. Efficacy of preoperative neck ultrasound in the detection of cervical lymph node metastasis from thyroid cancer. Laryngoscope 2011;121:487-91.
31. Wada N, Masudo K, Nakayama H, et al. Clinical outcomes in older or younger patients with papillary thyroid carcinoma: impact of lymphadenopathy and patient age. Eur J Surg Oncol 2008;34:202-7.
32. Leboulleux S, Girard E, Rose M, et al. Ultrasound criteria of malignancy for cervical lymph nodes in patients followed up for differentiated thyroid cancer. J Clin Endocrinol Metab 2007;92:3590-4.
33. Kim E, Park JS, Son KR, et al. Preoperative diagnosis of cervical metastatic lymph nodes in papillary thyroid carcinoma: comparison of ultrasound, computed tomography, and combined ultrasound with computed tomography. Thyroid 2008;18:411-8.
34. Roh JL, Park JY, Kim JM, et al. Use of preoperative ultrasonography as guidance for neck dissection in patients with papillary thyroid carcinoma. J Surg Oncol 2009;99:28-31.
35. Wang TS, Evans DB, Fareau GG, et al. Effect of prophylactic central compartment neck dissection on serum thyroglobulin and recommendations for adjuvant radioactive iodine in patients with differentiated thyroid cancer. Ann Surg Oncol 2012;19:4217-22.
36. Wong KP, Lang BH. The role of prophylactic central neck dissection in differentiated thyroid carcinoma: issues and controversies. J Oncol 2011;2011:127929.
37. Raffaelli M, De Crea C, Sessa L, et al. Prospective evaluation of total thyroidectomy versus ipsilateral versus bilateral central neck dissection in patients with clinically node-negative papillary thyroid carcinoma. Surgery 2012;152:957-64.
38. Hughes DT, White ML, Miller BS, et al. Influence of prophylactic central lymph node dissection on postoperative thyroglobulin levels and radioiodine treatment in papillary thyroid cancer. Surgery 2010;148:1100-6; discussion 1006-7.
39. Segal K, Friedental R, Lubin E, et al. Papillary carcinoma of the thyroid. Otolaryngol Head Neck Surg 1995;113:356-63.
40. Simon D, Goretzki PE, Witte J, et al. Incidence of regional recurrence guiding radicality in differentiated thyroid carcinoma. World J Surg 1996;20:860-6; discussion 866.
41. Moley JF, Lairmore TC, Doherty GM, et al. Preservation of the recurrent laryngeal nerves in thyroid and parathyroid reoperations. Surgery 1999;126:673-7; discussion 677-9.
42. Kim MK, Mandel SH, Baloch Z, et al. Morbidity following central compartment reoperation for recurrent or persistent thyroid cancer. Arch Otolaryngol Head Neck Surg 2004;130:1214-6.
43. Uruno T, Miyauchi A, Shimizu K, et al. Prognosis after reoperation for local recurrence of papillary thyroid carcinoma. Surg Today 2004;34:891-5.
44. Shen WT, Ogawa L, Ruan D, et al. Central neck lymph node dissection for papillary thyroid cancer: comparison of complication and recurrence rates in 295 initial dissections and reoperations. Arch Surg 2010;145:272-5.
45. Shindo M, Stern A. Total thyroidectomy with and without

selective central compartment dissection: a comparison of complication rates. Arch Otolaryngol Head Neck Surg 2010;136:584-7.
46. Palestini N, Borasi A, Cestino L, et al. Is central neck dissection a safe procedure in the treatment of papillary thyroid cancer? Our experience. Langenbecks Arch Surg 2008;393:693-8.
47. Giordano D, Valcavi R, Thompson GB, et al. Complications of central neck dissection in patients with papillary thyroid carcinoma: results of a study on 1087 patients and review of the literature. Thyroid 2012;22:911-7.
48. Lang BH, Ng SH, Lau LL, et al. A systematic review and meta-analysis of prophylactic central neck dissection on short-term locoregional recurrence in papillary thyroid carcinoma after total thyroidectomy. Thyroid 2013;23:1087-98.
49. Chisholm EJ, Kulinskaya E, Tolley NS. Systematic review and meta-analysis of the adverse effects of thyroidectomy combined with central neck dissection as compared with thyroidectomy alone. Laryngoscope 2009;119:1135-9.
50. Sadowski BM, Snyder SK, Lairmore TC. Routine bilateral central lymph node clearance for papillary thyroid cancer. Surgery 2009;146:696-703; discussion 703-5.
51. Sippel RS, Chen H. Controversies in the surgical management of newly diagnosed and recurrent/residual thyroid cancer. Thyroid 2009;19:1373-80.
52. So YK, Son YI, Hong SD, et al. Subclinical lymph node metastasis in papillary thyroid microcarcinoma: a study of 551 resections. Surgery 2010;148:526-31.
53. Roh JL, Park JY, Park CI. Total thyroidectomy plus neck dissection in differentiated papillary thyroid carcinoma patients: pattern of nodal metastasis, morbidity, recurrence, and postoperative levels of serum parathyroid hormone. Ann Surg 2007;245:604-10.
54. Randolph GW, Duh QY, Heller KS, et al. The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension. Thyroid 2012;22:1144-52.
55. Moreno MA, Edeiken-Monroe BS, Siegel ER, et al. In papillary thyroid cancer, preoperative central neck ultrasound detects only macroscopic surgical disease, but negative findings predict excellent long-term regional control and survival. Thyroid 2012;22:347-55.
56. Randolph GW. Papillary cancer nodal surgery and the advisability of prophylactic central neck dissection: primum, non nocere. Surgery 2010;148:1108-12.
57. Vergez S, Sarini J, Percodani J, et al. Lymph node management in clinically node-negative patients with papillary thyroid carcinoma. Eur J Surg Oncol 2010;36:777-82.
58. Tisell LE, Nilsson B, Mölne J, et al. Improved survival of patients with papillary thyroid cancer after surgical microdissection. World J Surg 1996;20:854-9.
59. Kukkonen ST, Haapiainen RK, Franssila KO, et al. Papillary thyroid carcinoma: the new, age-related TNM classification system in a retrospective analysis of 199 patients. World J Surg 1990;14:837-41; discussion 841-2.
60. Salvesen H, Njølstad PR, Akslen LA, et al. Papillary thyroid carcinoma: a multivariate analysis of prognostic factors including an evaluation of the p-TNM staging system. Eur J Surg 1992;158:583-9.
61. Shindo M, Wu JC, Park EE, et al. The importance of central compartment elective lymph node excision in the staging and treatment of papillary thyroid cancer. Arch Otolaryngol Head Neck Surg 2006;132:650-4.
62. Lang B, Lo CY, Chan WF, et al. Restaging of differentiated thyroid carcinoma by the sixth edition AJCC/UICC TNM staging system: stage migration and predictability. Ann Surg Oncol 2007;14:1551-9.
63. Lang BH, Lo CY, Chan WF, et al. Prognostic factors in papillary and follicular thyroid carcinoma: their implications for cancer staging. Ann Surg Oncol 2007;14:730-8.
64. Lang BH, Chow SM, Lo CY, et al. Staging systems for papillary thyroid carcinoma: a study of 2 tertiary referral centers. Ann Surg 2007;246:114-21.
65. Luster M, Clarke SE, Dietlein M, et al. Guidelines for radioiodine therapy of differentiated thyroid cancer. Eur J Nucl Med Mol Imaging 2008;35:1941-59.
66. Carballo M, Quiros RM. To treat or not to treat: the role of adjuvant radioiodine therapy in thyroid cancer patients. J Oncol 2012;2012:707156.
67. Lee SL. Complications of radioactive iodine treatment of thyroid carcinoma. J Natl Compr Canc Netw 2010;8:1277-86; quiz 1287.
68. Lang BH, Lo CY, Wong IO, et al. Impact of second primary malignancy on outcomes of differentiated thyroid carcinoma. Surgery 2010;148:1191-6; discussion 1196-7.

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Involvement of level IIb lymph node metastasis and dissection in thyroid cancer

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Abstract: Thyroid neoplasms are the most frequent neoplasm in the head and neck region. Most thyroid carcinomas are well-differentiated tumors of follicular cell origin. Thyroid papillary carcinoma (TPC) is the most common thyroid malignancy. It constitutes 60% to 90% of all the thyroid carcinomas and cervical lymph node metastases are commonly seen in these patients. Although cervical lymph node metastases are common in this cancer, the management and the prognostic role of lymph nodes in TPC remains controversial. In this paper we reviewed the currently available literature regarding the extent of lateral neck dissection in papillary thyroid carcinoma patients with lateral neck metastasis.

Keywords: Thyroid; cancer; papillary; level IIb; neck dissection

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Thyroid neoplasms represent almost 95% of all endocrine tumors, although they are relatively uncommon, accounting for approximately 2% of all human malignancies. Thyroid neoplasms are the most frequent neoplasm in the head and neck region. Most thyroid carcinomas are well-differentiated tumors of follicular cell origin. These lesions are histologically defined as papillary carcinoma, follicular carcinoma, and Hurthle cell carcinoma. Thyroid papillary carcinoma (TPC) is the most common thyroid malignancy. It constitutes 60% to 90% of all the thyroid carcinomas. Cervical lymph node metastases in patients with TPC are commonly seen. The rate of nodal metastases in TPC has been reported to be within the range of 30-90% (1,2). Although cervical lymph node metastases are common in TPC, the management and the prognostic role of lymph nodes in TPC remains controversial. Some studies suggest that the neck metastases have no adverse effect on neither the recurrence nor the survival (3-5). However, some recent articles showed that lymph node metastases were associated with an increase in recurrence rates and have a negative impact on survival (6,7). Neck dissections in the clinically involved lateral cervical lymph nodes are generally well-accepted procedures for TPC. However, the extent of the neck dissection necessary for oncologic management for positive lateral neck nodes is still debated (8,9). Current treatment guidelines of the American Thyroid Association (ATA) recommended, therapeutic central-compartment (level VI) neck dissection for patients with clinically involved central or lateral neck lymph nodes should accompany total thyroidectomy to provide clearance of disease from the central neck. Prophylactic level VI neck dissection may be performed in patients with TPC with clinically uninvolved central neck lymph nodes, especially for advanced primary tumors (T3 or T4). Near-total or total thyroidectomy without prophylactic central neck dissection may be appropriate for small (T1 or T2), noninvasive, clinically node-negative PTC and most follicular cancer. But elective cervical lymph node dissection has not been clearly defined (10).

Unlike squamous cell carcinoma of the head and neck, where regional metastasis have a definite negative prognostic impact, the effect of cervical nodal involvement on survival in differentiated thyroid carcinoma has not been demonstrated clearly. Elective neck dissection is generally recommended if the risk of occult neck metastasis is higher than 20% in head and neck squamous cell carcinomas (3).

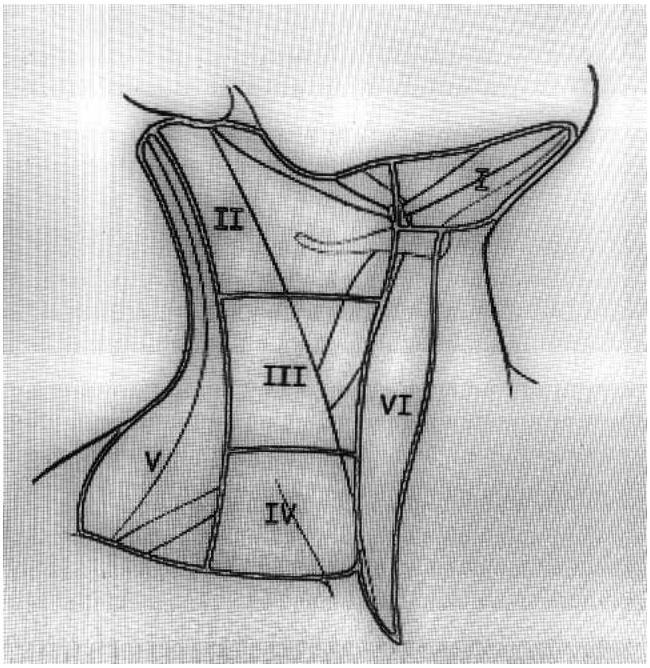

Figure 1 Neck lymph node levels (I-VI).

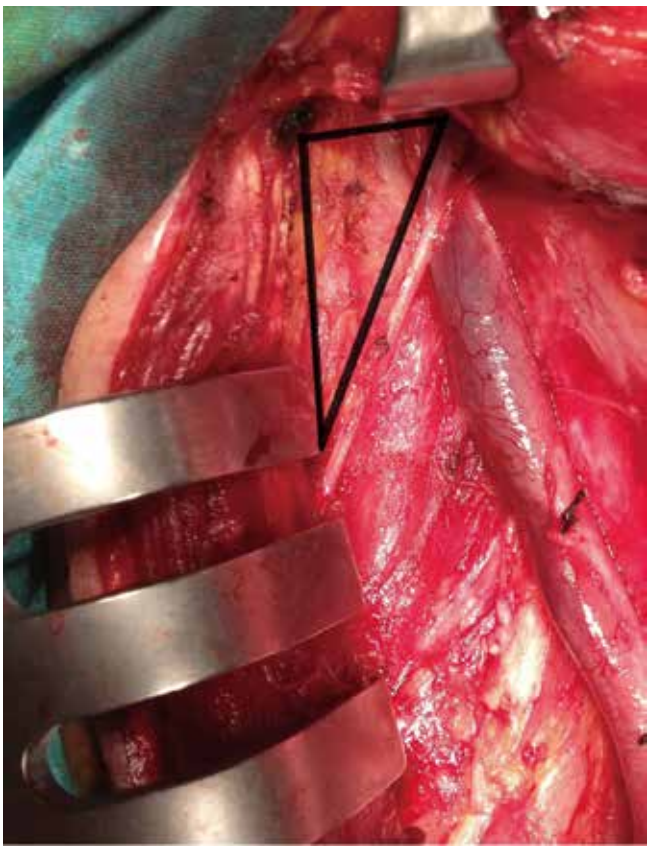

Figure 2 Level IIb seen during surgery.

However, the role of elective neck dissection in TPC has not been clearly defined yet.

In general regional lymph node spread from thyroid cancer can broadly be classified as central neck compartment and lateral neck compartment metastases (1). The lymph node regions of the neck were divided into six levels (levels I-VI). These levels classified as level I is submandibular and submental lymph nodes regions, level II is upper jugular lymph nodes region, level III is middle jugular lymph nodes region, level IV is lower jugular lymph nodes region, level V posterior triangle lymph nodes region and level VI is anterior lymph nodes region (*Figure 1*) (11). Level II divided into two parts by spinal accessory nerve known as levels IIa and IIb. Level IIb is also known as the submuscular recess or supraspinal recess. It comprises level II nodes that lay superficial to the fascia on the splenius capitis and levator scapulae muscles, superior to the spinal accessory nerve and bordered by the posterior belly of the digastric muscle superiolaterally, the skull base by superiorly and the sternocleidomastoid by muscle posterolaterally (*Figure 2*) (12-15).

The extent of neck dissection at the time of initial thyroidectomy has become a topic of contention (16). The cervical lymph nodes metastases initiates in the perithyroidal nodes of the central neck and progresses to the lateral cervical compartments (level I to V) and the superior mediastinum. However, the contralateral lateral and mediastinal compartments are affected more rarely. Skip metastases to the lateral compartment without central neck nodal involvement may occur but it is seen rare (17-20).

The neck dissection indication may be decided by clinically or radiologically lymph node metastasis suspicion. Fine needle aspiration biopsy (FNAB) or intraoperative frozen section usage might be useful reduce the negative neck dissection results. Lymph nodes metastasis assessment has high value to neck dissection decisions in patient with PTC. Various methods are used to assess the extent of lymph node involvement. Physical examination evaluation of the lateral neck for metastatic disease screens for visible or palpable lymph nodes. Because of their anatomic locations, enlarged cervical lymph nodes may not be easily visible or palpable, especially when they are small, located behind the sternocleidomastoid muscles, or located behind a carotid artery or jugular vein and in level VI. Therefore, in order to make treatment decisions regarding neck dissection, it is very important that adequately evaluation of cervical lymph nodes for metastasis. Imaging modalities, such as ultrasonography (US) with or without FNAB, iodine scans,

computed tomography (CT), hybrid imaging modalities such as single photon emission CT/CT and positron emission tomography/CT (PET/CT), technetium-99m methoxyisobutylisonitrile scintigraphy (MIBI scan), and magnetic resonance imaging (MRI) can each be important in the assessment of the lateral neck. Also intraoperative frozen section may be helpful for lateral neck lymph node metastasis (21-24). US performed by experienced hands are considered by the ATA, as the screening and surveillance imaging modality of choice for detection of lateral neck metastases. As recommended by the ATA thyroid cancer guidelines surveillance imaging of the lateral neck should include US. In cases when a lateral neck node is enlarged (>1.5 cm in levels I and IIa or >1.0 cm in levels IIb-Vb) or has ultrasonographic features worrisome for disease, an US-guided fine-needle aspiration should be attempted to confirm disease including possibly testing the aspirate for thyroglobuline (Tg) in an aspiration specimen (24). The introduction of these imaging modalities has increased detection of non-palpable cervical lymph node metastases.

The most common morbidities associated with neck dissections are spinal accessory nerve dysfunction and related shoulder disabilities. Shoulder dysfunction is due to traction injury or interruption of blood supply of the spinal accessory nerve during dissection of level IIb. This dysfunction may be avoided by preserving the level IIb lymph nodes during neck dissection in selected patients (25). However, some studies have shown temporary functional deterioration of the spinal accessory nerve even when level IIb is not dissected (26,27). Level IIb is rarely involved in patients with a metastatic neck disease. Metastases at level IIb are not expected in patients with N0 neck. Koybasioğlu *et al.* (28) showed no metastases at level IIb in dissection specimens of patients with laryngeal cancer. Silverman *et al.* (26) reported a 1.6% incidence of metastases at level IIb for N0 necks, 1.1% for N1 cases, and total incidence was 4.4% in cases with head and neck cancers. Similarly, Sezen *et al.* (27) reported that routine level IIb dissection was not necessary in N0 necks. According to them, if the level IIa showed positive metastatic changes, preoperative pathologic examination by frozen section that includes level IIb could be an alternative approach. Recently, similarly reports have been shown for TPC (28-30).

Generally, selective neck dissection, dissecting levels II-V with preservation of the sternocleidomastoid muscle, spinal accessory nerve, and internal jugular vein, is recommended for patients with TPC presenting with clinically palpable cervical lymph nodes or showing pathological appearance seen by imaging studies (31-33). Initial nodal spread from TPC occurs in the central compartment of the ipsilateral neck (level VI) (34-37). However, Gimm *et al.* (21) and Noguchi *et al.* (7) reported that some patients had posterolateral lymph node metastasis without involvement of the central compartment. In our previous study (38) all patients with posterolateral lymph node metastases had involvement of central compartment. When there is a metastasis in the lymph nodes of the lateral neck, levels II-V are predictably affected, usually with multiple areas of spread in more than one of these levels. As spread of TPC to the level I lymph nodes is so rare, routine dissection of this area can be omitted (31,37). In addition, levels I and V lymph nodes were never found to be involved without lymph node involvement at other lymph nodes level such as levels II, III or IV (37,38). In our previous study (39), the majority of patients with lateral cervical lymph node metastasis had multiple involved lymph node levels. The lateral cervical lymph nodes (levels II, III, and IV) are at the greatest risk for metastasis in TPC patients. It has been reported that lateral nodes were commonly involved, and level III nodes were the most common sites for metastasis (28,30,37). Although Roh *et al.* (9) and Vayisoglu *et al.* (39) reported that level IV nodes were the most common sites for metastasis.

Although level IIb lymph nodes dissection has been routinely included in lateral neck dissection performed for metastatic neck disease with TPC, the incidence of nodal metastasis in this area has not been well established. Recently, some studies investigated the frequency and pattern of level IIb lymph node metastasis for TPC. *Table 1* summarizes the studies of incidence of metastatic lymph nodes at level IIa and IIb of PTC patients with lateral neck metastasis. Pingpank *et al.* reported that level IIb lymph node metastases were common. Therefore, they suggested that neck dissection should include all lymph nodes of levels I-V (40). Kim (43) reported that lymph node metastasis involving level IIb is not rare (20%), and careful level IIb lymph node dissection should be considered. Yanir and Doweck recommended that elective dissection of levels II-VI in patients with clinically positive lateral neck lymph node metastasis in spite of a low incidence of level IIb metastases, due to the possibility of skip metastasis at level IIb (33). Also King *et al.* reported that the high incidence of multilevel cervical metastasis associated with PTC and suggest the importance of including level IIb when performing a neck dissection (42). In contrast, some studies suggested that level IIb dissection would probably not be necessary in

Table 1 Results of the studies showing the incidences of lymph nodes metastasis at level IIa and IIb in patients with TPC

Authors [years]	Total patients [ND]	Metastasis rates (%)		Comment
		IIa	IIb	
Pingpank *et al*. (40) [2002]	44 [51]	43.1	20.6	Level IIb metastasis is common
Lee *et al*. (30) [2007]	46 [55]	58.2	21.8	Level IIb dissection should be performed if level IIa LNM is found
Roh *et al*. (9) [2008]	52 [57]	72.7	16.7	Level IIb metastasis always accompanied by level IIa metastasis
Lee *et al*. (29) [2008]	167 [191]	55.5	6.8	Level IIb dissection is not necessary if level IIa LNM is negative
Yanir *et al*. (34) [2008]	27 [28]	50.0	7.1	Level II-VI dissection should be performed in clinically +N
Farrag *et al*. (41) [2009]	53 [60]	56.0	8.5	Level IIb dissection should be performed if level IIa LNM is found
Koo *et al*. (31) [2009]	76 [76]	51.3	11.8	Level IIb dissection may be omitted in multilevel involvement including level IIa (-)
Vayisoglu *et al*. (39) [2010]	33 [47]	12.7	2.1	Level IIb dissection may be required if multilevel metastasis or intraoperatively (+) LN
King *et al*. (42) [2011]	32 [39]	48.7	61.5	Level IIb metastasis is common
Kim *et al*. (43) [2012]	18 [18]	46.7	20.0	Level IIb dissection should be considered

Abbrevation: TPC, thyroid papillary carcinoma; LMN, lymph node metastasis.

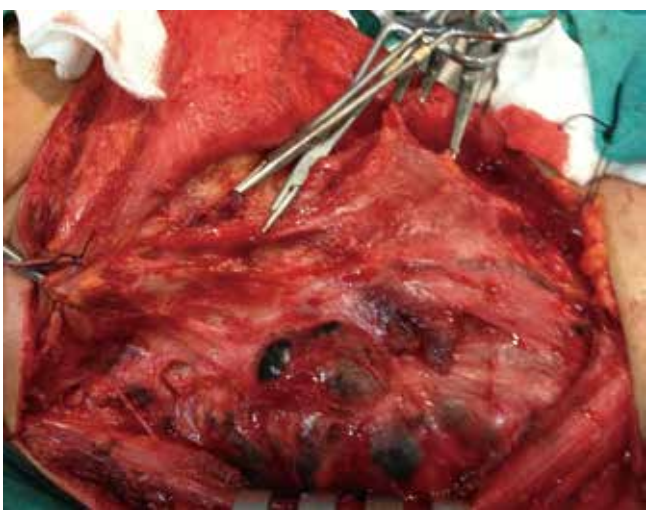

Figure 3 Aggressive multilevel involvement in patient with TPC. Abbreviation: TPC, thyroid papillary carcinoma.

the absence of level IIa involvement because the incidence of metastasis to level IIb has been low if level IIa has not been involved (43-45). In our previous study (39), level IIb metastases were found in only one patient (2.1%), and this patient also had metastasis at levels IIa, III, IV, and V (*Figure 3*). In five specimens, metastasis was detected at level IIa without level IIb involvement. Koo *et al.* (31) reported that 11.8% (9 of 76) of the patients had level IIb lymph nodes metastases in TPC patients. Only one of these patients was positive for level IIa. They all had primary tumors of >1 cm, as well as lymphovascular invasion, capsular invasion, or multilevel involvement of metastatic nodes. They suggested that level IIb lymph node dissection might not be necessary in TPC patients with positive lymph nodes in the absence of multilevel involvement (30). Lee *et al.* (29) also suggested that level IIb dissection has not been necessary in the absence of level IIa involvement. In their study, the metastasis in levels IIa and IIb were 55.5% and 6.8%, respectively. Also all level IIb lymph node metastasis was accompanied by level IIa metastasis. In another study, it has been reported that the metastasis in level II was 60% (33 specimens) among 55 specimens. The incidence of lymph node metastasis at level IIb was 22% (12 specimens). Of 12 specimens with metastasis at level IIb, 11 specimens also had metastasis at level IIa. Therefore, they suggested that level IIb dissection is probably unnecessary when level IIa lymph nodes are uninvolved (30).

Conclusions

The balance between surgical morbidity and oncological safety should be considered if the lateral neck dissection in PTC patients with lateral cervical metastasis is being decided. In most studies, level IIa lymph nodes metastasis and multilevel lymph nodes metastasis were predictive factors of level IIb metastasis in PTC. Therefore when there is no suspicious lymph node metastasis at levels II or

there is not multilevel aggressive neck metastasis, dissection of level IIb may not be necessary in PTC patients with lateral neck metastasis. Consideration of the individualized surgical extent of lateral neck dissection is important in the treatment of PTC patients with lateral cervical metastasis.

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References

1. Davidson HC, Park BJ, Johnson JT. Papillary thyroid cancer: controversies in the management of neck metastasis. Laryngoscope 2008;118:2161-5.
2. Shaha AR. Implications of prognostic factors and risk groups in the management of differentiated thyroid cancer. Laryngoscope 2004;114:393-402.
3. Andersen PE, Saffold S. Management of cervical metastasis. In: Shah JP. eds. Cancer of the head and neck. Hamilton, London: BC Decker editors CITA, 2001:274-87.
4. Hughes CJ, Shaha AR, Shah JP, et al. Impact of lymph node metastasis in differentiated carcinoma of the thyroid: a matched-pair analysis. Head Neck 1996;18:127-32.
5. Shah JP, Loree TR, Dharker D, et al. Prognostic factors in differentiated carcinoma of the thyroid gland. Am J Surg 1992;164:658-61.
6. Beasley NJ, Lee J, Eski S, et al. Impact of nodal metastases on prognosis in patients with well-differentiated thyroid cancer. Arch Otolaryngol Head Neck Surg 2002;128:825-8.
7. Noguchi S, Murakami N, Yamashita H, et al. Papillary thyroid carcinoma: modified radical neck dissection improves prognosis. Arch Surg 1998;133:276-80.
8. Rotstein L. The role of lymphadenectomy in the management of papillary carcinoma of the thyroid. J Surg Oncol 2009;99:186-8.
9. Roh JL, Kim JM, Park CI. Lateral cervical lymph node metastases from papillary thyroid carcinoma: pattern of nodal metastases and optimal strategy for neck dissection. Ann Surg Oncol 2008;15:1177-82.
10. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167-214.
11. Cooper DS, Doherty GM, Haugen BR, et al. Management guidelines for patients with thyroid nodules and differentiated thyroid Cancer. Thyroid 2006;16:109-42.
12. Robbins KT, Clayman G, Levine PA, et al. Neck dissection classification update: revisions proposed by the American Head and Neck Society and the American Academy of Otolaryngology-Head and Neck Surgery. Arch Otolaryngol Head Neck Surg 2002;128:751-8.
13. Talmi YP, Hoffman HT, Horowitz Z, et al. Patterns of metastases to the upper jugular lymph nodes (the "submuscular recess"). Head Neck 1998;20:682-6.
14. Cappiello J, Piazza C, Nicolai P. The spinal accessory nerve in head and neck surgery. Curr Opin Otolaryngol Head Neck Surg 2007;15:107-11.
15. Ferlito A, Silver CE, Suárez C, et al. Preliminary multi-institutional prospective pathologic and molecular studies support preservation of sublevel IIB and level IV for laryngeal squamous carcinoma with clinically negative neck. Eur Arch Otorhinolaryngol 2007;264:111-4; discussion 109.
16. Koybasioğlu A, Uslu S, Yilmaz M, et al. Lymphatic metastasis to the supraretrospinal recess in laryngeal squamous cell carcinoma. Ann Otol Rhinol Laryngol 2002;111:96-9.
17. Park JY, Koo BS. Individualized optimal surgical extent of the lateral neck in papillary thyroid cancer with lateral cervical metastasis. Eur Arch Otorhinolaryngol 2013. [Epub ahead of print].
18. Machens A, Hinze R, Thomusch O, et al. Pattern of nodal metastasis for primary and reoperative thyroid Cancer. World J Surg 2002;26:22-8.
19. Machens A, Holzhausen HJ, Dralle H. Skip metastases in thyroid Cancer leaping the central lymph node compartment. Arch Surg 2004;139:43-5.
20. Chung YS, Kim JY, Bae JS, et al. Lateral lymph node metastasis in papillary thyroid carcinoma: results of therapeutic lymph node dissection. Thyroid 2009;19:241-6.
21. Gimm O, Rath FW, Dralle H. Pattern of lymph node metastases in papillary thyroid carcinoma. Br J Surg 1998;85:252-4.
22. Watkinson JC, Franklyn JA, Olliff JF. Detection and surgical treatment of cervical lymph nodes in differentiated thyroid cancer. Thyroid 2006;16:187-94.
23. Nixon IJ, Shaha AR. Management of regional nodes in thyroid Cancer. Oral Oncol 2013;49:671-5.
24. Lee DW, Ji YB, Sung ES, et al. Roles of ultrasonography and computed tomography in the surgical management of cervical lymph node metastases in papillary thyroid carcinoma. Eur J Surg Oncol 2013;39:191-6.
25. Stack BC Jr, Ferris RL, Goldenberg D, et al. American

Thyroid Association consensus review and statement regarding the anatomy, terminology, and rationale for lateral neck dissection in differentiated thyroid cancer. Thyroid 2012;22:501-8.
26. Silverman DA, El-Hajj M, Strome S, et al. Prevalence of nodal metastases in the submuscular recess (level IIb) during selective neck dissection. Arch Otolaryngol Head Neck Surg 2003;129:724-8.
27. Sezen OS, Kubilay U, Haytoglu S, et al. Frequency of metastases at the area of the supraretrospinal (level IIB) lymph node in laryngeal Cancer. Head Neck 2007;29:1111-4.
28. Koybaşioğlu A, Bora Tokçaer A, Inal E, et al. Accessory nerve function in lateral selective neck dissection with undissected level IIb. ORL J Otorhinolaryngol Relat Spec 2006;68:88-92.
29. Lee J, Sung TY, Nam KH, et al. Is level IIb lymph node dissection always necessary in N1b papillary thyroid carcinoma patients? World J Surg 2008;32:716-21.
30. Lee BJ, Wang SG, Lee JC, et al. Level IIb lymph node metastasis in neck dissection for papillary thyroid carcinoma. Arch Otolaryngol Head Neck Surg 2007;133:1028-30.
31. Koo BS, Yoon YH, Kim JM, et al. Predictive factors of level IIb lymph node metastasis in patients with papillary thyroid carcinoma. Ann Surg Oncol 2009;16:1344-7.
32. Shah MD, Hall FT, Eski SJ, et al. Clinical course of thyroid carcinoma after neck dissection. Laryngoscope 2003;113:2102-7.
33. Palazzo FF, Gosnell J, Savio R, et al. Lymphadenectomy for papillary thyroid cancer: changes in practice over four decades. Eur J Surg Oncol 2006;32:340-4.
34. Yanir Y, Doweck I. Regional metastases in well-differentiated thyroid carcinoma: pattern of spread. Laryngoscope 2008;118:433-6.
35. Goropoulos A, Karamoshos K, Christodoulou A, et al. Value of the cervical compartments in the surgical treatment of papillary thyroid carcinoma. World J Surg 2004;28:1275-81.
36. Koo BS, Choi EC, Yoon YH, et al. Predictive factors for ipsilateral or contralateral central lymph node metastasis in unilateral papillary thyroid carcinoma. Ann Surg 2009;249:840-4.
37. Kupferman ME, Patterson M, Mandel SJ, et al. Patterns of lateral neck metastasis in papillary thyroid carcinoma. Arch Otolaryngol Head Neck Surg 2004;130:857-60.
38. Sivanandan R, Soo KC. Pattern of cervical lymph node metastases from papillary carcinoma of the thyroid. Br J Surg 2001;88:1241-4.
39. Vayisoglu Y, Ozcan C, Turkmenoglu O, et al. Level IIb lymph node metastasis in thyroid papillary carcinoma. Eur Arch Otorhinolaryngol 2010;267:1117-21.
40. Pingpank JF Jr, Sasson AR, Hanlon AL, et al. Tumor above the spinal accessory nerve in papillary thyroid cancer that involves lateral neck nodes: a common occurrence. Arch Otolaryngol Head Neck Surg 2002;128:1275-8.
41. Farrag T, Lin F, Brownlee N, et al. Is routine dissection of level II-B and V-A necessary in patients with papillary thyroid cancer undergoing lateral neck dissection for FNA-confirmed metastases in other levels. World J Surg 2009;33:1680-3.
42. King JM, Corbitt C, Miller FR. Management of lateral cervical metastases in papillary thyroid cancer: patterns of lymph node distribution. Ear Nose Throat J 2011;90:386-9.
43. Kim YS. Patterns ans predictive factors of lateral lymph node metastasis in papillary thyroid microcarcinoma. Otolaryngol Head Neck Surg 2012;147:15-9.
44. Eskander A, Merdad M, Freeman JL, et al. Pattern of spread to the lateral neck in metastatic well-differentiated thyroid cancer: a systematic review and meta-analysis. Thyroid 2013;23:583-92.
45. Merdad M, Eskander A, Kroeker T, et al. Metastatic papillary thyroid cancer with lateral neck disease: Pattern of spread by level. Head Neck 2013;35:1439-42.

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The prognostic implication and potential role of *BRAF* mutation in the decision to perform elective neck dissection for thyroid cancer

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Abstract: The *BRAF V600E* mutation is the most common genetic change in patients with papillary thyroid cancer (PTC). Many studies have shown that detection of the *BRAF V600E* mutation is useful for confirming or establishing the preoperative diagnosis of PTC. Moreover, the mutation is associated with aggressive tumor characteristics or poor prognostic factors in most. However, whether preoperative detection of this mutation changes the treatment strategy or surgical extent, including prophylactic central neck dissection (CND), remains controversial. In this paper, we review the currently available literature regarding the potential role of the *BRAF V600E* mutation in the decision to perform elective neck dissection for PTC.

Keywords: Papillary thyroid carcinoma; lymph node metastasis (LNM); neck dissection; BRAF mutation

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Introduction

Papillary thyroid cancer (PTC) is the most common thyroid malignancy (1,2). Although PTC generally follows an indolent course with an excellent prognosis, lymph node metastases (LNMs), especially to the central compartment (level VI), are common and occur in an average of 60% of cases (3-5). LNM is commonly associated with an increased rate of locoregional recurrence in patients with PTC (6,7). The performance of therapeutic central neck dissection (CND) is generally accepted in patients with PTC with clinical evidence of lymph node involvement in the central compartment. However, prophylactic CND in clinically node-negative central necks remains controversial because of the limited survival benefit and an increasing rate of complications associated with the procedure (8,9). Unfortunately, methods with which to preoperatively assess the presence of central LNM preoperatively have not been established. Although ultrasonography and intraoperative assessment can help to identify grossly apparent LNM, both modalities have low sensitivity for the detection of central LNM (10,11). Therefore, many researchers have reported the identification of various factors (larger tumors, extrathyroidal extension, and aggressive histological subtypes) associated with occult metastasis to the central compartment to avoid unnecessary CND (12). However, some factors such as extrathyroidal extension and aggressive histological subtypes, associated with occult metastasis to the central compartment, can't help in the decision regarding prophylactic CND because these factors are clear only postsurgical histology.

Many recent studies have reported that the *BRAF V600E* mutation is a novel prognostic marker that may be useful for risk stratification. The *BRAF V600E* mutation is the most common genetic change in patients with PTC, being observed in 30-80% of all cases (13-16). Among the various histological subtypes of PTC, conventional and tall-cell variants are most commonly associated with the mutation (67-68% and 80-83%, respectively); the mutation is least associated with the follicular variant (12-18%) (17,18). Detection of the *BRAF V600E* mutation in fine needle aspiration biopsy (FNAB) specimens may be useful

for confirming or establishing the preoperative diagnosis of PTC (19-21), and the mutation has been associated with aggressive tumor characteristics or poor prognostic factors (22-26). Furthermore, some studies have examined the utility of preoperative detection of the *BRAF V600E* mutation for optimizing the surgical management of PTC and have suggested that *BRAF*-positive patients may benefit from a more extensive initial surgery, including the performance of CND (27,28). However, these issues remain very controversial.

Therefore, we reviewed the currently available literature regarding the prognostic and therapeutic role of the *BRAF V600E* mutation, especially its potential role in the decision to perform elective neck dissection for PTC.

Studies published in English were identified from PubMed and the Cochrane Register of Controlled Trials up to October 2013 with the search terms such as '*BRAF* mutation', 'neck dissection', 'LNM' and 'papillary thyroid carcinoma'.

The *BRAF V600E* mutation as a prognostic factor

Several clinicopathological risk factors have been used for stratifying PTC, including older age of patients at diagnosis, larger tumor size, cervical LNM, extrathyroidal invasion, distant metastasis, and advanced disease staging (29-31). Many recent studies have shown an association between the *BRAF V600E* mutation and aggressive clinicopathological characteristics of PTC, including LNM, extrathyroidal invasion, loss of radioiodine avidity, and failure of radioiodine treatment and resultant disease recurrence (22,32). Consequently, the mutation has drawn considerable attention and interest as a potential prognostic factor for PTC.

Kebebew *et al*. followed 314 patients with thyroid cancer prospectively for a median of six years and found that the *BRAF V600E* mutation was independently associated with recurrent and persistent PTC (24). Lupi *et al*. evaluated retrospectively 500 patients with PTC, 43% of whom had the mutation, and found that those patients had a higher incidence of extrathyroidal extension, nodal metastasis, multicentricity, and advanced tumors than patients without the mutation (33). Kim *et al*. suggested in prospective study that the mutation is associated with a higher clinical recurrence of disease in low-risk patients with conventional PTC (34). An association between the *BRAF V600E* mutation and disease-specific survival has also been demonstrated. Elisei *et al*. retrospectively evaluated a small cohort of PTC patients with a median follow-up of 15 years and observed shorter survival in the group with the mutation (35). Xing *et al*. investigated the relationship between the mutation and PTC-related mortality in 1,849 patients with PTC. In their retrospective multicenter study, the presence of the mutation was significantly associated with increased cancer-related mortality among patients with PTC (36). On the other hand, some investigators have shown that the *BRAF V600E* mutation is not associated with aggressive features in patients with PTC. Sancisi *et al*. reported in retrospective study that the mutation is not associated with the development of distant metastases or fatal outcomes in patients with PTC and may not predict aggressive behavior (37). Trovisco *et al*. reported in retrospective study that *BRAF*-mutated PTC does not exhibit signs of higher aggressiveness (size, vascular invasion, extrathyroid extension, and nodal metastasis) and is in fact less often multicentric than without the mutation (38).

Although most studies that have reported an association between the *BRAF V600E* mutation and poor prognostic features are impressive, some of the data are retrospective, and the *BRAF V600E* status has not yet been incorporated into a standard PTC management algorithm. It remains unclear whether identification of the *BRAF V600E* mutation in isolation, regardless of the presence or absence of other clinicopathologic characteristics, should prompt clinicians to treat patients with PTC with more aggressive adjuvant therapies and/or closer long-term surveillance. Further study in this regard is required.

The *BRAF V600E* mutation as a measure of surgical extent

The *BRAF V600E* mutation is associated with a higher risk of progression in patients with PTC. However, it is not yet known whether preoperative *BRAF V600E* analysis in cytologic specimens may aid the determination of surgical extent and thus facilitate prophylactic CND for occult central neck LNM in patients with PTC and a clinically node-negative neck. Many studies have investigated the role of the mutation in the decision of the most optimal initial surgical extent, including prophylactic CND for PTC.

Many researchers have reported that preoperative identification of the *BRAF V600E* mutation may guide not only the initial extent of total thyroidectomy, but also the need for and extent of lymphadenectomy. Yip *et al*. compared the clinical, cytologic, and pathologic parameters of 106 consecutive surgically treated patients with *BRAF*-

positive PTC with a concurrent cohort of 100 patients with *BRAF*-negative PTC (17). All patients was not performed initially routine CND (17). Eleven of the positive patients required reoperation for recurrent/persistent disease compared to three negative patients (P=0.04). Preoperative knowledge of *BRAF V600E* mutation positivity could have improved the initial surgical management of 24% of the patients. Therefore, they suggested that *BRAF V600E* mutations are associated with cervical recurrence and reoperation. They also insisted that preoperative cytologic identification of the *BRAF V600E* mutation has high specificity and may guide the initial extent of thyroidectomy and node dissection (17). Similarly, Xing *et al*. compared the clinical and pathologic parameters of 73 surgically treated patients with *BRAF*-positive PTC with a concurrent cohort of 117 patients with *BRAF*-negative PTC (39). In this study, CND was typically performed for treatment of lymph nodes that were suggestive of abnormality on intraoperative examination (39). They insisted that preoperative testing for the mutation in FNAB specimens provides a novel tool with which to preoperatively identify patients with PTC at higher risk for extensive disease (extrathyroidal extension and LNMs) and those who are more likely to show persistence/recurrence (39). In addition, they asserted that the *BRAF V600E* mutation, as a powerful prognostic risk marker, may be useful for appropriately tailoring the initial surgical extent for patients with PTC (39). We recently investigated whether preoperative *BRAF V600E* analysis may aid the determination of surgical extent, including prophylactic CND with variable clinicopathological risk factors for central LNM, in patients with PTC and a clinically node-negative neck (28). Our multivariate analysis showed that a tumor size of >1 cm [P=0.006; odds ratio (OR), 3.559], perithyroidal invasion (P=0.023; OR, 2.893), and preoperative positivity for the *BRAF V600E* mutation (P=0.029; OR, 2.727) were independent risk factors for the presence of occult central LNM. Therefore, we suggested that preoperative *BRAF V600E* analysis by FNAB and determination of primary tumor size based on ultrasonography may help predict occult central LNM in patients with PTC and a clinically node-negative neck (28). Alzahrani *et al*. reviewed records of 379 patients of PTC who underwent total or near-total thyroidectomy with or without CLN dissection (40). They reported that cervical LNMs found at the time of CND are closely associated with disease recurrence/persistence of PTC, both of which are strongly predicted by the *BRAF V600E* mutation (40). Therefore, they suggested that preoperative testing for the *BRAF V600E* mutation in thyroid needle biopsy specimens in combination with other conventional risk factors to determine the aggressiveness of CND may be a reasonable approach (40). Howell *et al*. investigated retrospectively records of 156 patients of PTC (41). Patients with suspicious or preoperatively detected LNM received a therapeutic CND (41). A prophylactic CND was performed for *BRAF V600E* mutation positive status without clinically or sonographically evident disease (41). They insisted that of the commonly used clinical parameters available preoperatively, the *BRAF V600E* mutation is the only independent predictor of central lymph node dissection in PTC and can be utilized to guide the extent of the initial surgery (41). So *et al*. investigated 71 patients with PTC prospectively (42). All patients were performed total thyroidectomy and CND (42). They reported that the mutation was a significant predictor of LNM, and that the mutation may have differential predictive values for LNM according to tumor size (42).

On the other hand, Barbaro *et al*. studied 110 patients with PTC who underwent *BRAF* analysis of FNAB specimens prospectively (43). In this study, total thyroidectomy and routine CND independent of *BRAF V600E* mutation was performed, and reported that the mutation did not appear to be a reliable risk factor for tumor aggressiveness (43). Therefore, they suggested that *BRAF V600E* analysis should not be the only guide for presurgical decisions regarding the extent of surgery or postsurgical decisions regarding the aggressiveness of the treatment (43). Lee *et al*. conducted a small series that included only 63 patients with PTC and underscored the prematurity of utilizing *BRAF V600E* mutation status to determine the surgical management of patients with PTC, specifically whether or not to perform CND (44). They suggested that prospective, multi-institutional studies that include only patients preoperatively known to have PTC and centers in which routine CND is performed are therefore greatly needed before we can accurately assess whether *BRAF V600E* mutation status should be incorporated into critical decisions regarding the appropriate operative management of patients with PTC. Dutenhefner *et al*. compared the clinical and pathologic parameters of 15 surgically treated patients with *BRAF*-positive PTC with a concurrent cohort of 36 patients with *BRAF*-negative PTC (45). In this study, total thyroidectomy and routine CND was performed (45). They showed that LNM is related to multifocality, angiolymphatic invasion, and age, but not to the *BRAF V600E* mutation, and concluded that *BRAF V600E* is not a helpful tool for deciding

Table 1 Summary of case series evaluating the role of the BRAF mutation in the decision to perform prophylactic CND in patients with PTC

Authors	Country	Study design	Number of patients	Comments on role of the BRAF mutation in the decision to perform prophylactic CND
Yip *et al.* (2009) (17)	USA	PS	N=206 (106 *BP*, 100 *BN*)	Preoperative cytologic identification of the *BRAF* mutation has high specificity and may guide the initial extent of thyroidectomy and node dissection
Joo *et al.* (2012) (28)	Korea	PS	N=148 (79 *BP*, 69 *BN*)	Preoperative *BRAF* analysis by FNAB and primary tumor size based on ultrasonography may aid the prediction of occult central LNM in patients with PTC and a clinically node-negative neck
Xing *et al.* (2009) (39)	USA	PS	N=190 (73 *BP*, 117 *BN*)	Preoperative knowledge of *BRAF* mutation status may be particularly useful for guiding surgical decision-making about prophylactic CND
Alzahrani *et al.* (2012) (40)	USA	RS	N=379 (96 *BP*, 185 *BN*, 98 unidentified *BRAF* status)	Use of preoperative testing of the *BRAF* mutation on FNAB specimens in combination with other conventional risk factors to determine the aggressiveness level of CND may be a reasonable approach
Howell *et al.* (2013) (41)	USA	RS	N=156 (72 *BP*, 84 *BN*)	The *BRAF V600E* mutation is the only independent predictor of central LNM in PTC and can be utilized to guide the extent of initial surgery
So *et al.* (2011) (42)	Korea	PS	N=102 (44 *BP*, 58 *BN*)	The *BRAF* mutation in PTC is a significant predictor of LNM. In addition, the *BRAF* mutation may have differential predictive values for LN metastasis according to tumor size
Barbaro *et al.* (2013) (43)	Italy	PS	N=110 (88 *BP*, 22 *BN*)	*BRAF* analysis should not be the only guide for presurgical decisions regarding the extent of surgery or postsurgical decisions regarding the aggressiveness of the treatment
Lee *et al.* (2012) (44)	USA	RS	N=63 (44 *BP*, 19 *BN*)	The results underscore the prematurity in utilizing *BRAF* mutation status to determine the surgical management of patients with PTC, specifically whether or not to perform CND
Dutenhefner *et al.* (2012) (45)	Brazil	PS	N=51 (15 *BP*, 36 *BN*)	The *BRAF* mutation does not help determine whether to perform CND

Abbreviations: PS, prospective study; RS, retrospective study; *BP*, *BRAF*-positive; *BN*, *BRAF*-negative; PTC, papillary thyroid cancer; FNAB, fine needle aspiration biopsy; LNM, lymph node metastasis; CND, central neck dissection.

whether to perform elective neck dissection of the central compartment. *Table 1* outlines the case series evaluating the role of the BRAF mutation in the decision to perform prophylactic CND in patients with PTC.

In summary, many studies have evaluated whether preoperative analysis of the *BRAF V600E* mutation and other risk factors may help delineate which patients with PTC should undergo prophylactic concurrent CND at the time of thyroidectomy because currently available methods, including ultrasonography, have been shown to be inaccurate for preoperatively identifying metastatic lymph nodes in the central compartment. However, the role of preoperative assessment of the *BRAF V600E* mutation status in decisions regarding the most optimal surgical extent in patients with PTC remains controversial. In the future, a prospective randomized study of a large population should be performed with a long-term follow-up period to assess the potential role of preoperative assessment of *BRAF V600E* mutation status in decisions regarding whether to perform prophylactic CND in patients with PTC.

Conclusions

Numerous studies have evaluated whether there is correlation between the *BRAF V600E* mutation and its usefulness as a prognostic factor for patients with PTC. In addition, many studies have attempted to confirm the value of the *BRAF V600E* mutation as a measure of the extent of surgery. Most reports agree that the mutation is associated with tumor aggressiveness, a poor prognosis, resistance to postoperative radioiodine therapy, and the need for a more extended surgery. However, the potential role of the preoperative assessment of *BRAF V600E* mutation status in decisions regarding whether to perform prophylactic CND remains controversial. When the necessity of prophylactic CND in patients with PTC is preoperatively determined, we should recommend to perform prophylactic CND if *BRAF V600E* mutation and other conventional clinical risk factors are coexistent.

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References

1. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. JAMA 2006;295:2164-7.
2. Jemal A, Siegel R, Xu J, et al. Cancer statistics, 2010. CA Cancer J Clin 2010;60:277-300.
3. Mirallié E, Visset J, Sagan C, et al. Localization of cervical node metastasis of papillary thyroid carcinoma. World J Surg 1999;23:970-3; discussion 973-4.
4. Wada N, Duh QY, Sugino K, et al. Lymph node metastasis from 259 papillary thyroid microcarcinomas: frequency, pattern of occurrence and recurrence, and optimal strategy for neck dissection. Ann Surg 2003;237:399-407.
5. Pereira JA, Jimeno J, Miquel J, et al. Nodal yield, morbidity, and recurrence after central neck dissection for papillary thyroid carcinoma. Surgery 2005;138:1095-100, discussion 1100-1.
6. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med 1994;97:418-28.
7. DeGroot LJ, Kaplan EL, McCormick M, et al. Natural history, treatment, and course of papillary thyroid carcinoma. J Clin Endocrinol Metab 1990;71:414-24.
8. Henry JF, Gramatica L, Denizot A, et al. Morbidity of prophylactic lymph node dissection in the central neck area in patients with papillary thyroid carcinoma. Langenbecks Arch Surg 1998;383:167-9.
9. Lee YS, Kim SW, Kim SW, et al. Extent of routine central lymph node dissection with small papillary thyroid carcinoma. World J Surg 2007;31:1954-9.
10. Hwang HS, Orloff LA. Efficacy of preoperative neck ultrasound in the detection of cervical lymph node metastasis from thyroid cancer. Laryngoscope 2011;121:487-91.
11. Shen WT, Ogawa L, Ruan D, et al. Central neck lymph node dissection for papillary thyroid cancer: the reliability of surgeon judgment in predicting which patients will benefit. Surgery 2010;148:398-403.
12. Iyer NG, Shaha AR. Central compartment dissection for well differentiated thyroid cancer … and the band plays on. Curr Opin Otolaryngol Head Neck Surg 2011;19:106-12.
13. Kimura ET, Nikiforova MN, Zhu Z, et al. High prevalence of BRAF mutations in thyroid cancer: genetic evidence for constitutive activation of the RET/PTC-RAS-BRAF signaling pathway in papillary thyroid carcinoma. Cancer Res 2003;63:1454-7.
14. Cohen Y, Xing M, Mambo E, et al. BRAF mutation in papillary thyroid carcinoma. J Natl Cancer Inst 2003;95:625-7.
15. Xing M. BRAF mutation in thyroid cancer. Endocr Relat Cancer 2005;12:245-62.
16. Espinosa AV, Porchia L, Ringel MD. Targeting BRAF in thyroid cancer. Br J Cancer 2007;96:16-20.
17. Yip L, Nikiforova MN, Carty SE, et al. Optimizing surgical treatment of papillary thyroid carcinoma associated with BRAF mutation. Surgery 2009;146:1215-23.
18. Nikiforova MN, Kimura ET, Gandhi M, et al. BRAF mutations in thyroid tumors are restricted to papillary carcinomas and anaplastic or poorly differentiated carcinomas arising from papillary carcinomas. J Clin Endocrinol Metab 2003;88:5399-404.
19. Handkiewicz-Junak D, Czarniecka A, Jarzab B. Molecular prognostic markers in papillary and follicular thyroid cancer: Current status and future directions. Mol Cell Endocrinol 2010;322:8-28.
20. Pelizzo MR, Boschin IM, Barollo S, et al. BRAF analysis by fine needle aspiration biopsy of thyroid nodules improves preoperative identification of papillary thyroid carcinoma and represents a prognostic factor. A mono-institutional experience. Clin Chem Lab Med 2011;49:325-9.
21. Mathur A, Weng J, Moses W, et al. A prospective study

evaluating the accuracy of using combined clinical factors and candidate diagnostic markers to refine the accuracy of thyroid fine needle aspiration biopsy. Surgery 2010;148:1170-6; discussion 1176-7.
22. Xing M. BRAF mutation in papillary thyroid cancer: pathogenic role, molecular bases, and clinical implications. Endocr Rev 2007;28:742-62.
23. Frasca F, Nucera C, Pellegriti G, et al. BRAF(V600E) mutation and the biology of papillary thyroid cancer. Endocr Relat Cancer 2008;15:191-205.
24. Kebebew E, Weng J, Bauer J, et al. The prevalence and prognostic value of BRAF mutation in thyroid cancer. Ann Surg 2007;246:466-70; discussion 470-1.
25. Jo YS, Li S, Song JH, et al. Influence of the BRAF V600E mutation on expression of vascular endothelial growth factor in papillary thyroid cancer. J Clin Endocrinol Metab 2006;91:3667-70.
26. Kim J, Giuliano AE, Turner RR, et al. Lymphatic mapping establishes the role of BRAF gene mutation in papillary thyroid carcinoma. Ann Surg 2006;244:799-804.
27. Melck AL, Yip L, Carty SE. The utility of BRAF testing in the management of papillary thyroid cancer. Oncologist 2010;15:1285-93.
28. Joo JY, Park JY, Yoon YH, et al. Prediction of occult central lymph node metastasis in papillary thyroid carcinoma by preoperative BRAF analysis using fine-needle aspiration biopsy: a prospective study. J Clin Endocrinol Metab 2012;97:3996-4003.
29. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167-214.
30. Tuttle RM, Ball DW, Byrd D, et al. Thyroid carcinoma. J Natl Compr Canc Netw 2010;8:1228-74.
31. Brown RL, de Souza JA, Cohen EE. Thyroid cancer: burden of illness and management of disease. J Cancer 2011;2:193-9.
32. Kim TH, Park YJ, Lim JA, et al. The association of the BRAF(V600E) mutation with prognostic factors and poor clinical outcome in papillary thyroid cancer: a meta-analysis. Cancer 2012;118:1764-73.
33. Lupi C, Giannini R, Ugolini C, et al. Association of BRAF V600E mutation with poor clinicopathological outcomes in 500 consecutive cases of papillary thyroid carcinoma. J Clin Endocrinol Metab 2007;92:4085-90.
34. Kim TY, Kim WB, Rhee YS, et al. The BRAF mutation is useful for prediction of clinical recurrence in low-risk patients with conventional papillary thyroid carcinoma. Clin Endocrinol (Oxf) 2006;65:364-8.
35. Elisei R, Ugolini C, Viola D, et al. BRAF(V600E) mutation and outcome of patients with papillary thyroid carcinoma: a 15-year median follow-up study. J Clin Endocrinol Metab 2008;93:3943-9.
36. Xing M, Alzahrani AS, Carson KA, et al. Association between BRAF V600E mutation and mortality in patients with papillary thyroid cancer. JAMA 2013;309:1493-501.
37. Sancisi V, Nicoli D, Ragazzi M, et al. BRAFV600E mutation does not mean distant metastasis in thyroid papillary carcinomas. J Clin Endocrinol Metab 2012;97:E1745-9.
38. Trovisco V, Soares P, Preto A, et al. Type and prevalence of BRAF mutations are closely associated with papillary thyroid carcinoma histotype and patients' age but not with tumour aggressiveness. Virchows Arch 2005;446:589-95.
39. Xing M, Clark D, Guan H, et al. BRAF mutation testing of thyroid fine-needle aspiration biopsy specimens for preoperative risk stratification in papillary thyroid cancer. J Clin Oncol 2009;27:2977-82.
40. Alzahrani AS, Xing M. Impact of lymph node metastases identified on central neck dissection (CND) on the recurrence of papillary thyroid cancer: potential role of BRAFV600E mutation in defining CND. Endocr Relat Cancer 2013;20:13-22.
41. Howell GM, Nikiforova MN, Carty SE, et al. BRAF V600E mutation independently predicts central compartment lymph node metastasis in patients with papillary thyroid cancer. Ann Surg Oncol 2013;20:47-52.
42. So YK, Son YI, Park JY, et al. Preoperative BRAF mutation has different predictive values for lymph node metastasis according to tumor size. Otolaryngol Head Neck Surg 2011;145:422-7.
43. Barbaro D, Incensati RM, Materazzi G, et al. The BRAF V600E mutation in papillary thyroid cancer with positive or suspected pre-surgical cytological finding is not associated with advanced stages or worse prognosis. Endocrine 2013. [Epub ahead of print].
44. Lee KC, Li C, Schneider EB, et al. Is BRAF mutation associated with lymph node metastasis in patients with papillary thyroid cancer? Surgery 2012;152:977-83.
45. Dutenhefner SE, Marui S, Santos AB, et al. BRAF, A tool in the decision to perform elective neck dissection? Thyroid 2013. [Epub ahead of print].

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Neck dissection with cervical sensory preservation in thyroid cancer

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Abstract: Thyroid cancer is the most common endocrine malignancy. Recently, controversy has focused on the management of lymph node metastases, which represent approximately 90% of disease recurrences and may require considerable time, effort, and resources to diagnose and treat. Neck dissections play an essential role in the management of head and neck cancer. A modified radical neck dissection (MND) refers to resection of the lymph nodes in levels II through V and often including the central nodes in level VI. When performing modified neck dissection, we recommend to protect more reserved cervical plexus. The purpose is to better protect patient's neck skin feeling.

Keywords: Thyroid cancer; modified radical neck dissection (MND); cervical sensory preservation

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Introduction

Neck dissections play an essential role in the management of head and neck cancer. Their role in the management of thyroid cancer is somewhat controversial and limited by the absence of prospective clinical trials. The dilemma is further complicated by the indolent history of most well-differentiated thyroid cancers and the common occurrence of both clinically significant and occult cervical lymph node metastases particularly in young patients with papillary carcinoma of the thyroid. A strong indication for modified radical neck dissection (MND) in the setting of well-differentiated thyroid cancer is the finding of cervical lymph-adenopathy by either palpation or an imaging study. Confirmation of metastatic disease can be obtained by a preoperative fine-needle aspiration (FNA) which can be performed under ultrasound guidance. Sentinel lymph node biopsy in the jugulo-carotid chain using methylene blue dye mapping may be a feasible and valuable method for estimating lymph node status in the lateral neck compartment. It may be helpful in the detection of true-positive but non-palpable lymph nodes, and in such cases may support the decision to perform MND in patients with differentiated thyroid carcinoma (1). Prophylactic MND is recommended for cases of papillary carcinoma demonstrating two or more of the following four characteristics; male gender, age 55 years or older, maximal tumor diameter larger than 3 cm, and massive extrathyroid extension (2).

Cervical lymphadenopathy is not uncommon in the setting of well-differentiated thyroid cancer. A recent series reported the frequent occurrence of metastases in both the central (64.1%) and lateral (44.5%) neck (3). In the past many surgeons advocated local "berry picking" resections designed to remove grossly enlarged nodes (4,5). These "berry picking" procedures are associated with a higher local recurrence rate necessitating remedial surgery that is associated with a higher complication rate (6). The complication rate associated with functional neck dissections is no higher than that associated with "berry picking" procedures (6). It is noteworthy that limited modified neck dissections in which the superior extent of surgery is limited to the spinal accessory nerve are also associated with residual and recurrent disease due to skip metastases (7). A carefully performed MND is well-tolerated and results in excellent cosmetic, functional, and oncologic outcomes (8,9).

The technique of radical neck dissection was described by George Crile in 1906 (10). This extirpative procedure was often used in the setting of metastatic head and neck cancers, often of squamous cell origin, with metastases

to the cervical lymph nodes. The operation encompassed removal of the cervical nodes and sacrifice of the internal jugular vein, spinal accessory and greater auricular nerves, as well as the sternocleidomastoid, digastric, and stylohyoid muscles. This radical neck dissection was modified to encompass an oncologically equivalent cervical lymphadenectomy while preserving functional structures including the sternocleidomastoid muscle, internal jugular vein, spinal accessory and greater auricular nerves, as well as the digastric and stylohyoid muscles. Accordingly, a MND is also referred to as a functional or Bocca neck dissection (11).

Patients with thyroid cancer are usually treated with a total or near-total thyroidectomy followed by radioactive iodine therapy and life-long thyroid hormone suppression. A subset of patients either present with metastatic nodal disease or develop metachronous nodal disease later in their course. The most frequent sites of metastases are the central cervical nodes (level VI) bounded by the hyoid bone superiorly, the innominate vein inferiorly, and bilaterally by the carotid sheath (12). Small lymph nodes are frequently encountered in this central region during initial thyroidectomy and should be resected when they are suspicious for metastatic disease as evidenced by enlargement, firmness, or irregularity by palpation.

A MND refers to resection of the lymph nodes in levels II through V and often including the central nodes in level VI. This review describes the operation in detail. It can be performed as an isolated procedure or in combination with a total thyroidectomy. It can also be performed bilaterally. It is often performed for well-differentiated thyroid cancers, most commonly papillary carcinoma of the thyroid. Occasionally patients with follicular or Hürthle cell carcinoma also require modified neck dissections. Patients with medullary carcinoma of the thyroid present a unique set of challenges and, due to the absence of effective adjuvant therapy, surgery plays an even more dominant role in their management. Furthermore, medullary cancer of the thyroid has an early predilection for both central and lateral nodal dissemination. Screening for MTC and primary treatment with total thyroidectomy and MND are essential for biochemical cure of MTC (13). The detailed management plan for medullary carcinoma of the thyroid is beyond the scope of this review.

Operative technique

The patient is placed on the operating table with the head extended and the neck and anterior chest are prepared for surgery (*Figure 1*). An inflatable thyroid pillow is placed behind the patient's back. A linear incision is made that extends from the mid-neck as a continuation of a Kocher incision extending superiorly to approximately 1 inch below the left earlobe. If a bilateral neck dissection is required this incision is extended bilaterally and an apron flap is raised superiorly. Because the spinal accessory nerve is superficial it is important for the surgeon to note the surface landmarks depicting the course of the accessory nerve. If one were to connect a line between the angle of the mandible and the mastoid process and transect this line at a right angle in its mid-portion, the inferior course of that line would be a close approximation of the course of the spinal accessory nerve. It is well worth drawing this on the patient's skin at the time of surgery. The marginal mandibular nerve is protected superiorly but is rarely seen in this exposure. Once the incision is made skin hooks are utilized to develop the anterior flap which is raised with an electrocautery (14).

In *Figure 2* the anterior and posterior flaps are completed and the underlying anatomy is demonstrated. The anterior flap is created in the subplatysmal layer and developed as the skin is pulled toward the medial neck. Once the anterior flap has been developed, the posterior flap is developed. The sternocleidomastoid muscle, external jugular vein, and greater auricular nerve are shown. The greater auricular nerve anatomy is extremely important serving as a landmark as the nerve emerges from the lateral aspect of the sternocleidomastoid muscle at Erb's point. The nerve then traverses upward over the muscle going toward the earlobe. Preservation of this nerve is readily accomplished thereby preserving sensation to the earlobe. As the posterior flap is developed, great care and attention must be focused on protecting the spinal accessory nerve which is superior to the greater auricular nerve. The trapezius muscle is identified posterolaterally and the accessory nerve will course from behind the sternocleidomastoid muscle eventually innervating the trapezius muscle. A nerve stimulator is quite useful in locating the accessory nerve. Once the flaps have been completed, a self-retaining retractor is used to hold the skin and platysma in place. Frequently the skin is sewn to the retractor for added exposure. At this point, the external jugular vein is identified superiorly and ligated to form the apex of the tissues that will be unwrapped from the sternocleidomastoid muscle (14).

The fascial sheath covering the sternocleidomastoid muscle is shown being unwrapped in *Figure 3*. The flap, once developed, is mobilized from superior to inferior (*Figure 4*). Once this has been performed (*Figure 4*) a

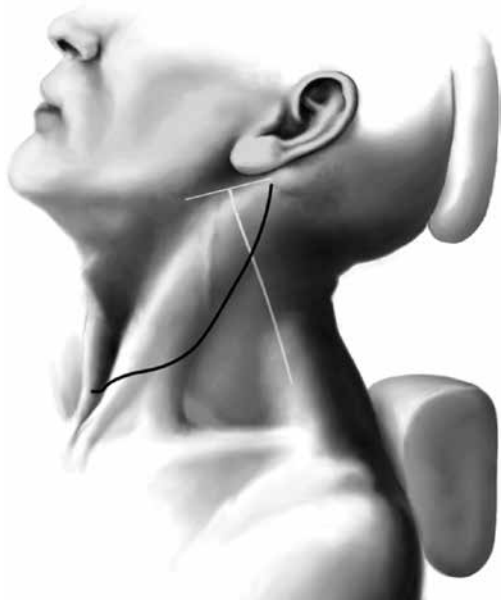

Figure 1 An inflatable pillow is placed behind the patient's back and the head is extended and supported by a head ring. The course of the spinal accessory nerve is marked on the patient's skin. The most commonly employed incision for thyroid cancer is a continuation of a Kocher incision along the posterior border of the sternocleidomastoid muscle superiorly to approximately 1 inch below the ipsilateral ear lobe (14).

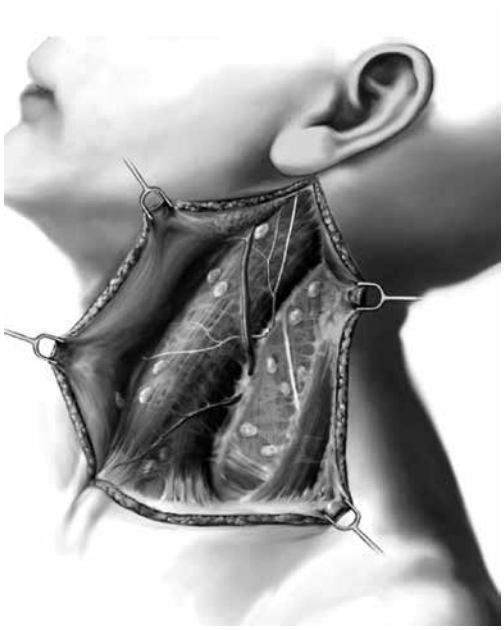

Figure 2 The subplatysmal flaps have been developed anteriorly and posteriorly. The greater auricular and spinal accessory nerves have been identified and preserved. The sternocleidomastoid muscle and the external jugular vein are visualized (14).

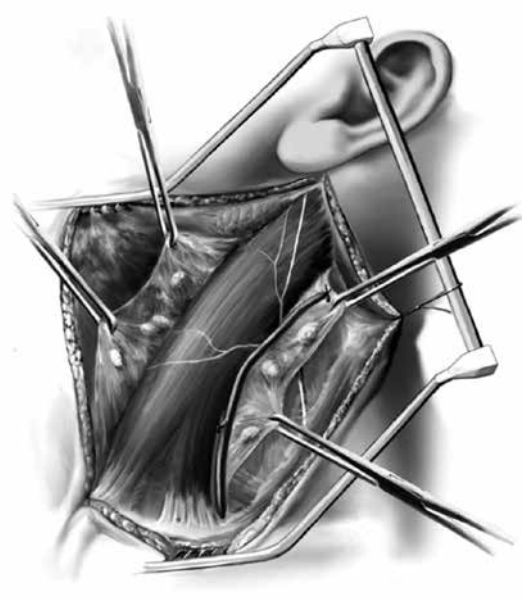

Figure 3 The external jugular vein is ligated superiorly and the fascial sheath covering the sternocleidomastoid muscle is unwrapped. Lymph nodes along the great vessels of the neck are commonly encountered at this point (14).

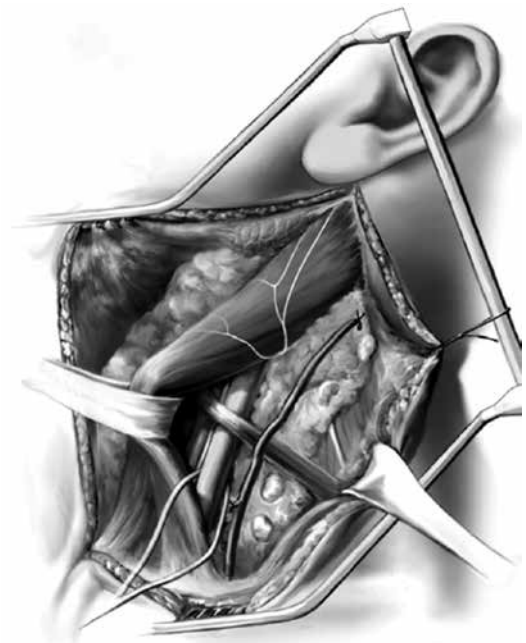

Figure 4 A Penrose drain is placed around the sternocleidomastoid and the muscle is pulled anteriorly. The omohyoid muscle is preserved and the carotid sheath is identified (14).

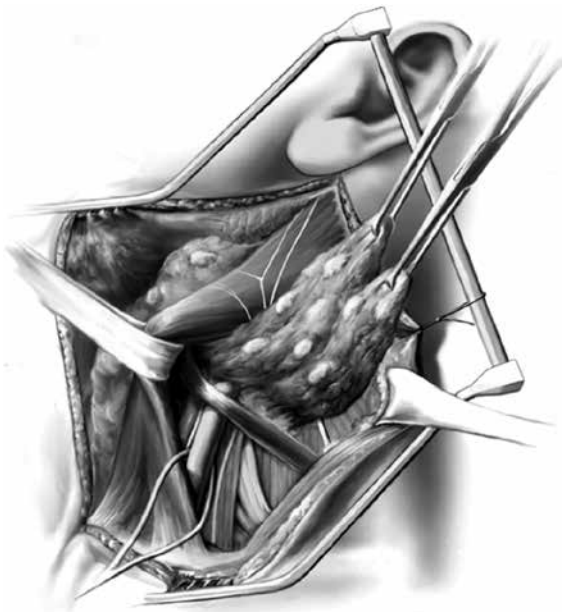

Figure 5 The cervical fat pad containing lymphatics and nodes is mobilized from below the clavicle and pulled superiorly. The thoracic duct, phrenic nerve, and brachial plexus are protected. As the specimen is mobilized it is passed under the omohyoid muscle and traction is applied to the specimen superiorly (14).

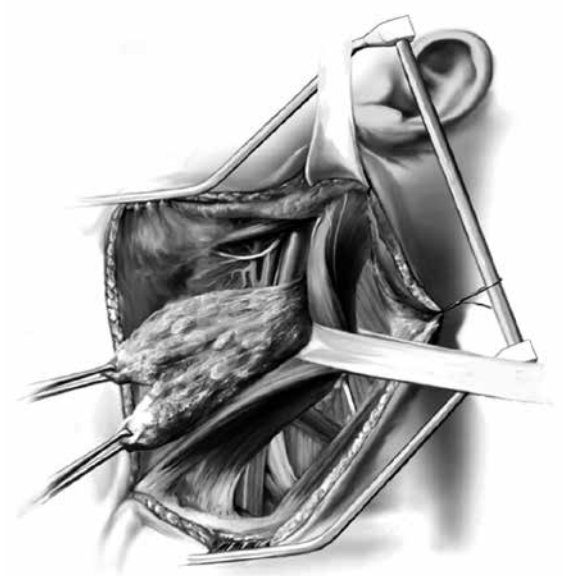

Figure 6 The specimen is passed from its lateral position underneath the sternocleidomastoid muscle and is pulled from an inferior-medial direction. A thyroid retractor is used to pull the mandible superiorly and the digastric muscle is identified. The hypoglossal and proximal spinal accessory nerves are identified and preserved. The cervical fat tissues with their contained lymphatics are resected in continuity as the specimen is pulled off the great vessels (14).

Penrose drain is placed around the sternocleidomastoid muscle (note there are two heads, a sternal head and a clavicular head) and the muscle is pulled medially. If the patient is particularly muscular, it is useful to place separate drains around each head facilitating enhanced exposure. The omohyoid muscle is identified and deep to it the carotid sheath is located. A thin Penrose drain is placed around the omohyoid and in the majority of cases this muscle is preserved. The three structures of the sheath, the common carotid artery, vagus nerve, and internal jugular vein, are carefully protected. Frequently vessel loops are placed around these structures to assist with mobilization. One must be very careful not to injure the sympathetic trunk that lies deep to the common carotid artery as injury to this structure will result in Horner's syndrome. Occasionally, it is necessary to sacrifice the internal jugular vein due to tumor invasion; however, this is unusual in the setting of well-differentiated thyroid cancer. Maintaining the integrity of the anterior jugular veins is important as they become an effective collateral drainage system when the internal jugular vein is sacrificed (14).

At this point the cervical fat pad extending below the clavicle is mobilized from inferior to superior. The carotid sheath structures and particularly the thoracic duct are protected. An unrecognized injury to the thoracic duct can cause a troublesome postoperative lymphatic leak which often leads to a lymphocele and infection. It is prudent to tie the lymphatic tissues inferiorly to minimize lymphatic leaks.

The next step is to identify the phrenic nerve which lies lateral to the vagus nerve (*Figure 5*). This is an important landmark to identify as it innervates the diaphragm. It also represents the deep margin of the specimen lying superficial to the anterior scalene muscle. All superficial fat and lymph node-bearing tissues are resected anterior to the phrenic nerve as this block of tissue is swept from inferior to superior. The specimen is then passed beneath the omohyoid muscle as the dissection continues as shown and the specimen is pulled superiorly. The omohyoid muscle and phrenic nerve are shown, the brachial plexus is identified laterally, and superiorly the accessory nerve is seen. Branches of the transverse cervical nerves are usually sacrificed. However, it is not difficult to preserve one or more of these branches and thereby maintain sensation to the skin of the ipsilateral shoulder. The soft tissues underneath the accessory nerve are mobilized and included with the specimen.

Figure 6 shows the specimen has now been mobilized off the sternocleidomastoid muscle and has been passed

from the lateral aspect of the muscle underneath the muscle belly anteriorly. At this point, a thyroid retractor is placed underneath the mandible and the mandible is pulled superiorly. The parotid and submandibular glands are preserved and the digastric muscle is identified. Inferior to the digastric muscle is the hypoglossal nerve which must be identified. A useful trick to help locate the hypoglossal nerve is to follow the branch of the ansa cervicalis nerve as it courses superiorly along the anterior surface of the carotid artery until it joins the hypoglossal nerve at a right angle. Stimulation of the hypoglossal nerve will result in a movement of the tongue. In addition, the proximal accessory nerve must be identified at the medial aspect of the sternocleidomastoid muscle as soft tissues along the accessory nerve are included with the specimen. The nerve can be felt like a violin string if one distracts the sternocleidomastoid muscle posteriorly. It is extremely important to protect this nerve. All tissues inferior to the digastric muscle and hypoglossal nerve are resected in continuity with the specimen as the final tissues are removed from the great vessels and vagus nerve (14).

At the completion of the operation, a Penrose drain has been placed around the sternocleidomastoid muscle and the omohyoid muscle; the common carotid artery, vagus nerve, internal jugular vein, phrenic nerve, brachial plexus, accessory nerve, and greater auricular nerve are all preserved. Closure is obtained by reapproximating the platysma muscle with interrupted sutures and a subcuticular closure of the skin. A drain is always placed due to the extensive lymphadenectomy (14).

The operation is well-tolerated and the vast majority of patients are extubated in the operating room.

Since the introduction of endoscopic techniques in thyroid surgery, several trials of endoscopic lateral neck dissection have been conducted with the aim of avoiding a long cervical scar, but these endoscopic procedures require more effort than open surgery, mainly because of the relatively non-sophisticated instruments used. However, the recent introduction of surgical robotic systems has simplified the operations and increased the precision of endoscopic techniques. Some people have described their initial experience with robot-assisted MND in thyroid cancer using the da Vinci S system. Robot-assisted MND is technically feasible, safe, and produces excellent cosmetic results. Based on their initial experience, robot-assisted MND should be viewed as an acceptable alternative method in patients with low-risk, well-differentiated thyroid cancer with lateral neck node metastasis (15).

Cervical sensory preservation

Cervical plexus consist of four cervical spinal nerves, namely form occipital nerve, great auricular nerve, neck cutaneous nerve, supraclavicular nerve and phrenic nerve. Sensory branches of the cervical roots provide sensation to skin of the neck and shoulder. As the skin flaps are elevated in subplatysmal plane, several branches of the cervical plexus are immediately encountered overlying the SCM. Sacrifice of these branches will results in a sensory deficit that extends from pinna to the chest wall below the clavicle (16). In another study, Saffold *et al*. found that preservation of the cervical root branches resulted in a small, limited, and uniform area of the neck rendered permanently anesthetic. Conversely, sacrifice of the nerve branches led to a pattern of anesthesia involving the entire neck (17). Most of this sensory deficit will spontaneously resolve postoperatively over a period of months. Branches of the cervical plexus can also form neuromas, which present as firm, painful masses in the lateral neck that are exquisitely tender to palpation (18).

When performing modified neck dissection, we can find the superficial cutaneous branches of the cervical plexus at the superficial fascia midpoint of the trailing edge of the sternocleidomastoid muscle: (I) auricular nerve along the sternocleidomastoid surface upward, dominate the ear and the parotid gland skin feel; (II) the transverse cervical nerve along the front line of muscle to the anterior surface area; (III) occipital nerve piercing point is higher along the posterior border of sternocleidomastoid backward and upward to occiput; (IV) supraclavicular nerve run out below the midpoint of the trailing edge of the muscle slightly, depending on the starting position is deeper, so we can look for the chest and shoulder branch sections in the clavicle 2/3 above the superficial fascia, then up to track trunk.

During neck dissection including level V, the cervical sensory branches were identified and preserved after careful separation from fibrofatty tissue of the posterior cervical triangle. The nerves were isolated and traced into the SCM, and cervical nerve rootlets were found after the posterior border of the SCM was incised and elevated (19).

The cervical nerve rootlets were identified and preserved after mobilizing the anterior aspect of the SCM along its full extent. Dissection was carried underneath this muscle so that it could be fully mobilized and elevated as a bipedicle flap. The dissection was carried forward along the deep cervical fascial plane. The other cervical root branches were preserved after careful separation from fibrofatty tissue of the neck if the tumors or lymph nodes

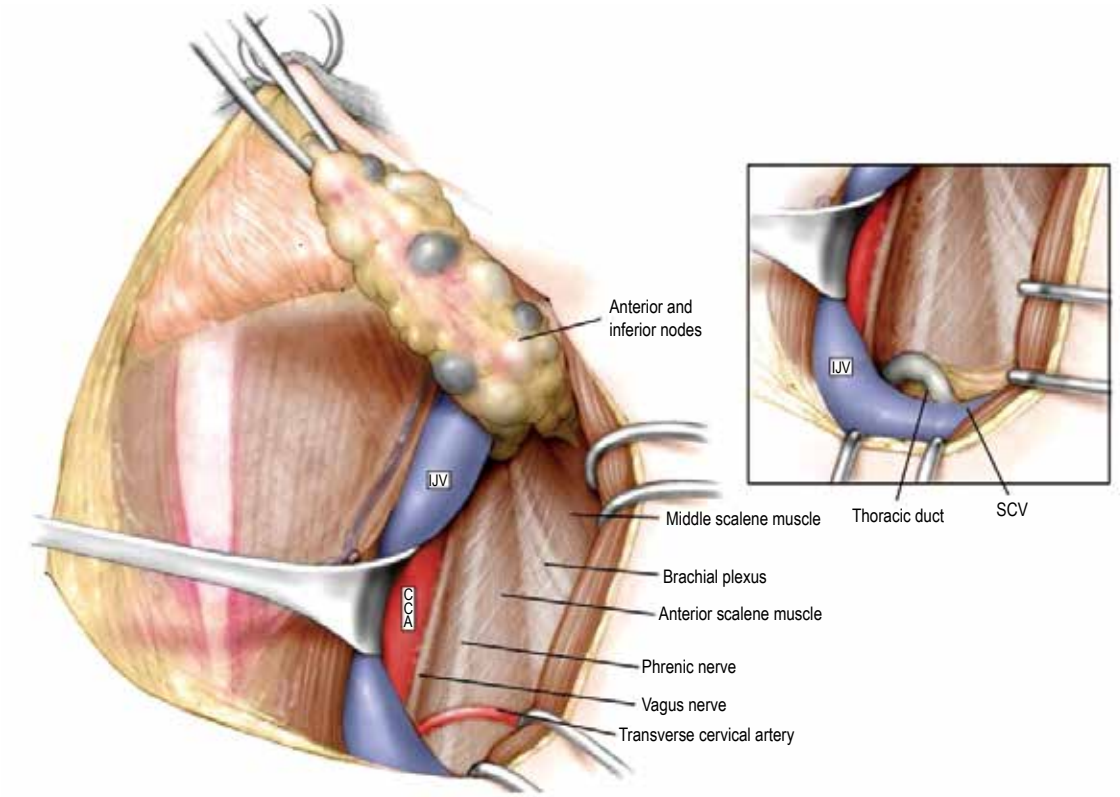

Figure 7 En bloc dissection of internal jugular vein (IJV) lymph nodes and exposure of floor of neck. ASM indicates anterior scalene muscle; BP, brachial plexus; CCA, common carotid artery; MSM, middle scalene muscles; PN, phrenic nerve; SCM, sternocleidomastoid muscle; SCV, subclavian vein; TD, thoracic duct.

had not directly invaded the nerves. During selective neck dissection excluding level V, the cervical root branches were usually accessed after mobilizing the anterior aspect of the SCM, reflecting off the muscles, and dissecting back along its medial surface. The SCM was then reflected off the underlying soft tissues, dissecting back along its medial surface until the cervical rootlets were identified wrapping around its posterior border. The cervical root branches were preserved after deep plane dissection and careful separation from fibrofatty tissue of the bloc neck (19) (*Figure* 7).

Because the neck skin are widely separated, if cutaneous sensory nerves are damaged, postoperative patients' skin often feel wood swelling, sluggish or formication, paresthesia etc. This feeling usually began to recover in a few weeks after surgery, disappear in three months. The surgeon should explain to the patient before surgery that this feeling does not need special treatment. Before the return to normal sensation, facial skin should be protected because it feels relatively slow and is vulnerable to trauma. At the time, the connection between separated skin and basal blood is not perfect, it is easy to become injured scarring.

Sensory nerve trunk injury can cause permanent feeling disappear in its disposal zone. And it can not be rebuilt. Therefore, surgery should be taken to avoid damage sensory nerve trunk, as in the separation of the ear flap, pay attention to not cut auricular nerve. Once damaged, nerve anastomosis or transplantation should be considered to be repaired.

The practice of neck dissection has greatly advanced from radical to function-preserving surgery (20). To avoid postoperative neck and shoulder morbidity, current techniques of neck dissection tend to be more selective (21,22). When performing modified neck dissection, we recommend to protect more reserved cervical plexus. The purpose is to better protect patients' neck skin feeling.

Acknowledgements

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References

1. Dzodic R, Markovic I, Inic M, et al. Sentinel lymph node biopsy may be used to support the decision to perform modified radical neck dissection in differentiated thyroid carcinoma. World J Surg 2006;30:841-6.
2. Ito Y, Higashiyama T, Takamura Y, et al. Risk factors for recurrence to the lymph node in papillary thyroid carcinoma patients without preoperatively detectable lateral node metastasis: validity of prophylactic modified radical neck dissection. World J Surg 2007;31:2085-91.
3. Wada N, Duh QY, Sugino K, et al. Lymph node metastasis from 259 papillary thyroid microcarcinomas: frequency, pattern of occurrence and recurrence, and optimal strategy for neck dissection. Ann Surg 2003;237:399-407.
4. Raina S, Rocko JM, Swaminathan AP, et al. Current attitudes in the management of thyroid cancer. Am Surg 1983;49:110-2.
5. Nicolosi A, Malloci A, Esu S, et al. The role of node-picking lymphadenectomy in the treatment of differentiated carcinoma of the thyroid. Minerva Chir 1993;48:459-63.
6. Musacchio MJ, Kim AW, Vijungco JD,et al. Greater local recurrence occurs with "berry picking" than neck dissection in thyroid cancer. Am Surg 2003;69:191-6; discussion 196-7.
7. Pingpank JF Jr, Sasson AR, Hanlon AL, et al. Tumor above the spinal accessory nerve in papillary thyroid cancer that involves lateral neck nodes: a common occurrence. Arch Otolaryngol Head Neck Surg 2002;128:1275-8.
8. Gemsenjäger E, Perren A, Seifert B, et al. Lymph node surgery in papillary thyroid carcinoma. J Am Coll Surg 2003;197:182-90.
9. Kupferman ME, Patterson DM, Mandel SJ, et al. Safety of modified radical neck dissection for differentiated thyroid carcinoma. Laryngoscope 2004;114:403-6.
10. Crile G. Landmark article Dec 1, 1906: excision of cancer of the head and neck. With special reference to the plan of dissection based on one hundred and thirty-two operations. By George Crile. JAMA 1987;258:3286-93.
11. Bocca E, Pignataro O, Sasaki CT. Functional neck dissection. A description of operative technique. Arch Otolaryngol 1980;106:524-7.
12. Greene FL, Page DL, Fleming ID, et al. eds. AJCC cancer staging manual, 6th edition. New York: Springer, 2002.
13. Weber T, Schilling T, Frank-Raue K, et al. Impact of modified radical neck dissection on biochemical cure in medullary thyroid carcinomas. Surgery 2001;130:1044-9.
14. Daniel O, Robert U. eds. Surgery of the thyroid and parathyroid glands. Berlin: Springer-Verlag, 2007.
15. Kang SW, Lee SH, Ryu HR, et al. Initial experience with robot-assisted modified radical neck dissection for the management of thyroid carcinoma with lateral neck node metastasis. Surgery 2010;148:1214-21.
16. Saki N, Nikakhlagh S. Complications of neck dissection. Rijeka: In Tech, 2012.
17. Saffold SH, Wax MK, Nguyen A, et al. Sensory changes associated with selective neck dissection. Arch Otolaryngol Head Neck Surg 2000;126:425-8.
18. Weiss KL, Wax MK, Haydon RC 3rd, et al. Intracranial pressure changes during bilateral radical neck dissections. Head Neck 1993;15:546-52.
19. Roh JL, Yoon YH, Kim SY, et al. Cervical sensory preservation during neck dissection. Oral Oncol 2007;43:491-8.
20. Harish K. Neck dissections: radical to conservative. World J Surg Oncol 2005;3:21.
21. Spiro RH, Gallo O, Shah JP. Selective jugular node dissection in patients with squamous carcinoma of the larynx or pharynx. Am J Surg 1993;166:399-402.
22. Traynor SJ, Cohen JI, Gray J, et al. Selective neck dissection and the management of the node-positive neck. Am J Surg 1996;172:654-7.

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The pros and cons of prophylactic central neck dissection in papillary thyroid carcinoma

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Abstract: Prophylactic central neck dissection (pCND) for management of papillary thyroid carcinoma (PTC) is controversial. Compared to many malignancies, PTC has a high overall survival but local recurrence due to lymph node metastases continue to present management challenges. Unlike lateral cervical nodal metastasis metastasis, central neck nodal metastasis are unable to be reliably detected clinically or radiologically at pre-operative assessment. Residual disease (recurrent or persistent) typically requires re-operative surgery in the central compartment, which carries a heightened risk of significant morbidity. These nodal groups can be accessed during the index thyroidectomy for PTC. Thus, pCND offers potential to reduce the rates of recurrence and the need for re-operative surgery in the central neck. This benefit needs to be balanced with the potential morbidity risk from pCND itself at the index resection. This review will discuss the advantages and disadvantages of pCND with regard to long-term outcomes and potential morbidity. The rationale of pCND will be discussed, along with the indications for ipsilateral and contralateral pCND, the role of re-operative surgery for recurrence and the use of selective versus routine pCND. Strategies to select higher risk patients for pCND with the use of molecular markers will be addressed, along with a discussion of quality of life (QoL) research in PTC.

Keywords: Lymph node; metastasis; prophylactic; elective; morbidity

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Introduction

Compared to many malignancies, most patients diagnosed with differentiated thyroid carcinomas have an excellent prognosis, with five-year overall survival of well over 90% (1,2). However, recurrence following treatment is common, occurring in up to 30% of patients and can occur up-to 20 years after the initial diagnosis (3-5). Recurrence most commonly occurs in the cervical lymph nodes and is generally managed with surgical resection (6). Prophylactic central neck dissection (pCND) is performed to remove occult nodal metastases that are not detected by clinical examination or pre-operative radiological assessment. pCND offers the possibility of reducing the risk of central neck recurrence by removing central compartment nodal tissue during the initial thyroidectomy; thereby reducing the need for re-operative surgery in the central neck with the attendant risks of injury to the recurrent laryngeal nerves and parathyroid glands. It should be noted that a pCND is not devoid of risk and still carries a risk of nerve and parathyroid morbidity itself. The indications and role of pCND therefore remain a controversial area of thyroid cancer management (7).

This review will focus on pCND for papillary thyroid cancer. The evidence and arguments for and against pCND, within the context of long-term outcomes and quality of life (QoL), will be discussed (*Table 1*).

Papillary thyroid carcinoma (PTC) and nodal metastasis

Approximately 85% of differentiated thyroid cancers

Table 1 Arguments for and against pCND

For	Against
Subclinical central lymph node metastasis is common and preoperative and intraoperative evaluations of central compartment lymph node metastasis are not reliable	Most subclinical central lymph node metastasis are micrometastatic and it is unclear if they would develop clinically significant recurrences
May reduce recurrence by ~5% and may improve survival	The evidence is conflicting with no level one evidence
May lower postoperative thyroglobulin levels leading to more effective detection of persistent or recurrent disease	Increased surgical morbidities for a marginal benefit
More accurate staging of PTC, aiding in decision making regarding radio-iodine ablation	Tumor upstaging leads to more radio-iodine ablation which might not be necessary
Reduces the need for reoperation in central neck recurrence which is associated with greater morbidity	Operation in recurrent cases can be safely performed by experienced surgeons
pCND can be safely performed with comparable morbidity to thyroidectomy alone by experience surgeons	Majority of thyroidectomies are performed by low-volume surgeons for which pCND is not appropriate

Adapted from Wong KP and Lang BH (4).

are PTC. Up to 35% of PTC patients present with macrometastatic cervical lymph node metastasis, and up to 80% will possess undetectable, microscopic cervical lymph node disease (8-10). The presence of macrometastatic nodal metastasis is an independent predictor for recurrence, while the significance of micrometastatic disease is controversial and may have little prognostic significance (6,11,12). Due to this high rate of lymph node metastasis, preoperative cervical ultrasound with fine needle aspiration biopsy of suspicious lymph nodes and therapeutic neck dissection for patients with confirmed metastatic lymph nodes is recommended treatment (7,13).

While ultrasound is a sensitive and specific test for detecting lateral cervical lymph node metastasis, diagnosing central lymph node metastasis is much more difficult. Central lymph nodes are positioned over the trachea and closely located to the thyroid making identification of nodal metastasis problematic (14). Pre-operative imaging with ultrasound or computerised tomography have limited sensitivity at detecting metastatic central lymph nodes. Ultrasound has a sensitivity of 53-61% with a specificity of 80-93%, whilst computerised tomography has been found to have a sensitivity of 67% with a specificity of 79-91% (14). Positron emission tomography is even more limited in detecting central lymph node metastasis pre-operatively with sensitivities of less than 40% reported (15,16). Given these findings, radiological investigations cannot be relied on to accurately detect most central lymph node metastasis pre-operatively. As the incidence of metastasis in the central lymph nodes is estimated to be between 30-70% (10,17,18), and due to the fact that the central lymph nodes can be accessed during, and through the same incision as for thyroidectomy, it has been standard practice in a number of specialist units to clear the central lymph nodes during the initial thyroidectomy.

Clearance of the central lymph nodes requires identification and preservation of the recurrent laryngeal nerves and avoidance of parathyroid devascularisation. The potential risks of nerve injury and permanent hypoparathyroidism using this approach must be carefully considered against the benefit of prophylactic nodal dissection.

Definitions

Due to the controversy and number of publications regarding central neck dissection (CND), it is important to employ agreed definitions for discussion. The American Thyroid Association Surgery Working Group has defined the anatomy and surgical terminology as follows:

- The central compartment (level VI) of the neck is described anatomically as being bound superiorly by the hyoid bone, laterally by the carotid arteries, anteriorly by the superficial layer of the deep cervical fascia and posteriorly by the deep layer of the deep cervical fascia, inferiorly by the innominate artery on the right and corresponding axial plane on the left. Included in this definition of the central neck is the anterior superior mediastinum above the innominate artery (level VII);
- CND is defined as a comprehensive, compartment-orientated removal of the prelaryngeal and pretracheal nodes and at least one paratracheal basin;

- CND can be bilateral or unilateral. Bilateral CND removes both the right and left para-tracheal nodes along with the pre-laryngeal and pre-tracheal nodes. Unilateral CND removes one side of the para-tracheal nodes along with the pre-laryngeal and pre-tracheal lymph nodes. It is important to note that CND is a compartmental clearance of lymph nodes and does not include 'berry picking' of selected lymph nodes within the central compartment;
- Lymph node dissection can be therapeutic: where patients have clinically or radiologically detectable lymph node disease prior to surgery; or prophylactic: where lymph node metastasis is not identified pre-operatively (19).

A further important point relates to the definition of micro- *vs.* macro-metastatic disease. In the literature, the definition of macro-metastatic ranges from greater than 2 mm, to over 10 mm (10,12,20). The definition of micro-metastatic disease is controversial with the limit of less than 2 mm being adapted from the description from breast cancer metastasis and used for most studies of pCND (11). An accepted definition is important as micro-metastatic disease has a significantly lower risk of recurrence compared to macro-metastatic disease (10-12).

Significance of lymph node metastasis in PTC

Unlike most malignancies where nodal metastasis correlates with more advanced disease and a substantially worse prognosis, PTC related nodal metastases have traditionally been considered to have little impact on recurrence or survival outcomes. This is typified by numerous prognostic scoring systems such as the MACIS (Metastasis, Age, Completeness of Resection, Invasion, Size) and European Organization for Research and Treatment of Cancer (EORTC) which do not include nodal metastasis as a prognostic indicator.

Despite this conventional reasoning, large scale SEER database analyses have shown that lymph node metastasis is a significant predictor of overall survival (21). This is reflected in the American Joint Committee on Cancer (AJCC) Tumour, Nodal disease and distant Metastasis (TNM) staging system which classifies lymph node metastasis as a prognostic factor for patients aged over 45 years and can have a marked impact on staging of disease. For instance, according to the TNM system, lymph node metastasis (in a patient aged older than 45 years) moves the stage from I to III (22). However the TNM classification does not differentiate between micro- or macro-metastatic lymph nodes and does not sub-classify lymph node disease between the lateral and central cervical compartments.

The presence of lymph node metastasis is also an independent risk factor for recurrence (23). To predict the risk of recurrence it is important to consider a number of factors. A spectrum of recurrence risk is seen from 4% to 34%, depending on the primary tumour characteristics, patient age and number of metastatic nodes (12,24). The risk of recurrence has also been shown to relate to the specific burden of lymph node metastasis, with recurrence rates of 32% and 5% when comparing macro- (≥2 mm) versus micro-metastasis respectively (11). The use of lymph node ratio also has potential to classify recurrence risk, with a high lymph node ratio (defined as being >40% of metastatic to total resected nodes) being found to be an independent predictor of recurrence on multivariate analysis (20). The use of lymph node ratios based on central compartment dissection may also facilitate tailored management plans (25). A weakness of using lymph node ratio is the extent of central lymph node dissection. If only abnormal lymph nodes are removed and the central compartment not cleared as recommend by guidelines it will result in a spuriously elevated lymph node ratio, limiting its use as a prognostic system.

For unilateral PTC, the location of central lymph node metastasis is predominantly ipsilateral with less than 10% involving the contralateral central lymph nodes (26,27). Multi-focal PTCs and cancers of the isthmus are more likely to have contralateral nodal metastasis in the central compartment.

Loco-regional control with pCND

The central argument employed to justify pCND relates to the assertion that it reduces the rate of central neck recurrence and thereby minimises the need for re-operative surgery. This argument is controversial, and has been questioned on the basis of largely retrospective studies justifying its utility. Until recently, no studies had shown a significant reduction in the rate of central lymph node recurrence following pCND (28). A number of meta-analyses of retrospective cohort series have also not shown any beneficial reduction in recurrence when comparing the use of pCND and total thyroidectomy to thyroidectomy alone (29,30).

Conversely, a recent series by Barczyński *et al.* with an appropriate follow-up period has shown that pCND can

lead to a significantly reduced loco-regional recurrence rate. This cohort study with a median follow up of 120 months, demonstrated that locoregional control is significantly better with pCND (6.9% difference seen at 10 years; P=0.003) (31). These results were supported by Popadich *et al.* who showed a significant 4.6% reduction in central compartment recurrence requiring re-operation when compared to patients undergoing total thyroidectomy alone across three specialised endocrine surgery units (P=0.004) (32). A subsequent meta-analysis (including these recent series), has shown that by restricting prophylactic resection to adults with PTCs >1 cm there is a trend towards lower recurrence rates; with a number needed to treat of 31 patients (to avoid one recurrence) (33).

Conflicting evidence regarding the benefit of pCND on outcomes such as recurrence are likely to continue. Given the small differences observed between those treated with and without pCND, a randomised controlled trial is not feasible from both a power analysis and economic viewpoint (34).

Beyond recurrence rates, defining any difference in survival with pCND is also difficult owing to the typically good prognosis that the majority of PTC patients enjoy. Despite these challenges, Barczyński *et al.* has previously shown that patients treated with bilateral pCND had significantly improved survival compared to a historical control group of patients treated with total thyroidectomy alone, with ten-year disease-specific survival improved from 92.5% to 98.0% (31). A significant criticism of this study involved the increased use of radioactive iodine (RAI) in the pCND group due to the information gained from lymph node staging, which may have affected disease specific survival. Whilst potentially confounding outcome data, it could be argued that improved outcomes would not have been obtained without this additional prognostic information; further highlighting the prophylactic, as opposed to purely therapeutic benefit of pCND.

Staging and RAI ablation

As discussed, an additional argument in favour of pCND is the staging information it provides, which can guide use of RAI (^{131}I). A substantial number of patients undergoing pCND may be upstaged, allowing for more stage appropriate post-operative RAI ablation therapy (35). This upstaging effect was typified by Hughes *et al.*, who showed that for patients aged over 45, one third were upstaged due to lymph node metastasis detected by pCND and recommended for RAI (17). Staging information obtained from pCND can be used to personalise the use of RAI. This approach has been shown by Lang *et al.* (36), who has shown the utility of using size of the central lymph node metastases to predict the response to RAI ablation. In this study, patients with macrometastatic lymph node disease (≥2 mm) were found to be six times more likely to have detectable stimulated thyroglobulin nine months after surgery, leading the authors to suggest that the RAI dose could be tailored according to the size of metastatic disease (36).

Staging information obtained from pCND is of particular use when deciding if patients with PTCs of 1-2 cm should undergo RAI, as it is selectively recommended in this scenario (13). Lymph node involvement from pCND has been shown to be an indication for treatment in up to 30% of these patients allowing for a more tailored approach to treatment (37). The additional benefit of this approach for patients staged as having no nodal metastasis (pN0) after CLND involves being able to safely receive lower doses of ^{131}I or not receive it at all (37). This approach may also lead to an increase in the number of patients found to have a negative low-dose total body scan, thereby reducing the number of patients who require RAI ablation (7).

Conversely, the potential upstaging from pCND can lead to overtreatment with RAI. When making decisions regarding RAI based on lymph node metastasis it is essential that the factors that predict increased risk of recurrence such as macro-metastatic lymph node disease are considered (28). Treatment with RAI carries morbidity risks, such as salivary and lacrimal gland dysfunction, dysphagia and an increased risk of secondary malignancies (28).

In addition to providing information used to tailor RAI treatment, staging information from pCND can facilitate follow-up protocols, allowing for closer follow-up for patients deemed at higher risk of recurrence on the basis of positive central compartment nodes (38).

Thyroglobulin normalization

A treatment goal of PTC is to facilitate long-term surveillance for PTC recurrence, for which thyroglobulin levels are used as a marker of persistent and recurrent disease (13). Advocates for pCND argue that by removing subclinical metastases, postoperative serum thyroglobulin will be lower and assists in achieving the goal of athyroglobulinemia. This suggestion would appear to make theoretical sense and has been justified in two studies comparing pCND to no pCND (31,39). However, other units have failed to demonstrate differences in thyroglobulin

levels between similar patient groups (17). The ability of pCND to increase the rate of athyroglobulinemia and the long-term prognostic and management significance of this remain to be evaluated in further studies.

Re-operative surgery following CND

An argument against pCND is that secondary operation for lymph node recurrence can be performed safely in the central neck compartment by experienced thyroid surgeons with similar morbidity seen with pCND (40-42). This statement is controversial however with other studies reporting higher rates of hypoparathyroidism and vocal cord paralysis with re-operative surgery, due to tumour recurrence and local invasion (43).

The diagnosis of recurrence and the requirement for re-operation is also highly significant to the patient and treating clinician. It could be argued that such considerable anxiety may be avoided if the central lymph nodes are cleared at initial surgery (7). Furthermore it has been shown that patients who experience recurrence are at increased risk for subsequent recurrence, with a number of patients needing multiple operations (44,45). Re-operative surgery is less likely to achieve a biochemical cure of disease with a minority of patients (27%) achieving undetectable serum thyroglobulin levels post-operatively (46,47). Evans has used these findings to justify his assertion that 'the best chance to remove all disease is at the first operation' (7).

Complications of pCND

Given the contentious benefits of pCND, the risk of pCND related complications are of critical importance and are the most serious disadvantage of offering pCND. The risks of pCND are the same as at thyroidectomy and include recurrent laryngeal nerve injury, hypoparathyroidism and hematoma. For total thyroidectomy, permanent hypoparathyroidism and nerve injury rates less than 1-2% have been suggested as being acceptable for experienced surgeons (48).

With regard to the addition of pCND to total thyroidectomy, multiple studies have shown a significantly increased risk of temporary hypoparathyroidism, presumably due to the vasculature of the parathyroids being at risk of manipulation and division during dissection (28,32,49). Whilst surgery by a specialist unit can minimise permanent complications to similar levels as seen with total thyroidectomy alone, multiple studies have shown a trend towards increased permanent hypoparathyroidism and recurrent laryngeal nerve injury when comparing total thyroidectomy with pCND to thyroidectomy alone (28).

The choice between unilateral and bilateral pCND is also important and it could be assumed that a bilateral dissection would be associated with a higher complication rate. This has been borne out by the works of Giordano *et al.*, who showed in a retrospective analysis of 1,087 patients that ipsilateral pCND caused significantly less permanent hypoparathyroidism when compared to bilateral pCND (7% *vs.* 16.2%, P<0.001) (50).

The morbidity and potential threat to life of recurrent laryngeal nerve palsy and subsequent vocal cord paralysis has been known since the times of Galen in the second century A.D. and do not require additional discussion (51). Permanent hypoparathyroidism can also cause considerable morbidity due to the requirement for calcium replacement and monitoring with the need to avoid hypercalcemia, nephrocalcinosis and renal failure. Rates of chronic kidney disease in patients with permanent hypoparathyroidism have been estimated at 2- to 17-fold greater than age adjusted controls (52). Surgery in a specialist unit with liberal use of parathyroid autotransplantion and replacement of calcium post-operatively with high dosages of oral calcium and vitamin D has been suggested as an important strategy to prevent permanent hypoparathyroidism (31,39,53).

In general, complications can be limited by careful attention to operative technique. During dissection of the central lymph nodes, it is essential to have clear visualisation of the recurrent laryngeal nerve throughout its cervical course. When in close proximity to the recurrent laryngeal nerve, sharp dissection should be used instead of electrocautery to minimise the chance of lateral thermal spread and injury (39).

Due to the possibility of significant morbidity, it is essential that pCND is offered by units with large thyroid workloads, who regularly review complication rates (49). pCND in experienced thyroid units is able to be performed with no significant increase in the rates of permanent complications (32).

QoL studies in thyroid cancer

Long term survival rates, the nature of treatment with initial surgery, subsequent RAI ablation and the need for long-term monitoring impose significant challenges on thyroid cancer survivors and can affect health-related QoL (54). QoL research in PTC has been restricted due to the lack

Table 2 Summary of guidelines for pCND

Guidelines	Recommendation
American Thyroid Association, 2009 (13)	pCND (ipsilateral or bilateral) may be performed, especially for advanced primary tumours (T3 or T4)
National Comprehensive Cancer Network, 2013 (58)	Consider if age <15 or >45 years, radiation history, T3/T4 tumours, aggressive variant (tall cell variant, columnar cell or poorly differentiated features), bilateral nodularity, extrathyroidal extension or distant metastases
British Thyroid Association, 2007 (59)	In patients who are deemed high risk (i.e., they have any of the following features: male sex, age >45 years, tumours greater than 4 cm in diameter, extracapsular or extrathyroidal disease)
European Thyroid Association, 2006 (60) and European Society for Medical Oncology Guidelines, 2009 (61)	Not recommended
Japanese Society of Thyroid Surgeons and Japanese Association of Endocrine Surgeons, 2011 (62)	Routinely recommended

of a specific thyroid cancer model (55). However, with the advent of a thyroid cancer disease specific health related quality of life questionnaire (THYCA-QoL) it is hoped that this area of thyroid cancer research will develop and provide further evidence to support best practice (56). The 24 questions identified in this survey include many that are relevant to pCND, including symptoms of hypoparathyroidism, vocal cord palsy and recurrence. Furthermore, symptoms related to hypoparathyroidism have been found to be significantly increased in thyroid cancer survivors (57). These findings are important for clinicians to discuss with patients when considering pCND.

Routine versus selective pCND and the importance of specialized surgical practice

Table 2 presents a summary of the recommendations for pCND in PTC. pCND is increasingly being recommended only for those with a higher risk of recurrence (63). However, some prognostic features used to distinguish those at a higher recurrence risk (such as aggressive variants and extrathyroidal extension) can be difficult to diagnose pre-operatively making selection of patients difficult.

Population studies suggest that those who would gain the most benefit (e.g., older patients) are not undergoing pCND as regularly as lower risk patients and the adequacy of surgery as defined by lymph node retrieval patterns varies widely (64,65). Some units recommend the selection of patients for pCND by use of intra-operative factors, such as frozen section analysis of lymph nodes (66). The practice of the authors' unit (University of Sydney Endocrine Surgery Unit) is to offer routine ipsilateral pCND for patients with PTCs >1 cm. This unit is able to practice pCND with similar outcomes to total thyroidectomy alone with a technique involving full visualisation and protection of the recurrent laryngeal nerves and liberal use of autotransplantion of the inferior parathyroids (67).

Whether routine or selective pCND is practiced, it should only be offered by units with experience in thyroid surgery. It is well recognized that the complications of thyroid surgery, especially recurrent laryngeal nerve injury and hypo-parathyroidism are higher in low volume units (63,68). As these complications are the same with pCND and given the potential benefit of pCND can be small it is essential that the risks of complications be minimized. pCND cannot be recommended for low volume surgeons and patients should be referred to specialist thyroid surgeons performing at least 50 endocrine operations annually and with experience in central lymph node dissection (63).

Future treatment strategies

Advances in knowledge regarding the underlying molecular pathogenesis of PTC offers potential novel stratification tools that may be employed to select patients who would most benefit from pCND (69). B-type Raf kinase ($BRAF^{V600E}$) mutation has been associated with aggressive disease and loss of RAI avidity in recurrent disease. The ability to diagnose the mutation on pre-operative biopsy means it could be a useful tool for selecting patients who would most benefit from pCND (69). Alzahrani and Xing have

shown that $BRAF^{V600E}$ mutation is associated with high-risk characteristics of PTC such as extrathyroidal extension and could be used as an indication for CND (70). In addition, Howell *et al*. has shown that $BRAF^{V600E}$ mutation is an independent predictor of central lymph node metastasis (71). The use of translational molecular markers offers great promise, however this strategy remains to be confirmed in clinical trials.

The role of sentinel node biopsy is also under investigation and is currently used in some treatment centres, however given the high rates of lymph node metastasis with PTC it may not be an effective operative strategy in selecting patients for pCND (72).

Conclusions

The successful treatment of PTC requires careful consideration by the patient and clinician of the potential benefits and morbidity of each treatment modality. While PTC has high overall survival, recurrence is common and pCND has a potentially significant role in the management of PTC if it can be offered with minimal morbidity. Morbidity from pCND is directly related to surgical experience, and its use must be carefully evaluated by patients and clinicians depending on local resources. The potential use of molecular markers will hopefully offer a further strategy to stratify the risk of recurrence with PTC and allow a more tailored approach to offer pCND to patients with the greatest benefit.

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References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin 2012;62:10-29.
2. Enewold L, Zhu K, Ron E, et al. Rising thyroid cancer incidence in the United States by demographic and tumor characteristics, 1980-2005. Cancer Epidemiol Biomarkers Prev 2009;18:784-91.
3. Hay ID, Thompson GB, Grant CS, et al. Papillary thyroid carcinoma managed at the Mayo Clinic during six decades (1940-1999): temporal trends in initial therapy and long-term outcome in 2444 consecutively treated patients. World J Surg 2002;26:879-85.
4. Wong KP, Lang BH. The role of prophylactic central neck dissection in differentiated thyroid carcinoma: issues and controversies. J Oncol 2011;2011:127929.
5. Sippel RS, Chen H. Controversies in the surgical management of newly diagnosed and recurrent/residual thyroid cancer. Thyroid 2009;19:1373-80.
6. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med 1994;97:418-28.
7. Evans DB. Papillary carcinoma of the thyroid: balancing principles of oncology with emerging technology. Surgery 2011;150:1015-22.
8. Hundahl SA, Fleming ID, Fremgen AM, et al. A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985-1995 [see commetns]. Cancer 1998;83:2638-48.
9. Kouvaraki MA, Shapiro SE, Fornage BD, et al. Role of preoperative ultrasonography in the surgical management of patients with thyroid cancer. Surgery 2003;134:946-54; discussion 954-5.
10. Clark OH. Thyroid cancer and lymph node metastases. J Surg Oncol 2011;103:615-8.
11. Cranshaw IM, Carnaille B. Micrometastases in thyroid cancer. An important finding? Surg Oncol 2008;17:253-8.
12. Randolph GW, Duh QY, Heller KS, et al. The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension. Thyroid 2012;22:1144-52.
13. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167-214.
14. Mulla M, Schulte KM. Central cervical lymph node metastases in papillary thyroid cancer: a systematic review of imaging-guided and prophylactic removal of the central compartment. Clin Endocrinol (Oxf) 2012;76:131-6.
15. Kim BS, Ryu HS, Kang KH. The value of preoperative PET-CT in papillary thyroid cancer. J Int Med Res 2013;41:445-56.
16. Jeong HS, Baek CH, Son YI, et al. Integrated 18F-FDG PET/CT for the initial evaluation of cervical node level of patients with papillary thyroid carcinoma: comparison with ultrasound and contrast-enhanced CT. Clin Endocrinol (Oxf) 2006;65:402-7.
17. Hughes DT, White ML, Miller BS, et al. Influence of prophylactic central lymph node dissection on

postoperative thyroglobulin levels and radioiodine treatment in papillary thyroid cancer. Surgery 2010;148:1100-6; discussion 1006-7.
18. Takada H, Kikumori T, Imai T, et al. Patterns of lymph node metastases in papillary thyroid carcinoma: results from consecutive bilateral cervical lymph node dissection. World J Surg 2011;35:1560-6.
19. American Thyroid Association Surgery Working Group, American Association of Endocrine Surgeons, American Academy of Otolaryngology-Head and Neck Surgery, et al. Consensus statement on the terminology and classification of central neck dissection for thyroid cancer. Thyroid 2009;19:1153-8.
20. Jeon MJ, Yoon JH, Han JM, et al. The prognostic value of the metastatic lymph node ratio and maximal metastatic tumor size in pathological N1a papillary thyroid carcinoma. Eur J Endocrinol 2013;168:219-25.
21. Podnos YD, Smith D, Wagman LD, et al. The implication of lymph node metastasis on survival in patients with well-differentiated thyroid cancer. Am Surg 2005;71:731-4.
22. Cancer AJCO. AJCC Cancer Staging Manual. 7 ed. In: Edge SB, Byrd DR, Compton CC, et al. eds. Springer, 2010.
23. Mazzaferri EL, Young RL. Papillary thyroid carcinoma: a 10 year follow-up report of the impact of therapy in 576 patients. Am J Med 1981;70:511-8.
24. Ducoudray R, Trésallet C, Godiris-Petit G, et al. Prophylactic lymph node dissection in papillary thyroid carcinoma: is there a place for lateral neck dissection? World J Surg 2013;37:1584-91.
25. Schneider DF, Chen H, Sippel RS. Impact of lymph node ratio on survival in papillary thyroid cancer. Ann Surg Oncol 2013;20:1906-11.
26. Roh JL, Kim JM, Park CI. Central lymph node metastasis of unilateral papillary thyroid carcinoma: patterns and factors predictive of nodal metastasis, morbidity, and recurrence. Ann Surg Oncol 2011;18:2245-50.
27. Nam IC, Park JO, Joo YH, et al. Pattern and predictive factors of regional lymph node metastasis in papillary thyroid carcinoma: a prospective study. Head Neck 2013;35:40-5.
28. Gyorki DE, Untch B, Tuttle RM, et al. Prophylactic central neck dissection in differentiated thyroid cancer: an assessment of the evidence. Ann Surg Oncol 2013;20:2285-9.
29. Zetoune T, Keutgen X, Buitrago D, et al. Prophylactic central neck dissection and local recurrence in papillary thyroid cancer: a meta-analysis. Ann Surg Oncol 2010;17:3287-93.
30. Shan CX, Zhang W, Jiang DZ, et al. Routine central neck dissection in differentiated thyroid carcinoma: a systematic review and meta-analysis. Laryngoscope 2012;122:797-804.
31. Barczyński M, Konturek A, Stopa M, et al. Prophylactic central neck dissection for papillary thyroid cancer. Br J Surg 2013;100:410-8.
32. Popadich A, Levin O, Lee JC, et al. A multicenter cohort study of total thyroidectomy and routine central lymph node dissection for cN0 papillary thyroid cancer. Surgery 2011;150:1048-57.
33. Wang TS, Cheung K, Farrokhyar F, et al. A meta-analysis of the effect of prophylactic central compartment neck dissection on locoregional recurrence rates in patients with papillary thyroid cancer. Ann Surg Oncol 2013;20:3477-83.
34. Carling T, Carty SE, Ciarleglio MM, et al. American Thyroid Association design and feasibility of a prospective randomized controlled trial of prophylactic central lymph node dissection for papillary thyroid carcinoma. Thyroid 2012;22:237-44.
35. Shindo M, Wu JC, Park EE, et al. The importance of central compartment elective lymph node excision in the staging and treatment of papillary thyroid cancer. Arch Otolaryngol Head Neck Surg 2006;132:650-4.
36. Lang BH, Tang AH, Wong KP, et al. Significance of size of lymph node metastasis on postsurgical stimulated thyroglobulin levels after prophylactic unilateral central neck dissection in papillary thyroid carcinoma. Ann Surg Oncol 2012;19:3472-8.
37. Bonnet S, Hartl D, Leboulleux S, et al. Prophylactic lymph node dissection for papillary thyroid cancer less than 2 cm: implications for radioiodine treatment. J Clin Endocrinol Metab 2009;94:1162-7.
38. Hartl DM, Leboulleux S, Al Ghuzlan A, et al. Optimization of staging of the neck with prophylactic central and lateral neck dissection for papillary thyroid carcinoma. Ann Surg 2012;255:777-83.
39. Sywak M, Cornford L, Roach P, et al. Routine ipsilateral level VI lymphadenectomy reduces postoperative thyroglobulin levels in papillary thyroid cancer. Surgery 2006;140:1000-5; discussion 1005-7.
40. Shen WT, Ogawa L, Ruan D, et al. Central neck lymph node dissection for papillary thyroid cancer: comparison of complication and recurrence rates in 295 initial dissections and reoperations. Arch Surg 2010;145:272-5.
41. Alvarado R, Sywak MS, Delbridge L, et al. Central lymph node dissection as a secondary procedure for papillary thyroid cancer: Is there added morbidity? Surgery 2009;145:514-8.
42. Schuff KG, Weber SM, Givi B, et al. Efficacy of nodal

dissection for treatment of persistent/recurrent papillary thyroid cancer. Laryngoscope 2008;118:768-75.
43. Roh JL, Kim JM, Park CI. Central compartment reoperation for recurrent/persistent differentiated thyroid cancer: patterns of recurrence, morbidity, and prediction of postoperative hypocalcemia. Ann Surg Oncol 2011;18:1312-8.
44. Clayman GL, Agarwal G, Edeiken BS, et al. Long-term outcome of comprehensive central compartment dissection in patients with recurrent/persistent papillary thyroid carcinoma. Thyroid 2011;21:1309-16.
45. Marshall CL, Lee JE, Xing Y, et al. Routine pre-operative ultrasonography for papillary thyroid cancer: effects on cervical recurrence. Surgery 2009;146:1063-72.
46. Steward DL. Update in utility of secondary node dissection for papillary thyroid cancer. J Clin Endocrinol Metab 2012;97:3393-8.
47. Al-Saif O, Farrar WB, Bloomston M, et al. Long-term efficacy of lymph node reoperation for persistent papillary thyroid cancer. J Clin Endocrinol Metab 2010;95:2187-94.
48. Mazzaferri EL, Doherty GM, Steward DL. The pros and cons of prophylactic central compartment lymph node dissection for papillary thyroid carcinoma. Thyroid 2009;19:683-9.
49. Chisholm EJ, Kulinskaya E, Tolley NS. Systematic review and meta-analysis of the adverse effects of thyroidectomy combined with central neck dissection as compared with thyroidectomy alone. Laryngoscope 2009;119:1135-9.
50. Giordano D, Valcavi R, Thompson GB, et al. Complications of central neck dissection in patients with papillary thyroid carcinoma: results of a study on 1087 patients and review of the literature. Thyroid 2012;22:911-7.
51. Kaplan EL, Salti GI, Roncella M, et al. History of the recurrent laryngeal nerve: from Galen to Lahey. World J Surg 2009;33:386-93.
52. Mitchell DM, Regan S, Cooley MR, et al. Long-term follow-up of patients with hypoparathyroidism. J Clin Endocrinol Metab 2012;97:4507-14.
53. Sitges-Serra A, Ruiz S, Girvent M, et al. Outcome of protracted hypoparathyroidism after total thyroidectomy. Br J Surg 2010;97:1687-95.
54. Singer S, Lincke T, Gamper E, et al. Quality of life in patients with thyroid cancer compared with the general population. Thyroid 2012;22:117-24.
55. Lee JI, Kim SH, Tan AH, et al. Decreased health-related quality of life in disease-free survivors of differentiated thyroid cancer in Korea. Health Qual Life Outcomes 2010;8:101.
56. Husson O, Haak HR, Mols F, et al. Development of a disease-specific health-related quality of life questionnaire (THYCA-QoL) for thyroid cancer survivors. Acta Oncol 2013;52:447-54.
57. Husson O, Haak HR, Buffart LM, et al. Health-related quality of life and disease specific symptoms in long-term thyroid cancer survivors: a study from the population-based PROFILES registry. Acta Oncol 2013;52:249-58.
58. Thyroid Carcinoma. 2nd ed. NCCN Guidelines; 2010:1-104. Available online: http://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf, accessed 25/8/2013
59. Association BT. Guidelines for the Management of Thyroid Cancer - British Thyroid Association - Google Books. 2007.
60. Pacini F, Schlumberger M, Dralle H, et al. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol 2006;154:787-803.
61. Pacini F, Castagna MG, Brilli L, et al. Differentiated thyroid cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2009;20 Suppl 4:143-6.
62. Takami H, Ito Y, Okamoto T, et al. Therapeutic strategy for differentiated thyroid carcinoma in Japan based on a newly established guideline managed by Japanese Society of Thyroid Surgeons and Japanese Association of Endocrine Surgeons. World J Surg 2011;35:111-21.
63. Stavrakis AI, Ituarte PH, Ko CY, et al. Surgeon volume as a predictor of outcomes in inpatient and outpatient endocrine surgery. Surgery 2007;142:887-99; discussion 887-99.
64. Enyioha C, Roman SA, Sosa JA. Central lymph node dissection in patients with papillary thyroid cancer: a population level analysis of 14,257 cases. Am J Surg 2013;205:655-61.
65. Lang BH, Yih PC, Shek TW, et al. Factors affecting the adequacy of lymph node yield in prophylactic unilateral central neck dissection for papillary thyroid carcinoma. J Surg Oncol 2012;106:966-71.
66. Shaha AR. Controversies about the central compartment in thyroid cancer. Editorial regarding the article "Clinical impact of cervical lymph node involvement and central neck dissection in patients with papillary thyroid carcinoma: a retrospective analysis of 368 cases" by Alexandre Bozec et al. Eur Arch Otorhinolaryngol 2011;268:1097-9.
67. Grodski S, Cornford L, Sywak M, et al. Routine level VI

lymph node dissection for papillary thyroid cancer: surgical technique. ANZ J Surg 2007;77:203-8.
68. Sosa JA, Bowman HM, Tielsch JM, et al. The importance of surgeon experience for clinical and economic outcomes from thyroidectomy. Ann Surg 1998;228:320-30.
69. Xing M, Haugen BR, Schlumberger M. Progress in molecular-based management of differentiated thyroid cancer. Lancet 2013;381:1058-69.
70. Alzahrani AS, Xing M. Impact of lymph node metastases identified on central neck dissection (CND) on the recurrence of papillary thyroid cancer: potential role of BRAFV600E mutation in defining CND. Endocr Relat Cancer 2013;20:13-22.
71. Howell GM, Nikiforova MN, Carty SE, et al. BRAF V600E mutation independently predicts central compartment lymph node metastasis in patients with papillary thyroid cancer. Ann Surg Oncol 2013;20:47-52.
72. Cunningham DK, Yao KA, Turner RR, et al. Sentinel lymph node biopsy for papillary thyroid cancer: 12 years of experience at a single institution. Ann Surg Oncol 2010;17:2970-5.

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Remote access thyroid surgery

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Abstract: Robot assisted thyroid surgery has been the latest advance in the evolution of thyroid surgery after endoscopy assisted procedures. The advantage of a superior field vision and technical advancements of robotic technology have permitted novel remote access (trans-axillary and retro-auricular) surgical approaches. Interestingly, several remote access surgical ports using robot surgical system and endoscopic technique have been customized to avoid the social stigma of a visible scar. Current literature has displayed their various advantages in terms of post-operative outcomes; however, the associated financial burden and also additional training and expertise necessary hinder its widespread adoption into endocrine surgery practices. These approaches offer excellent cosmesis, with a shorter learning curve and reduce discomfort to surgeons operating ergonomically through a robotic console. This review aims to provide details of various remote access techniques that are being offered for thyroid resection. Though these have been reported to be safe and feasible approaches for thyroid surgery, further evaluation for their efficacy still remains.

Keywords: Robotic-assisted; thyroidectomy; retro-auricular; trans-axillary; remote access; face-lift thyroidectomy

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Introduction

The adoption of remote access thyroid surgery; especially robot-assisted thyroidectomy, has gained popularity in recent times. Advancement in the use of ultrasound (US) and Doppler US for screening thyroid pathologies have resulted in an increased detection of thyroid nodules as well as thyroid cancer consequently increasing the number of thyroid surgeries performed. Conventionally, open thyroidectomy has been the treatment of choice, however, the visible neck scar is undesirable for many patients. With technical advancement, these procedures transitioned from conventional to video-assisted thyroidectomy and, lately, to robot-assisted approach for better cosmesis. Video-assisted endoscopic thyroidectomies were first pioneered by Miccolli *et al.* (1). Shortly after, Bellantone *et al.* reported the safety and feasibility of performing central and lateral lymph node dissections endoscopically (1,2). There have been several reports of remote access techniques for thyroidectomy utilizing surgical ports in several locations outside the neck including the anterior chest wall, post auricular-occipital area, axillary region and sub-clavicular region. Although it requires patience and a particularly sophisticated skill set, the axillary approach has been proved to be among the most feasible approaches. To facilitate the ease of remote access thyroid surgery, the application of robotic technology in thyroid surgery emerged to overcome some of the technical challenges associated with endoscopic remote-access thyroid surgery.

Since then many surgeons have advanced their experiences to robotic thyroid surgery in their current practice. This transition marked a hike by 30% from 2010 to 2011 (3). The two most common approaches that are currently seen in practice: (I) robotic-assisted trans-axillary; and (II) retro-auricular thyroidectomy using the Da Vinci Si surgical system (Intuitive Surgical, Sunnyvale, CA, USA). It was in earlier 2000's that the use of gasless endoscopic thyroidectomy was practiced using a transaxillary incision (4). However, the heavier robotic arms of the older Da Vinci robotic system made it difficult to utilize it in the deep and

narrow working space (4).

Different minimally invasive approaches to thyroid surgery

We will group these different remote access approaches into two: (I) the cervical/direct approaches; and (II) the extra-cervical/remote access approaches.

The cervical/direct approaches

These approaches involve placing a small incision in the anterior or lateral neck. Blunt dissection is used to create the operating space, and it is maintained either with low pressure CO_2 insufflation or by external skin retraction. Such approaches include:

Video-assisted central approach, gasless or MIVAT (minimally invasive video-assisted thyroidectomy)

A central incision above the sternal notch that is approximately one inch in size is made, which provides direct access to the thyroid bilaterally. It is highly recommended to have a two assisting surgeons: one to retract, and the other to hold the endoscope. The strap muscles are identified and separated at the midline and then elevated off the anterior and lateral surface of the thyroid gland with standard optics. Small retractors are then utilized to retract the strap muscles laterally and the upper pole of the thyroid gland medially. A 5 mm angled endoscope is then inserted directly into the incision. Blunt dissection of the pertinent cervical anatomy is performed under video-assisted control. Gentle dissection of the superior thyroid vascular pedicle is initiated along the long axis of these vessels. To free the medial aspect of the superior pole of the thyroid gland, the harmonic scalpel is used. If the pyramidal lobe is present, it's freed via lateral approach first then superiorly from its infra-hyoid tract. The inferior and lateral aspects of the thyroid gland are then mobilized and the middle thyroid vein is transected. The inferior parathyroid gland is then visualized and dissected laterally and maintained on its vascular supply. The thyroid gland is then extracted through the cervical incision and the isthmus and the ligament of berry are divided.

The main advantage of this approach is the direct access and small neck incision. There have been multiple published articles reporting less operative pain, better cosmesis, shorter hospital stay and the ability to perform these surgeries on outpatient basis (1,5). Furthermore, some surgeon would argue the safety and feasibility of such approach in patients with a nodule size >3 cm in diameter and >30 mL in volume (6).

Lateral endoscopic approach

A plane between the SCM and the carotid sheath laterally and the strap muscles medially is used. It needs to be mentioned that this approach is best used for unilateral lesions and revision cases.

Three to four ports are utilized during this procedure, a 10 mm optic port and two to three operating ports. The operating port is placed on the medial border of the sternocleidomastoid (SCM) muscle on the side of the lesion. This approach allows a direct access to the posterior aspect of the thyroid lobe. This eliminates the need for dissection of the strap muscles. CO_2 insufflation (~8 mmHg) is used to maintain the working space. The superior vascular pedicle is then divided with the harmonic scalpel and the recurrent laryngeal nerve (RLN) is identified and traced along its entire length. The superior and inferior parathyroid glands are identified and preserved and the inferior thyroid vessels are then divided. The ligament of berry is then divided and the specimen is extracted through the 1.5 cm incision for division of the isthmus.

Anterior endoscopic approach

This approach permits a bilateral dissection of the thyroid gland due to its utilization of a midline access. Four trocar sites are site are used for this approach. The first is for a 5 mm optical trocar, which is inserted just above the suprasternal notch. Two sites are used for 2 mm trocars each, and the fourth site is used for a 5 mm trocar all of which are placed at the superior medial border of the SCM muscle. All vital structures are identified and dissected using ultrasonic shears. The thyroid gland is then extracted through the superolateral trocar.

The extra-cervical/remote access approaches

These approaches require placing incisions outside the neck, requiring extensive dissection under the skin. The operating space is then maintained by either CO_2 insufflation or external retraction by specially designed skin retractors. Recently, the application of robotic technology to further assist the surgeon in accomplishing these techniques facilitated remote access thyroid surgery and helped avoid the need for insufflation. There are several advantages of robotic surgery that overlay endoscopic approach such as its high definition 3-dimensional camera

Table 1 Equipment needed for the robotic-assisted trans-axillary approach

Equipment	Manufacturer
The Da Vinci Si robot	Intuitive Surgical, Sunnyvale, CA, USA
The robotic instruments	
Pro grasp forceps	Intuitive Surgical, Sunnyvale, CA, USA
Maryland dissector	Intuitive Surgical, Sunnyvale, CA, USA
Harmonic scalpel	Ethicon, Cincinnati, OH, USA
The 30 degrees endoscope	Intuitive Surgical, Sunnyvale, CA, USA
Modified Chung retractor	Marina Medical, Sunrise, FL, USA
NIM endotracheal tube	Medtronic, Minneapolis, MI, USA
SSEP	Biotronic, Ann Arbor, Michigan, USA
Handheld recurrent laryngeal nerve stimulator	Nerveana, Ventura, CL, USA
Alexis wound protector/retractor	Applied Medical, Rancho Santa Margarita, CA, USA
Electrocautery with a short, regular and long tip	
Vascular DeBakey	
Army-navy retractors	
Right-angled retractors	
Breast lighted retractors	

NIM, nerve integrity monitor; SSEP, somatosensory evoked potentials.

Table 2 Equipment needed for the robotic-assisted retro-auricular approach

Equipment	Manufacturer
The da Vinci Si robot	Intuitive Surgical, Sunnyvale, CA, USA
The robotic instruments	
Maryland dissector	Intuitive Surgical, Sunnyvale, CA, USA
Harmonic scalpel	Ethicon, Cincinnati, OH, USA
The 30 degrees endoscope	Intuitive Surgical, Sunnyvale, CA, USA
A handheld recurrent laryngeal nerve stimulator	Nerveana, Ventura, CL, USA
NIM endotracheal tube	Medtronic, Minneapolis, MI, USA
Modified Chung retractor	Marina Medical, Sunrise, FL, USA
Greenberg retractor	Codman Greenberg, Tucson, AZ, USA

NIM, nerve integrity monitor.

system, greater freedom of motion, and multi-articulated tremor free endoscopic arms that facilitates surgeons to perform easier in a restricted narrow space favoring surgical completeness. Thus, the safety and efficacy of these approaches allow many head and neck surgeons to remove the thyroid gland with highly improved cosmetic outcomes (7-9). Despite its successful outcomes in resection of thyroid lesions, its financial burden and associated post-operative complications preclude its use by many surgeons.

The surgical robot is designed in such a way that allows the surgeon to facilitate retraction, surgical field vision, and provides two arms to operate, while still maintaining traction and counter-traction. The three robotic instruments (Maryland dissector, ProGrasp forceps and Harmonic curved shears) are utilized to orient thyroid tissue using a dual channeled camera system. The camera is placed through the axillary/retro-auricular incision using an endoscope with a 30-degree down orientation. Electrocautery, a vascular DeBakey forceps and various retractors (army-navy, right-angled and lighted breast retractors) are used to create and elevate a subcutaneous flap (*Tables 1*,*2*). This leads to a greater working space that allows the surgeon to operate

Table 3 Patient selection for robotic thyroidectomy

Absolute contraindications
Previous neck surgery or radiation
T3 thyroid cancer or any suspicious gross invasion
A large substernal or retropharyngeal goiter
Medullary thyroid cancer with need for concomitant lymph node dissection
Relative contraindications
Hashimoto thyroiditis
Grave's disease
Morbid obesity
Thyroid nodule >5 cm
Large goiters (thyroid volume >40 mL)
History of MIVAT
T2 well differentiated thyroid cancer.
Medical conditions that affect patient positioning (e.g., rotator cuff pathology and cervical spine disease)
Ideal patients
Indeterminate nodules
Unilateral thyroid lobectomy
BMI <30 kg/m^2
History of hypertrophic scar or keloid formation
A thyroid nodule <3 cm in largest diameter
Total thyroid volume <40 mL (after appropriate experience with thyroid lobectomy)

MIVAT, minimally invasive video-assisted thyroidectomy; PTC, papillary thyroid cancer.

with a superior field vision. Though the learning curve for novice surgeons showed excellent results, however, it is still essential to have a significant experience for this approach (10). Literature reports a significant reduction in console time after 40-50 cases (11,12).

Absence of a visible neck scar attracts patients, especially females, to opt for remote access procedures. However, it is essential to carefully select patients and adequate work up with physical examinations and screening imaging procedures are necessary when considering remote access approaches. Thyroid nodules should be properly assessed for size, location, laterality, and presence of metastatic lymph nodes. Patient's preferences in order to achieve favorable scar should be properly addressed. The location, length, design and healing assess the overall quality of the surgery. *Table 3* outlines various guidelines that are necessary for its safe implementations (*Table 3*). Ideal candidates for robot-assisted thyroidectomy are (I) small or average body

Figure 1 Patient is positioned supine under general anesthesia and intubated with an NIM endotracheal tube.

habitus (body mass index <30 kg/m^2) young patients, with history of keloid or hypertrophic scar formation or do not desire a visible neck scar. It is crucial to conserve the selection criteria, primarily, during the beginning of the surgeon's learning curve. However, our group has reported successful outcomes for the trans-axillary approach with 60% of our patients being overweight or obese with a thyroid nodule size of 2.5 cm (7).

Trans-axillary approach

Patient positioning

Patient is placed supine under general anesthesia with arm and shoulder placed at the same vertical height. The neck is slightly extended. Adequate padding of the forearm and elbow is required to prevent nerve stretch. Intubation with a NIM endotracheal tube (Medtronic Xomed, Jacksonville, FL, USA) is used to allow intraoperative RLN monitoring (*Figure 1*). The arm of the lesion side is placed in a cephalad position and flexed above the head (Modified Ikeda's arm position). In the case of a total thyroidectomy, arm ipsilateral to the larger lobe of the thyroid is positioned for incision. One should note that patients with disabled cervical or shoulder range of motion are not ideal candidate for this approach. Additionally, median and ulnar nerves (*Figure 2*) are routinely monitored using somatosensory evoked potentials (SSEP) (Biotronic, Ann Arbor, MI, USA). The SSEP had not been universally adopted by surgeons performing these approaches. Instead, the ipsilateral arm is careful positioned and fixed on an arm board to manage shortest distance from axilla to thyroid bed. However, this,

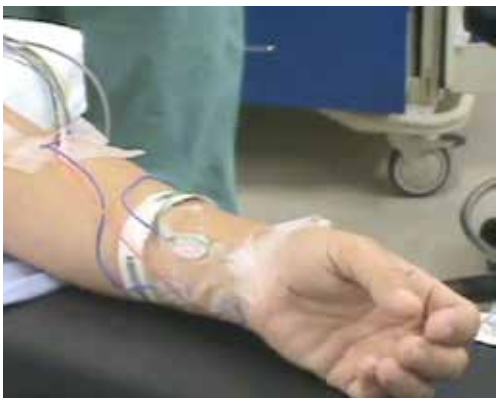

Figure 2 Ulnar and median nerves are routinely monitored using Somatosensory evoked potentials (SSEP).

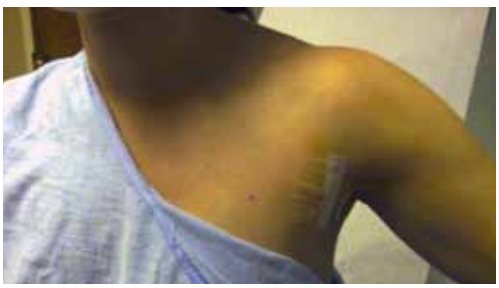

Figure 3 Trans-axillary incision postoperatively.

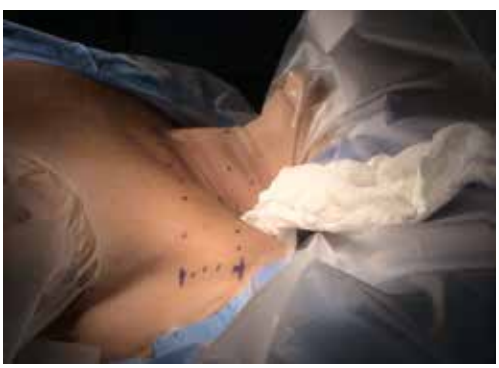

Figure 4 Landmarks for the robotic trans-axillary incisions.

in our opinion results in increasing the distance to dissect the thyroid bed.

Chung and colleagues described another arm position by rotating the ipsilateral arm to the lesion to 180 degrees cephalad, padding and then placing it on the board. However, this was not very well accepted by many patients in western population. It is a general practice by many robotic surgeons to perform an intraoperative US examination prior to skin incision. This aids in localizing the thyroid lesion and examine the relationship of the surrounding structures to the thyroid gland in the dissecting plane.

Skin incision

A transverse line is drawn between the sternal notch and axilla to mark the inferior limit of the incision that is directed posteriorly to ensure the incision will be hidden. *Figure 3* displays a well-hidden incision in the axillary fold (*Figure 3*). A 60-degree oblique line is drawn from the thyrohyoid membrane to the axilla (*Figure 4*) to determine the superior limit of the incision. 10 mL of 1% lidocaine with 1 in 200,000 adrenaline is infiltrated. A 5-6 cm vertical incision is made intersecting the oblique line and the anterior axillary line as the superior limit. The intersection of the transverse line with the anterior axillary line defines its inferior limit. Every attempt should be made to reduce cicatrix hypertrophy by proper handling of the skin. It is recommended to use a breast fold trocar for an easier operative technique for surgeons in learning process. A newer approach of robotic procedure requires two-incision technique. In addition to above, a single anterior chest 0.6-0.8 cm skin incision in the medial fold of the breast on the lesion side is made (13). A trocar is then used with one of the robotic arms docked to the cannula that assists in the manipulation, retraction and dissection of the thyroid gland.

In the setting of performing the procedure with CO_2 insufflation, three 5 mm incisions are placed below the anterior axillary line equidistant apart or one 30 mm incision is made for a 12 and 5 mm trocar, apart from the third trocar (5 mm). A modification of this approach has also been described using a second incision inferior to the axillary incision for the placement of the fourth arm for retraction. This inferior based access port can later be used as a site for surgical drain placement. This modification allows easier placement of a fourth arm while not creating an visible anterior chest wall incision; especially relevant for surgeons transitioning from a two incision to single incision trans-axillary approach (14).

Creating a working space

Using the monopolar electrocautery, a subcutaneous flap is prepared for dissection to create the subplatysmal plane anterior to the pectoralis fascia up to the clavicle. A wound protector (Alexis wound retractor system from Applied Medical, CA, USA) is used to protect the axillary wound edges from burns of electrocautery or the harmonic scalpel. Retractors are used to maintain a direct vision of

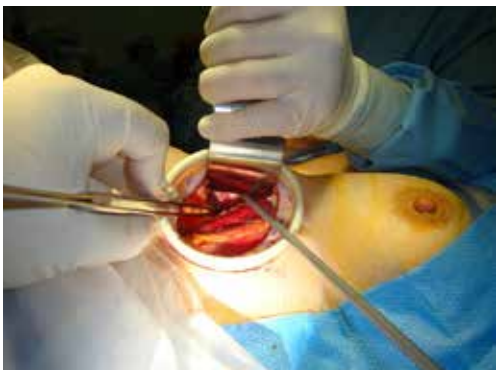

Figure 5 Subcutaneous plane is developed superficial to the pectoralis major muscle fascia and the heads of the SCM are identified (The plane can be developed using electrocautery or ultrasonic harmonic scalpel).

Figure 6 Retractor used for the trans-axillary approach.

dissection area using extended-tip bovie for deeper sections. Following clavicle identification, the 2-heads of the SCM muscle are dissected through (*Figure 5*) creating a wide access to the midline of the neck through the axilla. This could be challenging in the patients with large fad pad around neck such as in obese population. The assistant is, then, instructed to pull the skin away from the tunnel so as to avoid development of "buttonholes" into the skin. When using the lightened skin retractor, dissection should be carried out deep and lateral to the retractor, thus, minimizing risk of skin injury. The working space is defined by the clavicular head to just above the omohyoid muscle that correlates with the superior pole of the thyroid lobe. The sternothyroid muscle is approached through the small window between the sternal head of the SCM (medially) and the clavicular head of the SCM (laterally). The thyroid lobe is located under the strenothyroid muscle. Dissection of the uppermost fibers of sternothyroid muscle is carried out to reach the superior pole of the gland. The harmonic scalpel then creates an adequate space between the two heads of the SCM. Using Chung retractor the strap muscles are lifted anteriorly to create a working space exposing the anterior surface of the thyroid gland (*Figure 6*). After the Chung retractor is placed, the anesthesiologist should confirm adequate padding of the neck and shoulders. According to surgeon's preference, the two-incision technique is opted at this point. It should be noted that the placement of the chest wall trocar after the retractor apparatus confirms proper positioning of the chest wall retractor below the Chung retractor. Conversely, it would prevent the entry of the chest wall retractor under the Chung retractor.

For CO_2 insufflation, a flexible laparoscope with carbon dioxide insufflation at 4-9 mmHg pressure is introduced before starting sharp dissection to dissect an avascular plane between the platysma and the pectoralis major muscle. Next the plane between the SCM muscle and the sternohyoid muscle is developed to elevate the steronothyroid muscle and allow retraction anteriorly, exposing the ipsilateral thyroid gland.

Docking stage

After insertion of robotic arms through axillary skin incisions, the Da Vinci model Si robot (Intuitive, Sunnyvale, CA, USA) is docked at the contralateral side of the operative field. Three robotic arms, the 30-degree down looking endoscope, the harmonic scalpel and the Maryland forceps, are inserted through the axillary incision. The Harmonic curved shears are placed in the robotic arm that corresponds to the surgeons' dominant arm. Because harmonic scalpel does not provide freedom of motion, it can also be moved between the other robotic arms to improve visualization. Recent introduction of a vessel sealer, larger than the harmonic scalpel, with wristed movements has been utilized. It is necessary to maintain a distance between Maryland dissector and the Harmonic scalpel to avoid risk of possible collision between the two robotic arms. The 30 degrees endoscope is then place in a downward view angle onto the thyroid bed.

Surgical resection of thyroid gland

Retraction of thyroid gland is carried out using the ProGrasp retractor (*Figure 7*). The middle thyroid vein is, then, divided using the Harmonic scalpel. The superior pole of the thyroid gland is pulled into medio-inferior direction using the ProGrasp forceps, and the superior thyroid vessels are ligated individually using the Harmonic curved shears. Special attention should be paid to ligate all the vessels

close to the thyroid gland to avoid any injury to the external branch of the superior laryngeal nerve. The thyroid gland is carefully and gradually dissected from the cricopharyngeal and cricothyroid muscles (CTMs). Dissection of the superior pole is continued until the superior parathyroid gland is exposed and released. Dissection of RLN near the inferior thyroid pedicle in tracheoesophageal groove is then carried out to reduce any risk of injury to anatomical structure. Traction in the tracheoesophageal groove can facilitate easy identification of the RLN, cranially. To assure functional integrity of the nerve, it is recommended to perform intraoperative nerve stimulation using RLN stimulator (Nerveana, Ventura, CA, USA) that is introduced through the incision (*Figure 8*).

Hemostasis is achieved by Harmonic scalpel by sealing the branches of inferior thyroid artery. However, it is extremely important to allow 3-5 seconds to elapse before the instrument gets activated as it may lead to burn injury due to its increased temperature (80 to 100 ℃) during activation. After dissection of the gland, the isthmus is then divided using the Harmonic scalpel, and the resected thyroid lobe is removed through the incision. For patients being operated for carcinoma, the resected lobe is removed in an endo-catch bag to avoid tumor spillage. Closure is facilitated in a standard fashion with the placement of a surgical drain.

Figure 7 Thyroid is retracted medially using the ProGrasp forceps.

Robotic retro-auricular thyroid surgery

The retro-auricular approach is advantageous over the trans-axillary approach in several ways such as (I) easier positioning of the patient; (II) shorter distance to the thyroid gland, hence, less dissection leading to faster wound healing (15); (III) eliminating risk of brachial plexus paralysis; and (IV) easier flap elevation in obese patients (4). Walvekar *et al*. first described the feasibility of retro-auricular thyroidectomy approach with endoscopic assistance in a cadaveric model in 2010 (16). The authors mentioned the value of incorporation of robotic technology to be of advantage with this approach. Terris *et al*. first reported the clinical feasibility and application of robotic technology to a retro auricular approach and described as well as reported early experiences with robotic facelift thyroidectomy in 2011 (17). Terris and Singer favored a superior to inferior approach to the thyroid gland over a series of trans-axillary methods (18). Using an insufflation technique, this technique has been combined with the axillary approach to access the thyroid space (19). Interestingly, Terris's hybrid technique, has made it possible to integrate the facelift parathyroidectomy incision (19), the Chung gasless robotic thyroidectomy (20), with the implementation of intra-operative laryngeal nerve monitoring.

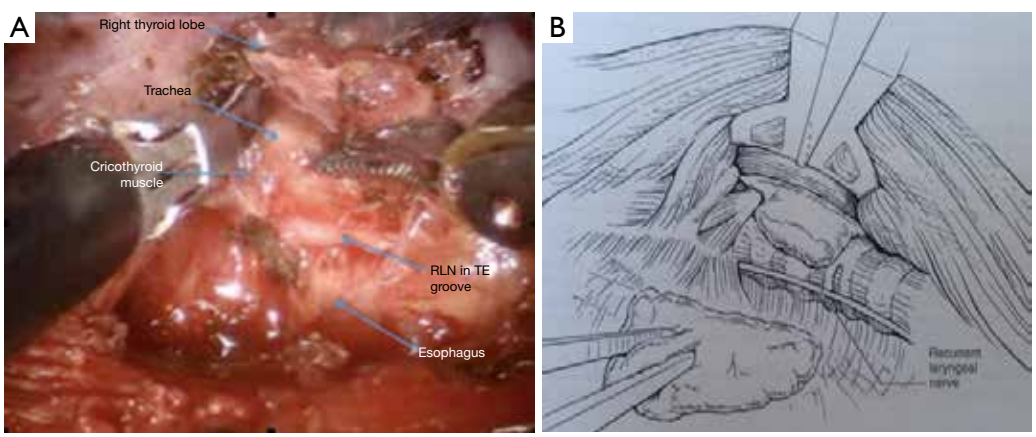

Figure 8 Identification of the recurrent laryngeal nerve (RLN) in the tracheosophageal groove.

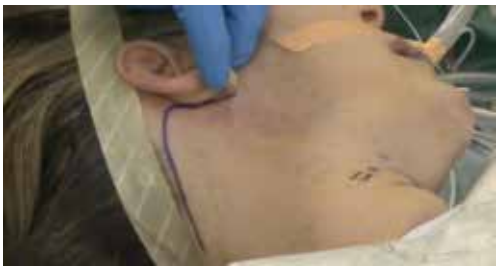

Figure 9 Retro-auricular marking posterior to the ear lobe and adjacent to the occipital hairline.

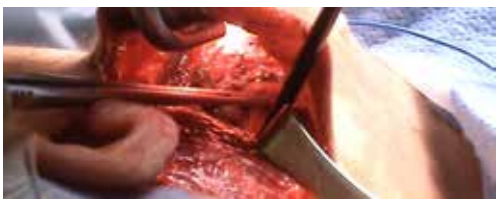

Figure 10 Flap creation superficial to the platysma.

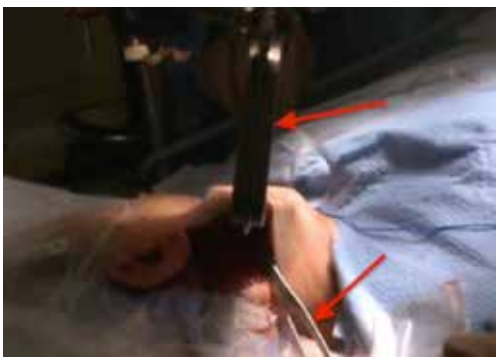

Figure 11 Special retractor placed under sternocleidomastoid (SCM) muscle and the strap muscles to allow continuous exposure to the surgical field.

Figure 12 Da Vinci Si docking using the 30° scope, Maryland dissector and a harmonic scalpel.

Patient positioning

Under general anesthesia, the patient is placed on the operating room table in supine position. Intubation is carried out using a NIM endotracheal tube size 6.0 (Medtronic Xomed, Jacksonville, FL, USA) to allow intraoperative RLN monitoring.

Skin preparation and incision

The post-auricular area is cleanly shaved to mark the planned incision lines into the hair-bearing skin. The incision then is placed into post-auricular crease extending to the occipital hairline. The incision is descended 1 cm at a position that is obscured by ear and hair at rest completely (*Figure 9*).

Creating a working space

A subcutaneous flap superficial to the platysma is created using a Metzenbaum scissor and preserving the greater auricular nerve (*Figure 10*). Dissection is continued in the plane superficial to the platysma is till the head of the SCM muscle. The window between the two heads (sternal and clavicular heads) of the SCM muscle is identified and a working space is created using harmonic scalpel (Ethicon, Somerville, NJ). The strap muscles are identified and reflected medially to clearly expose the upper pole of thyroid gland. A modified Chung retractor (Marina Medical, Sunrise, FL, USA) is used to secure the operative pocket by placed it under the sternal head of the SCM muscle while continuing the dissection of strap muscles to allow exposure of the surgical field, and expanding the access to the parathyroid gland (*Figure 11*). It takes approximately 30 minutes to create a subcutaneous flap.

Docking stage

The Da Vinci Si system (Intuitive Surgical, Inc., Sunnyvale, CA, USA) is docked at the contralateral side. The robotic arms are inserted through the incision (*Figure 12*). The endoscope is positioned centrally, a Maryland grasper is placed in the non-dominant hand, and the Harmonic is placed in the dominant hand. At this time, nerve dissection is performed at the cricothyroid membrane entrance, and integrity is confirmed by stimulation of the nerve just proximal to the inferior margins of the inferior constrictor muscle. It takes seven minutes to dock the robot. Dissection of the thyroid gland is performed as described above in the transaxillary approach.

Breast approach

This approach allows for bilateral dissection of both thyroid

lobes. A trocar size range from 10-15 mm ports are inserted on both of the upper circumareolar areas of the breast. CO_2 insufflation up to a pressure of 6 mmHg is used to establish the working space. This technique has two different approaches:

(I) The axilo-bilateral breast approach (ABBA), which utilizes a third port inserted in the axilla, which allows for specimen extraction. A 5 mm harmonic scalpel is inserted in the left breast, while an optical trocar is inserted in the right breast. To achieve good exposure, the ipsilateral strap muscles are divided. The gland is then removed through the axillary incision;

(II) A bilateral axillo-breast approach (BABA) has also been developed to obtain optimal visualization of both lobes. With insertion of the third and the fourth port in the left and right axilla, a total thyroidectomy is possible with this approach. With introduction of the da Vinci surgical system, BABA endoscopic thyroidectomy was combined with robotic thyroid surgery in 2008. This allowed better visualization of critical structures such as the parathyroid glands, RLNs and superior and inferior thyroidal vessels.

Chest wall approach

It's also known as the subclavicular approach. This approach has been developed and commonly used in Asia. It's a favored approach for bilateral thyroid resection. A 30 mm skin incision is made below the inferior border of the clavicle ipsilateral to the lesion or the larger lobe is made. Next is retracting the myocutaneous flap above the pectoralis major muscle. A blunt instrument or an endoscopic dissector is used for the initial blunt dissection. A 12 mm trocar is introduced for a flexible laparoscope. To maintain the working space, CO_2 insufflation to a pressure of 4 mmHg is performed or the use of specially designed lifting devices. Two additional trocars are introduced, one 5 mm trocar is inserted inferior to the sternal notch and the other 5 mm is inserted below the ipsilateral clavicle. The strap muscles are then divided to improve exposure and dissection of the thyroid is performed with the use of ultrasonic shears. The thyroid gland is then extracted through a 30 mm incision, leaving no scar in the neck.

Experimental transoral video-assisted or robotic approaches

A German group reported transoral video-assisted thyroidectomy in a small series. This approach utilizes a 10 mm sublingual sagittal incision. Dissection through the floor of the mouth musculature to the subplatysmal plane is performed. Then carbon dioxide insufflation, followed by bilateral 10 mm vestibular incisions lateral to each mandibular canine is made. We have recently reported the addition of robotic technology to this approach in human cadavers. However, this is still considered as an experimental technique with a significantly reported conversion rate and complications. Robotic transoral periosteal thyroidectomy (TOPOT) is another trans-oral technique described in cadavers that uses sub-periosteal port placement with robot assistance to facilitate a midline access for thyroidectomy (21).

Potential complications and their management

Various concerns have arisen regarding post-operative outcomes and complications associated with robotic procedure. Therefore, it becomes crucial to adequately assess these new technologies before integrating into standard practice. At rare instances, there may arise a possibility of conversion to an open procedure, thus, should always be discussed with patients prior to undergoing surgery. Thyroidectomy via every approach accounts for the following complications:

Hypo-parathyroidism

Due to inadvertent injury to parathyroid glands, transient hypocalcemia is observed in 5-50% while permanent hypocalcemia (hypocalcemia >6 months) between 0.5-2%. Careful identification of parathyroid glands should be carried out in order to prevent ischemic injury of the glands. Patients should be warned about the presenting symptoms of hypocalcemia such as numbness, tingling, carpopedal spasm, seizures and changes in Electrocardiogram (EKG). Post-operative supplementation of calcium (oral/intravenous) is the mainstay of treatment in these patients. The dosage of oral calcium supplementation is adjusted according to serum calcium levels. If hypocalcemia persists despite receiving 2 grams of oral calcium, additional dose of 0.25-1 mcg/day calcitriol supplementation should be considered. Patients with severe hypocalcemic symptoms or refractory to oral supplementation require intravenous calcium supplementation. The American Thyroid Association guidelines on outpatient thyroidectomy require patients to be discharged with calcium, vitamin D and calcitriol supplementation if necessary (22).

Injury to the RLN

The transient and permanent injury to RLN has been reported by various studies. The rate of transient RLN palsy be 3-8% while permanent palsies (lasting more than 12 months) between 0.3-3% of cases (23). Post-operatively, patients are followed up for development of symptoms such as hoarseness, aspiration, and dysphagia. However, bilateral cord paralysis present with respiratory distress followed by immediate airway obstruction.

The patients referred to our institution are screened with a pre-and a post-operative vocal cord evaluation using a flexible laryngoscopy. This confirms the position, mobility, and functionality of the vocal cords. Patients with suspected bilateral vocal cord paralysis might require an urgent airway management with the possibility of definitive management with a tracheostomy. Therefore, utmost care is taken to prevent any intra-op injury to RLN. A standard practice to integrate visual identification and use Intraoperative Nerve Monitoring is recommended for all thyroidectomy cases.

Injury to the superior laryngeal nerve

The injury to the two branches of the superior laryngeal nerve, the external and internal branches, can go unnoticed during these surgeries. Therefore, identification and safety of these nerves are of paramount importance. The external branch innervates the CTM and the internal branch provides sensory innervation to the larynx. It has been reported that injury to these nerves are encountered in 58% of the cases (24). Symptoms such as hoarseness, vocal fatigue, and loss of high-pitched sounds may be present in the patients. Videostroboscopy and laryngeal electromyography (EMG) evaluate the affected vocal cord, which is seen to be lower than the normal cord on examination. Therefore, it is essential for surgeons to incorporate intraoperative nerve monitoring.

Neck hematoma

Approximately 1% of patients suffer neck hematoma. Though life-threatening, this can be prevented by achieving adequate hemostasis (24). Patients with suspected hematoma present with asphyxiation, airway compromise leading to re-exploration of the neck. In rare cases, immediate evacuation may be required. Surgeons are recommended to perform valsalva maneuver to minimize the risk of bleeding before closure of incision. A drain should be placed post-operatively to further reduce chances of imminent hematoma.

Infection

As any surgical procedure, the risk of infection cannot be neglected. However, there has been a significant reduction (1-2%) in reported cases of sepsis due to the advanced technology and sterilized instruments (25). Presenting signs of wound infection such as fever, cellulitis with warmth, erythema, and tenderness around incision site, superficial abscess, and leukocytosis should be looked for. Once abscess develops, these need to be drained and aspirated to send for culture. Broad-spectrum antibiotics (e.g., clindamycin, cefuroxime, ampicillin-sulbactam) are started until definitive culture results are available. Patients presenting with superficial cellulitis require antibiotic coverage for gram-positive organisms (e.g., streptococci and staphylococci). CT-guided imaging is considered preeminent for evaluation of deep abscesses in the neck. It is essential to follow the guidelines published by Infectious Disease Society of America (IDSA) on prevention of such infections following surgery.

Brachial plexus neuropraxia

Ikeda *et al*. describes that careful positioning of arm of lesion side prevents injury to brachial plexus during surgery (26). Diagnosis of injury to brachial plexus can be confirmed by EMG. Detection and prevention of positional related neuropathy involves SSEP (11,15). Neuropraxia of brachial plexus presents with diminished reflexes, sensory and motor deficits of the arm. Most of the patients resume function spontaneously, while, others require orthosis/splinting; physical/occupational therapy. Surgery is reserved for refractory cases.

It is important to perform the neck dissection with paying careful attention to the underlying neurovascular structures, while maintaining a complete cancer resection.

Our group has reported its safety and feasibility in a subset of patients with grave's disease, those having small-sized substernal goiters (27). We have also reported its safety and similar outcomes for postoperative complications when compared to conventional cervical thyroidectomy (9,28). Robotic thyroidectomy has shown same-day discharges in 83.2% of cases while conventional approach shows that in 34.5% (28). However, FDA restrictions have caused a number of North American surgeons to evade the

use of the robot-assisted approach.

Conclusions

Robotic surgery has enhanced the surgeon's capabilities in a very short period of time. We have successfully reported the safety and feasibility of robotic thyroidectomy in management patients with benign and malignant thyroid diseases, as well as in patients with grave's disease who don't have large substernal goiters. We have also reported no difference in postoperative complications in patients undergoing robotic thyroidectomy when compared to patients who underwent the conventional cervical approach. Robotic thyroidectomy has been shown to have 83.2% discharge rate on the same day of the procedure, compared to 34.5% in the conventional cervical approach. In spite of studies showing comparable outcomes, the adoption of robot assisted thyroid surgery has been measured in North American. There may be several reasons for this such as the additional training, cost, time associated with achieving proficiency in these techniques. Also, the current FDA restrictions on robot assisted thyroid surgery limit the opportunity for proctored learning and consequently rapid adoption of these techniques.

The future of robotic thyroid surgery and whether it is more widely adopted lies in the ability to standardize care that reliably establishes safe and high quality outcomes that are at least comparable to those achieved with traditional thyroidectomy. Until then, the concept of "do no harm" must be entertained, especially during the learning curve period of these techniques. A balanced investigation and a thorough data analysis are warranted to fully explore the advantages and the disadvantages of this new merging technology by multi-institutional clinical trials and maintaining a data registry.

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References

1. Miccoli P, Bellantone R, Mourad M, et al. Minimally invasive video-assisted thyroidectomy: multiinstitutional experience. World J Surg 2002;26:972-5.
2. Bellantone R, Lombardi CP, Raffaelli M, et al. Central neck lymph node removal during minimally invasive video-assisted thyroidectomy for thyroid carcinoma: a feasible and safe procedure. J Laparoendosc Adv Surg Tech A 2002;12:181-5.
3. Abdelgadir Adam M, Speicher P, Pura J, et al. Robotic thyroidectomy for cancer in the US: patterns of use and short-term outcomes. Ann Surg Oncol 2014;21:3859-64.
4. Kang SW, Jeong JJ, Yun JS, et al. Gasless endoscopic thyroidectomy using trans-axillary approach; surgical outcome of 581 patients. Endocr J 2009;56:361-9.
5. Ruggieri M, Straniero A, Pacini FM, et al. Video-assisted surgery of the thyroid diseases. Eur Rev Med Pharmacol Sci 2003;7:91-6.
6. Lombardi CP, Raffaelli M, Princi P, et al. Video-assisted thyroidectomy: report on the experience of a single center in more than four hundred cases. World J Surg 2006;30:794-800; discussion 801.
7. Kandil EH, Noureldine SI, Yao L, et al. Robotic transaxillary thyroidectomy: an examination of the first one hundred cases. J Am Coll Surg 2012;214:558-64; discussion 564-6.
8. Noureldine SI, Jackson NR, Tufano RP, et al. A comparative North American experience of robotic thyroidectomy in a thyroid cancer population. Langenbecks Arch Surg 2013;398:1069-74.
9. Noureldine SI, Lewing N, Tufano RP, et al. The role of the robotic-assisted transaxillary gasless approach for the removal of parathyroid adenomas. ORL J Otorhinolaryngol Relat Spec 2014;76:19-24.
10. Park JH, Lee J, Hakim NA, et al. Robotic thyroidectomy learning curve for beginning surgeons with little or no experience of endoscopic surgery. Head Neck 2014. [Epub ahead of print].
11. Landry CS, Grubbs EG, Perrier ND. Bilateral robotic-assisted transaxillary surgery. Arch Surg 2010;145:717-20.
12. Katz L, Abdel Khalek M, Crawford B, et al. Robotic-assisted transaxillary parathyroidectomy of an atypical adenoma. Minim Invasive Ther Allied Technol 2012;21:201-5.
13. Lee S, Ryu HR, Park JH, et al. Early surgical outcomes comparison between robotic and conventional open thyroid surgery for papillary thyroid microcarcinoma. Surgery 2012;151:724-30.
14. Wilson MN. Modification of two-incision trans-axillary robotic thyroidectomy. J Robot Surg 2014;8:325-327.
15. Berber E, Siperstein A. Robotic transaxillary total thyroidectomy using a unilateral approach. Surg Laparosc Endosc Percutan Tech 2011;21:207-10.
16. Walvekar RR, Wallace E, Bergeron B, et al. Retro-auricular video-assisted "gasless" thyroidectomy: feasibility

study in human cadavers. Surg Endosc 2010;24:2895-9.
17. Terris DJ, Singer MC, Seybt MW. Robotic facelift thyroidectomy: II. Clinical feasibility and safety. Laryngoscope 2011;121:1636-41.
18. Terris DJ, Singer MC. Robotic facelift thyroidectomy: Facilitating remote access surgery. Head Neck 2012;34:746-7.
19. Perrier ND, Randolph GW, Inabnet WB, et al. Robotic thyroidectomy: a framework for new technology assessment and safe implementation. Thyroid 2010;20:1327-32.
20. Park JH, Lee CR, Park S, et al. Initial experience with robotic gasless transaxillary thyroidectomy for the management of graves disease: comparison of conventional open versus robotic thyroidectomy. Surg Laparosc Endosc Percutan Tech 2013;23:e173-7.
21. Lee HY, Richmon JD, Walvekar RR, et al. Robotic transoral periosteal thyroidectomy (TOPOT): experience in two cadavers. J Laparoendosc Adv Surg Tech A 2015;25:139-42.
22. Terris DJ, Snyder S, Carneiro-Pla D, et al. American Thyroid Association statement on outpatient thyroidectomy. Thyroid 2013;23:1193-202.
23. Jeannon JP, Orabi AA, Bruch GA, et al. Diagnosis of recurrent laryngeal nerve palsy after thyroidectomy: a systematic review. Int J Clin Pract 2009;63:624-9.
24. Jansson S, Tisell LE, Hagne I, et al. Partial superior laryngeal nerve (SLN) lesions before and after thyroid surgery. World J Surg 1988;12:522-7.
25. Watkinson JC. Fifteen years' experience in thyroid surgery. Ann R Coll Surg Engl 2010;92:541-7.
26. Ikeda Y, Takami H, Niimi M, et al. Endoscopic thyroidectomy and parathyroidectomy by the axillary approach. A preliminary report. Surg Endosc 2002;16:92-5.
27. Jackson NR, Yao L, Tufano RP, et al. Safety of robotic thyroidectomy approaches: meta-analysis and systematic review. Head Neck 2014;36:137-43.
28. Noureldine SI, Abdelghani R, Saeed A, et al. Is robotic hemithyroidectomy comparable to its conventional counterpart? Surgery 2013;154:363-8.

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Transoral robotic thyroid surgery

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Abstract: There is currently significant demand for minimally invasive thyroid surgery; however the majority of proposed surgical approaches necessitate a compromise between minimal tissue dissection with a visible cervical scar or extensive tissue dissection with a remote, hidden scar. The development of transoral endoscopic thyroid surgery however provides an approach which is truly minimally invasive, as it conceals the incision within the oral cavity without significantly increasing the amount of required dissection. The transoral endoscopic approach however presents multiple technical challenges, which could be overcome with the incorporation of a robotic operating system. This manuscript summarizes the literature on the feasibility and current clinical experience with transoral robotic thyroid surgery.

Keywords: Transoral; robotic; minimally invasive; endoscopic; thyroidectomy; thyroid surgery

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Introduction

Surgical management of thyroid disease has undergone radical changes over the last century. Once feared, with a high mortality rate, thyroidectomies are now a routine procedure with more than 80,000 undertaken in the United States annually (1). As described by Kocher in the late 1880s, most cases are performed through a transcervical approach, which results in scarring that some patients find unsightly and difficult to conceal (2). Given the current epidemic of thyroid disease diagnosis and the young age of these patients, there is significant demand for minimally invasive surgery (3). Robotic transoral thyroid surgery provides an exciting minimally invasive alternative to the current transcervical approach to the thyroid gland.

History

To be considered minimally invasive, a procedure should be safe, respect surgical planes, minimize surgical trauma, tissue dissection, and avoid scarring (4,5). Since 1997, approximately 20 different thyroidectomy techniques have been proposed as minimally invasive alternatives to conventional transcervical thyroidectomies (4,6). These approaches, however, necessitate a compromise between minimal tissue dissection with a visible cervical scar and extensive tissue dissection with a remote, hidden scar. In 2007, Witzel *et al.* published a report where the feasibility of performing transoral endoscopic thyroid surgery was demonstrated in human cadavers and a porcine model was developed. In this natural orifice transluminal endoscopic surgical (NOTES) approach, the thyroid is accessed in the subplatysmal plane in the submental region through an incision made in the floor of the mouth (7). The advantages of this approach is the concealment of the incision within the floor of the mouth without significantly increasing the amount of required dissection and access to both sides of the neck. Since the publication of this proof of concept, there have been multiple reports in the literature on the use of transoral endoscopic thyroid surgery and different approaches to the thyroid gland in cadaver and porcine models. The first clinical use of transoral endoscopic thyroid surgery was reported by Wilhelm *et al.* (8). In this series of eight patients, there was a conversion rate of 38% and permanent recurrent laryngeal nerve injury in 13%. Subsequently, two small case series have been published on the clinical use of transoral

endoscopic thyroid surgery. Nakajo *et al*. reports a case series of eight patients who underwent transoral endoscopic thyroid surgery; although, in this method, two Kirschner wires were inserted through the cervical skin for retraction (9). The average time for a simple hemithyroidectomy (five patients) was 208 minutes and for subtotal thyroidectomy with central node dissection (three patients), 361 minutes. All patients had "sensory disorder" around the chin which persisted for more than six months. One patient developed a laryngeal palsy but no patient had mental nerve palsy. There were no reported postoperative infections. Woo reports on the use of transoral endoscopic thyroid surgery in a patient with papillary thyroid micro-carcinoma (10). This procedure did not require any incision in the neck and was performed in 120 minutes. There were no reported complications and the patient remained disease free with 12 months of follow-up. Although transoral endoscopic thyroid surgery provides a remarkably direct and minimally invasive approach to the thyroid gland, the high rate of reported complications is concerning for the safety of the approach. Furthermore, current technology limits surgeons to non-wristed instruments and requires manual control of the endoscope whilst performing dissection. This results in greater tissue strain and manipulation due to the long fulcrum of the rigid endoscopic instruments and the need to simultaneously manage multiple tasks whilst performing dissection, increasing the complexity and required learning curve for the procedure (4).

In 2010, Richmon *et al*. proposed modifying the transoral endoscopic thyroid surgery approach by incorporating a robotic operating system (4). The use of robots in remote thyroid surgery is not novel and has since been demonstrated to be safe and to provide oncologic outcomes that are equivalent to open thyroidectomy with improved cosmesis, patient satisfaction and quality of life (2). Currently the da Vinci system is the only Food and Drug Administration (FDA)-approved robotic system for surgery in humans (3). The system provides a high-resolution, 3-dimentional image, which provides the surgeon with both depth perception and high magnification which aids with tissue handling, and identification of structures such as the recurrent laryngeal nerve and parathyroid glands. The system has wristed instruments, tremor filtration and precise robotic movement which allows for a degree of control and accuracy currently not available with endoscopic equipment. These characteristics lend themselves to a transoral approach to the thyroid gland and overcome limitations seen with the video-assisted approach.

Surgical technique

Richmon *et al*. conducted a feasibility study for robotic transoral thyroid surgery in two cadavers (4). In this model, a 1.5-cm incision was made along the lingual frenulum just posterior to the mandible. The midline raphe between the genioglossus muscle was bluntly divided under direct visualization and the dissection was continued between the geniohyoid and mylohyoid muscle until the subplatysmal plane was identified and a subplatysmal pocket was created. Two 1.5-cm incisions were placed in the gingival-buccal sulcus at the level of the first molar to avoid the mental nerve, and blunt dissection was undertaken. These two pockets were connected with the submental pocket already created. The da Vinci system was then brought in and a 0 degree endoscope was advanced through the midline incision and into the submental, subplatysmal pocket. A Maryland dissector was placed through the left gingival-buccal incision and a bipolar forceps through the right gingival-buccal incision. Under endoscopic visualization, these instruments were used to dissect down to the level of the thyroid cartilage notch, where the strap muscles were identified and the midline raphe divided to expose the thyroid gland. Part of the superior and medial insertion of the sternothyroid muscle on the thyroid cartilage was divided to facilitate exposure. The overlying skin had to be manually elevated by an assistant to maintain the working space, as a seal could not be created to maintain CO_2 pressure. The superior lobe of the right thyroid gland was grasped and retracted inferomedially, this was continued until the superior vascular pedicle was identified and cauterized. The recurrent laryngeal nerve was then identified at its entry point and traced inferiorly using gentle blunt dissection. The gland was then retracted further medially, allowing for a capsular dissection. The isthmus was divided and the lobe was freed entirely. The left thyroid lobe was removed in a similar fashion and both lobes were delivered through the midline incision of the floor of the mouth. Richmon *et al*. however noted from this approach that placement of the camera through the floor of the mouth led to restricted movement due to collisions with the nose and maxilla (11). As a result, they subsequently modified their approach and placed the three ports through gingival-buccal incisions, all anterior to the mandible (*Figures 1,2*). The lateral ports were positioned posterior to the mental nerve and the endoscope port was placed in the midline between the fasciculus of the mentalis muscles. The dissection was continued around the inferior

Figure 1 Cadaver with three robotic ports placed anterior to the mandible to access the central neck.

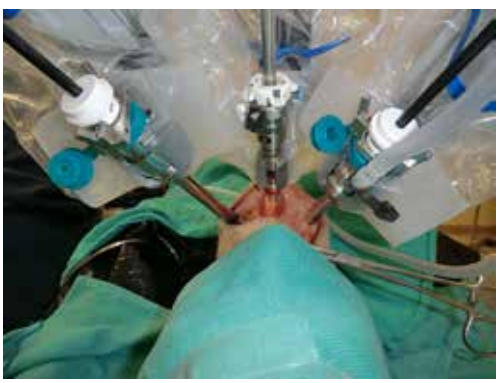

Figure 2 The robot docked with the three ports placed through the vestibule anterior to the mandible. The central camera port enters between the fasciculus of the mentalis muscles.

aspect of the mandible and a submental pocket created. Using this approach also allowed creation of a seal and CO_2 insufflation at 8 L/min was sufficient to maintain a working cavity which removed the need for external retraction. Excellent mobility and view of the central cavity was provided by this approach, and a right thyroid lobectomy and central neck dissection was successfully performed (*Figures 3*,*4*).

The feasibility of transoral robotic thyroid surgery was further supported by Hoon Yub Kim and his group

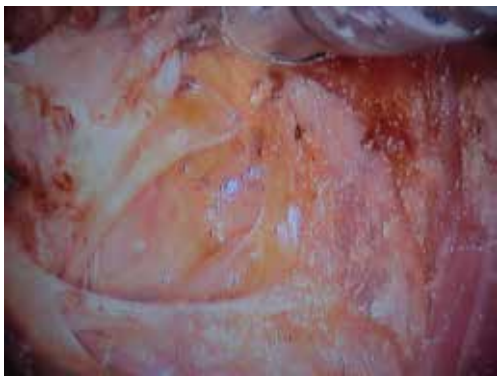

Figure 3 View through the console of the right recurrent laryngeal nerve after a central neck dissection has been performed.

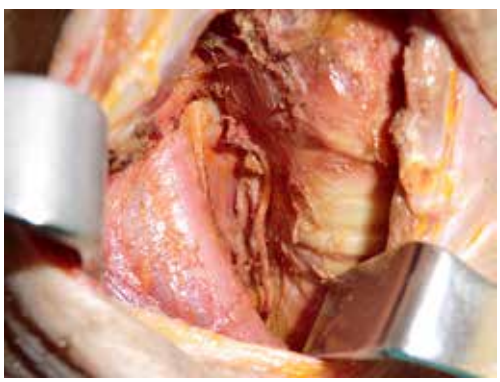

Figure 4 An external incision was made after the transoral robotic thyroidectomy to demonstrate the completeness of the thyroidectomy, nerve dissection, and central neck dissection.

at Korea University who created a porcine model for the procedure (12). Transoral robotic total thyroidectomies were successfully performed in seven pigs. Follow-up examinations were performed for seven days and followed by autopsy. The first three cases were noted to develop seromas post operatively (one of which was infected), as a result, in case 4 and onwards a drain was placed at time of surgery and no further seroma occurred. The recurrent nerves were noted to be intact in all cases. The two cadavers and one porcine study provide proof of concept for robotic transoral thyroid surgery and serve to identify advantages and potential pitfalls for the clinical application of this approach.

The clinical impact of robotic transoral thyroid surgery remains hard to predict. Since being described in the literature in 2010, actual clinical introduction has been slow. However, Dr. Kim's group recently reported their initial series of robotic transoral thyroidectomy in living patients. They used

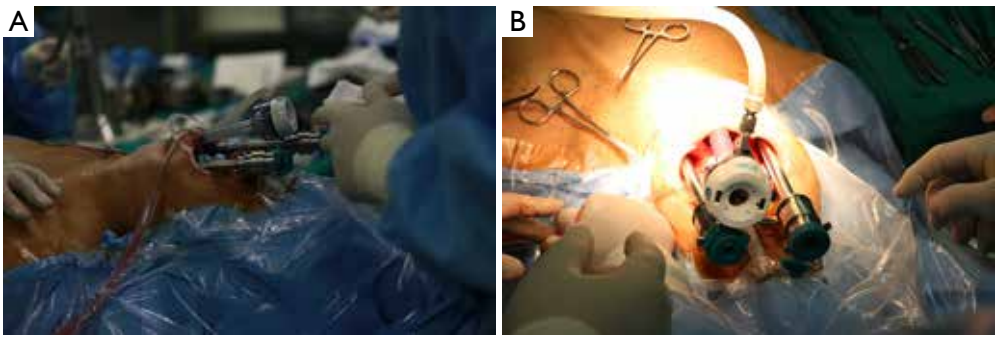

Figure 5 Port placement of robotic transoral periosteal thyroidectomy using three ports; (A) lateral and (B) anterior views. Three robotic arms were placed through the transoral ports.

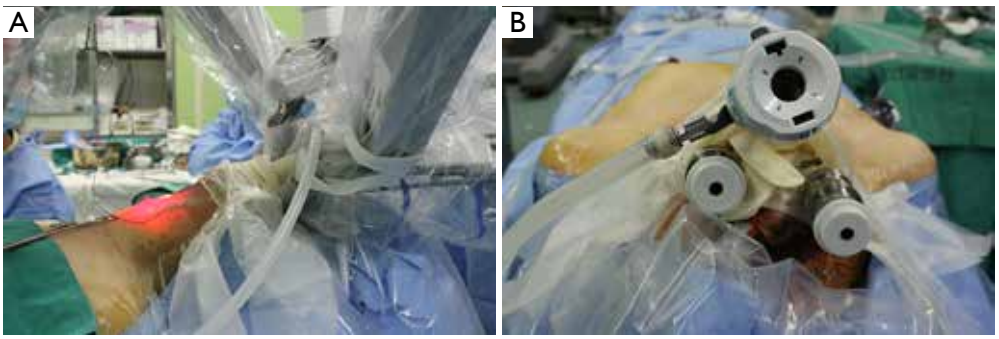

Figure 6 View during the robotic transoral periosteal thyroidectomy using three ports; (A) lateral and (B) anterior views. Three robotic arms were placed through the transoral ports. The da Vinci robotic system was docked at the patient's left side. The robotic camera was inserted through the central port.

transgingival-buccal approach for robotic assisted surgery in four patients, although an accessory port was placed in the axilla, which was used to retract the strap muscles laterally (13). Of the four cases, two were right lobectomies, one was a left lobectomy and one was a left lobectomy with a central neck dissection. All four cases were completed robotically, operative time ranged from 190-390 minutes, with console time ranging from 74-230 minutes. In two cases, the ipsilateral mental nerve was torn (repaired intraoperatively) and stretched in one case. In these cases, patients had paresthesia in a portion of their lower lip and chin but all improved by post-operative week four. There were no cases of temporary or permanent vocal cord palsy and no reported post-operative infections.

Although pending publication, Dr. Kim presented his team's experience of performing nine transoral robotic hemi-thyroidectomies without the need for an accessory port at the Johns Hopkins Hospital Transoral Robotic Surgery Symposium in Baltimore MD, July 24-25, 2014 (*Figures 5-7*). All cases were completed without the need to open, and three cases also included central neck dissection. The average time for the whole procedure was 234 minutes with on average 126 minutes at the consol. There were no recurrent nerve injuries although 4 mental nerves were torn and 2 stretched. These case series, although promising, highlight the significant amount of time required for a robotic transoral approach, which is comparable to transoral endoscopic thyroid surgery and significantly slower than an open procedure. Furthermore, the high rate of mental nerve injury precludes this approach with current instrumentation. The known literature regarding transoral robotic thyroidectomy is highlighted in *Table 1*.

The da Vinci system provides a clear magnified 3-dimensional view of the surgical field and has wristed instruments to aid mobility in limited space. This, however, comes at the lack of tactile feedback. The use of the da Vinci system in robotic transoral thyroid surgery is limited by high cost, non-ideal instruments and lack of single port technology. This approach is also limited by the current need to dissect around the inferior aspect of the mandible to create a submental subplatysmal pocket, which is time-

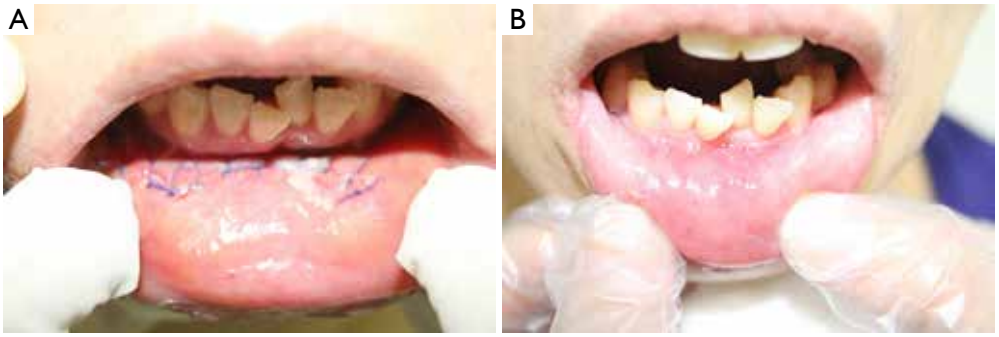

Figure 7 (A) The incision scar of the patient undergone robotic transoral periosteal thyroidectomy (TOPOT) (postoperative 1st day); (B) the incision scar of the patient is almost imperceptible (postoperative 2nd week).

Table 1 Summary of robotic transoral thyroid surgery literature

Author	Year	Country	Model [n]	Indication [n]	Operation [n]	Complication [n]
Richmon (4)	2011	USA	Cadaver [2]	Feasibility study [2]	Total thyroidectomy [2]	NA
Richmon (11)	2011	USA	Cadaver [2]	Feasibility study [2]	Total thyroidectomy [2]	NA
					Central neck dissection [2]	
Lee (12)	2014	Korea	Porcine [7]	Saftey [7]	Total Thyroidectomy [7]	Seroma [3]
Lee (13)	2015	Korea	Cadaver [8]	Feasibility study [8]	Total Thyroidectomy [8]	NA
			Porcine [7]	Feasibility study [7]	Total Thyroidectomy [9]	None
			Human [4]	Follicular adenoma [1]	Lobectomy [4]	Mental nerve stretching [3]
				Papillary carcinoma [1]	Central neck [1]	Mental nerve tear [1]
				Nodular hyperplasia [2]		

NA, not applicable.

consuming and complex. Although the gingival-buccal approach removes the need to violate the tongue and the floor of mouth musculature, which might impact speech and swallowing, this anterior midline approach can cause cosmetic deformity of the mentum and the placement of lateral ports risk mental nerve injury. In addition the transoral approach risks contamination of the neck with oral bacterial flora, although this has not been witnessed with transoral approaches to the sumandibular or sublingual gland. Surgeons should however be cognizant of this risk, irrigate copiously, and select prophylactic antibiotic coverage for oral flora. The transoral robotic thyroid approach is the only remote approach with a midline point-of-view and equal access to both sides of the neck, a considerable advantage over the transaxillary and facelift approaches which have limited capacity to address the contralateral neck.

The future of transoral robotic thyroid surgery is likely to be shaped by trends in the treatment of thyroid cancer and methods of reimbursement. Adam *et al*. analyzed the National Cancer Database [2010-2011] and found that less than 1% of all thyroid cancer surgeries were performed robotically. Furthermore, most of these cases were limited to a few institutes, with the majority of cases being performed at low-volume institutions (2). Currently there are many barriers to the adoption and evolution of robotic thyroid surgery in the US, particularly with the current uncertainty in reimbursement changes and the move towards preferential referral to high volume centers. At this time, robotic transoral thyroid surgery still needs further investigation and development to ensure its outcomes, cost effectiveness, and safety.

Conclusions

Robotic transoral thyroid surgery has been demonstrated to be feasible in cadaver, porcine models and in patients. The approach combines the advantages of a "scarless", remote access incision with the goals of minimally invasive surgery. Unfortunately, current instrumentation and technology

make this approach technically difficult and place unacceptable risk on the mental nerve. Further refinements to overcome these obstacles are necessary prior to a more generalized adoption of this approach, which at this point remains experimental.

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References

1. Becker AM, Gourin CG. New technologies in thyroid surgery. Surg Oncol Clin N Am 2008;17:233-48, x.
2. Adam M, Speicher P, Pura J, et al. Robotic thyroidectomy for cancer in the US: patterns of use and short-term outcomes. Ann Surg Oncol 2014;21:3859-64.
3. Davies L, Welch HG. Current thyroid cancer trends in the United States. JAMA Otolaryngol Head Neck Surg 2014;140:317-22.
4. Richmon JD, Pattani KM, Benhidjeb T, et al. Transoral robotic-assisted thyroidectomy: a preclinical feasibility study in 2 cadavers. Head Neck 2011;33:330-3.
5. Benhidjeb T, Wilhelm T, Harlaar J, et al. Natural orifice surgery on thyroid gland: totally transoral video-assisted thyroidectomy (TOVAT): report of first experimental results of a new surgical method. Surg Endosc 2009;23:1119-20.
6. Dionigi G, Rovera F, Boni L. Commentary on transoral access for endoscopic thyroid resection : Witzel K, von Rahden BH, Kaminski C, Stein HJ (2008) Transoral access for endoscopic thyroid resection. Surg Endosc 22(8):1871-1875. Surg Endosc 2009;23:454-5; discussion 456.
7. Witzel K, von Rahden BH, Kaminski C, et al. Transoral access for endoscopic thyroid resection. Surg Endosc 2008;22:1871-5.
8. Wilhelm T, Metzig A. Endoscopic minimally invasive thyroidectomy (eMIT): a prospective proof-of-concept study in humans. World J Surg 2011;35:543-51.
9. Nakajo A, Arima H, Hirata M, et al. Trans-Oral Video-Assisted Neck Surgery (TOVANS). A new transoral technique of endoscopic thyroidectomy with gasless premandible approach. Surg Endosc 2013;27:1105-10.
10. Woo SH. Endoscope-assisted transoral thyroidectomy using a frenotomy incision. J Laparoendosc Adv Surg Tech A 2014;24:345-9.
11. Richmon JD, Holsinger FC, Kandil E, et al. Transoral robotic-assisted thyroidectomy with central neck dissection: preclinical cadaver feasibility study and proposed surgical technique. J Robot Surg 2011;5:279-82.
12. Lee HY, Hwang SB, Ahn KM, et al. The safety of transoral periosteal thyroidectomy: results of Swine models. J Laparoendosc Adv Surg Tech A 2014;24:312-7.
13. Lee HY, You JY, Woo SU, et al. Transoral periosteal thyroidectomy: cadaver to human. Surg Endosc 2015;29:898-904.

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Robotic transaxillary thyroid surgery

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Abstract: Recent technological advances have led to a rapid progress in endocrine surgery. With the advent of minimally invasive techniques in thyroid surgery, robot-assisted transaxillary thyroid surgery (RATS) has emerged as one of the most promising approaches. Its main advantages are improved cosmetic outcome, avoiding cervical incisions, increased patient satisfaction, improved visualization, arms articulations, eliminating surgeon's natural tremor, thereby increasing precision. The main disadvantages are longer operative time, and increased cost compared to conventional thyroidectomy, as well as potential injuries to the brachial plexus, skin flap, esophagus, and trachea. Large-scale studies, mainly from South-Korea, have proved that in skilled hands, RATS is a safe alternative to conservative thyroidectomy and should be presented to patients with aesthetic concerns. As with any new emerging technique, careful patient selection is crucial, and further evidence must be sought to confirm its indications.

Keywords: Robot; thyroidectomy; transaxillary

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Introduction

Since the nineteenth century, when Kocher implemented the classical cervical thyroidectomy, little has changed in this procedure (1). When performed by experienced surgeons, the cervical approach is highly reliable and relatively short but unfortunately leaves a noticeable scar. Further advances in surgical instrumentation have introduced the minimally invasive thyroid surgery. The endoscopic thyroid surgery resulted in less morbidity and smaller surgical scars and developed into several different techniques (2). Nevertheless, the endoscopic cervical approach is surgically challenging since the neck is a very confined space to use CO_2 insufflation, with $PaCO_2$ elevation, subcutaneous emphysema and air embolism reported (3). The endoscopic approach can be applied today to a small group of patients.

The non-cervical, remote access approaches originally developed primarily due to cosmetic considerations—poor wound healing of certain ethnic groups and the aversion in the Asian culture to neck scars (4). Ikeda *et al*. in 2000 were the first to develop the transaxillary endoscopic approach to the thyroid (5).

With the introduction of the Da Vinci robot (Intuitive Surgical, Sunnyvale, CA, USA), some surgeons have recognized its potential advantages. The South Korean team from Seoul, led by Chung, pioneered the transaxillary approach to the thyroid gland in late 2007 (1,6). The robotic-assisted transaxillary thyroid surgery (RATS) approach was first described in North America by Kupersmith and Holsinger in 2011 (7). Since it was first introduced, more than 3,000 RATS procedures were performed in South Korea, and more than 6,000 worldwide (8). Among the other robot-assisted thyroidectomy (RT) approaches [facelift approach, bilateral-axillary breast approach (BABA)], the transaxillary became the most popular. The initial RATS was performed via two incisions (axillary and anterior chest wall), but later the modification using a single axillary incision was described (1,5).

Since the first report of RATS by the Seoul team, it has gained much popularity and interest in other parts of the world. Several groups have published their initial successful experience (9). However, since the conventional approach is safe, effective, and time-honored, some surgeons doubt

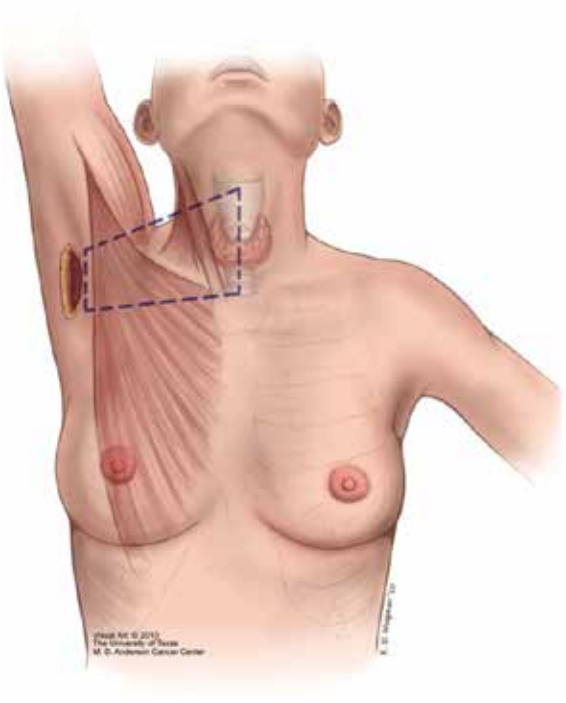

Figure 1 The outline of dissection of the working space. Received with permission from (14).

the value of using robotic thyroid surgery and its clinical use (10). Robotic thyroidectomy, including RATS, remains controversial, especially in the west and the USA, where the FDA has revoked the approval on the use of robotic thyroidectomy and parathyroidectomy in 2011 (9).

Although several eligibility criteria to RATS were described, no standard selection criteria have been established (11). Absolute contra-indications are previous neck surgery or irradiation, retrosternal thyroid extension, and advanced thyroid disease (invasion of trachea, esophagus, distant metastases). Relative contra-indications are patient co-morbidities, age, obesity, very large goiters, well-differentiated carcinomas with a diameter larger than 2 cm, lateral neck metastases, and previous ipsilateral shoulder dysfunction (5,12,13).

Surgical technique

Creation of the working space (Figure 1)

The axillary incision is defined in its inferior border by a horizontal line, from the sternal notch. The superior border—by an oblique line, is at a 60-degree angle from the thyroid notch. Some surgeons prefer to mark the incision while the patient is sitting, with the arms relaxed in a natural position, to verify it is camouflaged.

The use of endotracheal tube with laryngeal nerve monitoring is recommended. Following anesthesia, the patient's arm is placed in an extended position over the head, with a 90-degree flexion at the elbow. The arm should be carefully rotated and padded.

Following the axillary incision (5-6 cm), a dissection is performed in the subcutaneous plane, superficial to the pectoralis major muscle, to the clavicle. At the sternoclavicular joint, the sternal and clavicular heads of the sternocleidomastoid muscle, are identified. The dissection continues between these two heads to expose the strap muscles and deeper, the thyroid gland. Care should be taken during this step to avoid injury to the internal and external jugular veins. A this point, the retractor is inserted.

Docking of the robot (Figure 2)

The Da Vinci cart is placed in the contra-lateral side. All three arms are inserted through the axillary incision (Prograsp forceps, harmonic shears and Maryland dissector), as well as the 30 degrees camera. The proper alignment of the robotic arms is crucial to avoid collision of the robotic arms inside the working space and the general success of the procedure.

Robotic thyroidectomy (console time)

The thyroidectomy is performed in the classical fashion: first, dissecting and safely transecting the superior thyroid vessels; second, the lobe is retracted medially to help identify the parathyroid glands and the recurrent laryngeal nerve (RLN). After ligating the inferior thyroid vessels and identifying the trachea, the lobe is carefully dissected from Berry's ligament and extracted through the axillary incision. A drain is placed in the thyroid bed (11,16).

Advantages of RATS

The most obvious advantage of RATS over conventional cervical thyroidectomy is that it eliminates the need for any cervical incision. This cosmetic aspect makes RATS appealing especially to young female patients and those with a tendency toward keloid formation.

The RATS has several technical advantages over the open and endoscopic approaches. First, the robotic system provides three-dimensional magnified visualization,

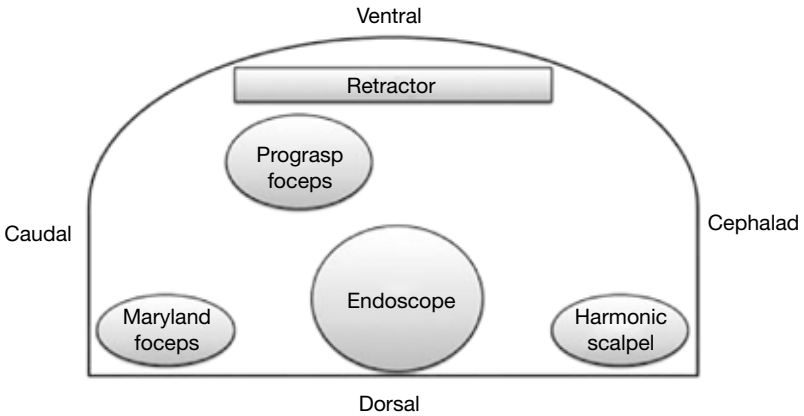

Figure 2 The recommended position of the robotic arms through the axillary incision (15).

which enables an easier identification of the RLN and parathyroid glands compared to the cervical approach; Second, it eliminates the natural surgeon tremor; and, third, it enables a wider range of motion through the robot's EndoWrist and the articulations of the arms. All of these result in minimal complication rates and excellent cancer control and functional results. In addition, the improved visualization and surgical ergonomics provide for reduced musculoskeletal discomfort to the surgeon compared with open or endoscopic surgery.

RATS was found to yield better patient outcomes, including reduced pain and increased cosmetic satisfaction, as well as lower rates of paresthesia, postoperative voice change, and swallowing discomfort (6,17).

Disadvantages of RATS

On the other hand, due to the new approach to the surrounding anatomy and the loss of tactile sensation, RATS introduces potential new complications such as tracheal and esophageal injury. Very few studies accounted for such complications and then only in a minor way with no need to convert to open thyroidectomy (OT) (1). In addition, due to the ipsilateral arm position, there is a risk of brachial plexus neuropathy. This risk can be reduced by placing the arm in a flexed overhead 90 degrees position, thereby reducing the chance of stretching the nerves. Intra-operative monitoring of the ulnar, radial, and median nerves may further reduce the possibility of brachial plexus injury, by identification of any impending damage to these nerves and enabling the patient to be repositioned (1).

Another disadvantage of RATS is the longer operative time due to the creation of the working space and the robot docking. However, several studies have examined the learning curves of the RT and have shown that increased experience led to decreased total operative time (1). RATS involves a steep learning curve, compared to the conventional approach. However, it has been demonstrated that compared to the endoscopic approach which requires 55-60 procedures, the RT required only 35-40 procedures (6). Park *et al*. examined the learning curves of surgeons with little or no experience, performing transaxillary RT on 125 patients. They showed excellent results compared to those in a larger series of more experienced surgeons and specifically, that the operation times gradually decreased, reaching a plateau after 20 procedures (18). Another disadvantage of RATS is the limitation in the body habitus and BMI. While obese patients (BMI >30) make the operation (particularly the working space preparation) challenging, it has been demonstrated that, in skilled hands, this obstacle can safely be overcome (1,19,20).

In terms of cost, the RT is a more expensive procedure compared to the OT, due to the cost of the equipment and the longer operative time. However, some studies have pointed out that RT eliminated the need for an additional surgical assistant, and, combined with the potentially shorter hospital stay and the expected decrease in the maintenance cost of the robot, this may eventually result in an equally cost-effective procedure.

RATS in papillary thyroid carcinoma

The incidence of thyroid cancer is increasing worldwide, and so does the proportion of papillary thyroid microcarcinoma. Since early-stage PTC has an excellent prognosis, the patients quality of life aspect, including

cosmetic concerns, may be emphasized (8,21). In 2011 Lee *et al*. published their experience with RT on 1,043 patients with low-risk well-differentiated thyroid carcinoma. They showed that the RATS was feasible and offered outcomes similar to conventional and endoscopic thyroidectomies. This study included several surgeons, including junior ones, from a number of medical centers (22). Another study published recently, explored the efficacy of RATS in North American population with thyroid cancer, compared to the conventional approach—they found similar operative times and blood loss, with negative margins for malignancy and similar thyroglobulin levels (3).

Ban *et al*. have described the surgical complications in their experience of 3,000 patients who underwent RT for thyroid cancer. Hypocalcemia was the most common complication—1% permanent; RLN injury—0.27% permanent; tracheal injury—0.2%; carotid artery injury—0.03%, skin flap injury—0.1% and brachial plexopathy in 0.13%. The mortality rate was 0% (23). Male gender, overweight BMI, a large thyroid gland and coexistent thyroiditis, are factors that were found to adversely affect the surgical outcome of RT in DTC cases, namely longer operative times (8).

The resection of the contralateral thyroid lobe in total or subtotal thyroidectomy is challenging via a single axillary incision. Therefore some surgeons doubted the surgical completeness of the RATS. A recently published meta-analysis, compared the surgical completeness and oncological outcome between RT and conventional OT in low-risk DTC. Ten studies were analyzed, including 752 patients who had RT and 1,453 patients who had OT. RT was associated with fewer central lymph nodes retrieval and less-complete resection (based on Tg levels), compared to OT, probably due to residual tissue in the contralateral side. Nevertheless, no locoregional recurrence was found in the RT group, therefore, the authors concluded that using RT was unlikely to compromise the outcomes of low-risk DTC (9). Several other studies investigated the completeness of the thyroidectomy, comparing it to conventional thyroidectomy using stimulated thyroglobulin levels, RAI uptake, and postoperative sonography. These studies ultimately demonstrated that the surgical completeness of RT is comparable to conventional thyroidectomy, if performed by experienced surgeons (24-28).

RATS experience

A meta-analysis comparing surgically related complications between robotic-assisted thyroidectomy (both BABA and RATS) and conventional OT summarized 11 studies, including 2,375 patients (1,536 of whom underwent RT), and concluded that RT had a longer operating time, longer hospital stay, and higher risk of temporary RLN injury than OT, but had comparable permanent complications and overall morbidity (29). Another meta-analysis published in 2014 by Jackson *et al*. (1) summarized a total of nine studies with 2,881 patients, 1,122 of whom underwent RT. They conclude that RT is as effective as endoscopic and OT, with equivalent post-operative results, shorter hospitalization, and higher patient satisfaction. Lee *et al*. have also published their experience with 2,014 patients who underwent RATS, with a low complication rate of 1% for major complications (e.g., permanent RLN or brachial injury, conversion) and 19% for minor ones (transient hypocalcemia, seroma, etc.). Interestingly, this group also compared the surgeons' perspectives on the musculoskeletal ergonomic parameters associated with RATS and endoscopic and open surgery. They concluded that RATS resulted in less neck and back discomfort than did the other approaches (29).

RATS is being practiced mainly in South Korea and Europe and, to a smaller extent, in the US. The authors experience in The American Hospital in Paris, France, is very promising, with 212 RATS from 2010 to 2013. The procedures included 110 total thyroidectomies, 90 partial thyroidectomies, 12 parathyroidectomies, and 17 central node dissections. The average age was 45 years (range, 20-84 years), the ratio of male to female was 1:7 and the average BMI was 23 (range, 15-40). The total operative time for partial thyroidectomy was 140 minutes, and 170 minutes for a total thyroidectomy. They reported only 4 (2%) conversions to open surgery, 4 revision surgeries (2%), 1% permanent RLN injury, no permanent brachial plexus injury (4% were transient and resolved in 4-8 weeks), and no cases of permanent hypocalcemia. It should be noted that 57% of patients had large-volume thyroid glands (whose volumes according to preoperative sonography or final pathology were over 20 mL). RLN monitoring was implemented in all patients. Hospital stay did not differ from conventional thyroidectomy patients, and neither did the amount of blood loss. There were no cases of esophageal or tracheal injuries. With careful patient selection and a detailed explanation of the possible complications, we found high rates of patient satisfaction.

One of the relative contra-indications of the robotic-assisted thyroidectomy is Grave's disease patients, due to the usually large-volume glands and hypervascularity.

However, some surgeons have already reported their positive experience with Grave's patients showing similar complication rates, blood loss and hospital stay. It should be noted that all patients received Potassium Iodide preoperatively (30,31). In skillful hands, RATS can be feasible and safe for patients with large-volume thyroid glands such as Grave's and MNG patients.

A newly reported use of the RATS for modified radical neck dissection (MRND) suggests that the precise movements and magnified 3D vision enable a meticulous and safe dissection with recovery of similar numbers of lymph nodes as an open procedure (22,28).

Conclusions

The cervical approach is currently the "gold standard" procedure for thyroidectomy. However, in skilled hands, RATS is considered a safe alternative and should be presented to patients, especially those with aesthetic concerns. Terris stated that "We are in a period where one size no longer fits all" (4)—there is a diversity of different approaches, and the surgeon should tailor the procedure to the patient's disease, general state, and desires. It is the surgeon's obligation to introduce the patient to the different surgical options and consult him on the most appropriate one. With increasing experience and continued improvement in the robotic technology, the indications for RT will continue to evolve (6). The use of the robot for neck dissection via a transaxillary incision will continue to evolve and the indications to perform RATS will continue to expand. RATS should be performed in high-volume centers, by skilled surgeons. As with any new emerging technique, careful patient selection is crucial, and further evidence must be sought to confirm its indications over time.

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References

1. Jackson NR, Yao L, Tufano RP, et al. Safety of robotic thyroidectomy approaches: meta-analysis and systematic review. Head Neck 2014;36:137-43.
2. Miccoli P, Bellantone R, Mourad M, et al. Minimally invasive video-assisted thyroidectomy: multiinstitutional experience. World J Surg 2002;26:972-5.
3. Noureldine SI, Jackson NR, Tufano RP, et al. A comparative North American experience of robotic thyroidectomy in a thyroid cancer population. Langenbecks Arch Surg 2013;398:1069-74.
4. Terris DJ. Surgical approaches to the thyroid gland: which is the best for you and your patient? JAMA Otolaryngol Head Neck Surg 2013;139:515-7.
5. Ikeda Y, Takami H, Sasaki Y, et al. Clinical benefits in endoscopic thyroidectomy by the axillary approach. J Am Coll Surg 2003;196:189-95.
6. Lee J, Kang SW, Jung JJ, et al. Multicenter study of robotic thyroidectomy: short-term postoperative outcomes and surgeon ergonomic considerations. Ann Surg Oncol 2011;18:2538-47.
7. Kuppersmith RB, Holsinger FC. Robotic thyroid surgery: an initial experience with North American patients. Laryngoscope 2011;121:521-6.
8. Son H, Park S, Lee CR, et al. Factors contributing to surgical outcomes of transaxillary robotic thyroidectomy for papillary thyroid carcinoma. Surg Endosc 2014;28:3134-42.
9. Lang BH, Wong CK, Tsang JS, et al. A systematic review and meta-analysis evaluating completeness and outcomes of robotic thyroidectomy. Laryngoscope 2015;125:509-18.
10. Chung WY. Pros of robotic transaxillary thyroid surgery: its impact on cancer control and surgical quality. Thyroid 2012;22:986-7.
11. Lin HS, Folbe AJ, Carron MA, et al. Single-incision transaxillary robotic thyroidectomy: challenges and limitations in a North American population. Otolaryngol Head Neck Surg 2012;147:1041-6.
12. Perrier ND, Randolph GW, Inabnet WB, et al. Robotic thyroidectomy: a framework for new technology assessment and safe implementation. Thyroid 2010;20:1327-32.
13. Lee YM, Yi O, Sung TY, et al. Surgical outcomes of robotic thyroid surgery using a double incision gasless transaxillary approach: analysis of 400 cases treated by the same surgeon. Head Neck 2014;36:1413-9.
14. Landry CS, Grubbs EG, Morris GS, et al. Robot assisted transaxillary surgery (RATS) for the removal of thyroid and parathyroid glands. Surgery 2011;149:549-55.
15. Nam KH, Owen R, Inabnet WB 3rd. Prevention of complications in transaxillary single-incision robotic thyroidectomy. Thyroid 2012;22:1266-74.
16. Holsinger FC, Chung WY. Robotic thyroidectomy. Otolaryngol Clin North Am 2014;47:373-8.
17. Sun GH, Peress L, Pynnonen MA. Systematic review and meta-analysis of robotic vs conventional thyroidectomy approaches for thyroid disease. Otolaryngol Head Neck

Surg 2014;150:520-32.
18. Park JH, Lee J, Hakim NA, et al. Robotic thyroidectomy learning curve for beginning surgeons with little or no experience of endoscopic surgery. Head Neck 2014. [Epub ahead of print].
19. Kandil E, Abdelghani S, Noureldine SI, et al. Transaxillary gasless robotic thyroidectomy: a single surgeon's experience in North America. Arch Otolaryngol Head Neck Surg 2012;138:113-7.
20. Kandil EH, Noureldine SI, Yao L, et al. Robotic transaxillary thyroidectomy: an examination of the first one hundred cases. J Am Coll Surg 2012;214:558-64; discussion 564-6.
21. Lee S, Lee CR, Lee SC, et al. Surgical completeness of robotic thyroidectomy: a prospective comparison with conventional open thyroidectomy in papillary thyroid carcinoma patients. Surg Endosc 2014;28:1068-75.
22. Lee J, Yun JH, Nam KH, et al. Perioperative clinical outcomes after robotic thyroidectomy for thyroid carcinoma: a multicenter study. Surg Endosc 2011;25:906-12.
23. Ban EJ, Yoo JY, Kim WW, et al. Surgical complications after robotic thyroidectomy for thyroid carcinoma: a single center experience with 3,000 patients. Surg Endosc 2014;28:2555-63.
24. Tae K, Song CM, Ji YB, et al. Comparison of surgical completeness between robotic total thyroidectomy versus open thyroidectomy. Laryngoscope 2014;124:1042-7.
25. Yi O, Yoon JH, Lee YM, et al. Technical and oncologic safety of robotic thyroid surgery. Ann Surg Oncol 2013;20:1927-33.
26. Lee S, Ryu HR, Park JH, et al. Excellence in robotic thyroid surgery: a comparative study of robot-assisted versus conventional endoscopic thyroidectomy in papillary thyroid microcarcinoma patients. Ann Surg 2011;253:1060-6.
27. Lee S, Lee CR, Lee SC, et al. Surgical completeness of robotic thyroidectomy: a prospective comparison with conventional open thyroidectomy in papillary thyroid carcinoma patients. Surg Endosc 2014;28:1068-75.
28. Lee J, Kwon IS, Bae EH, et al. Comparative analysis of oncological outcomes and quality of life after robotic versus conventional open thyroidectomy with modified radical neck dissection in patients with papillary thyroid carcinoma and lateral neck node metastases. J Clin Endocrinol Metab 2013;98:2701-8.
29. Lang BH, Wong CK, Tsang JS, et al. A systematic review and meta-analysis comparing surgically-related complications between robotic-assisted thyroidectomy and conventional open thyroidectomy. Ann Surg Oncol 2014;21:850-61.
30. Kwon H, Koo do H, Choi JY, et al. Bilateral axillo-breast approach robotic thyroidectomy for Graves' disease: an initial experience in a single institute. World J Surg 2013;37:1576-81.
31. Noureldine SI, Yao L, Wavekar RR, et al. Thyroidectomy for Graves' disease: a feasibility study of the robotic transaxillary approach. ORL J Otorhinolaryngol Relat Spec 2013;75:350-6.

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Transaxillary single-incision robotic neck dissection for metastatic thyroid cancer

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Abstract: In head and neck area, neck dissection (ND) is one of the most complex and precision-needed procedure. The long cervical scar and post-operative neck discomfort have been also inevitable brands after this procedure. Heretofore, few dare to try endoscopic surgical technique to the ND mainly due to its complexity and jeopardy of complication. Although, there have been several reports about the endoscopic approaches for functional ND or ND, they had so many technical and instrumental limitations. The dexterities of the surgical robotics have advanced the techniques of endoscopic surgery, and have facilitated the most precise and delicate endoscopic surgical procedure in head and neck area. The technical feasibility and early surgical outcomes of robotic ND using the transaxillary approach for the management of metastatic thyroid cancer have already been reported as satisfactory. Robotic ND can allow complete compartment-oriented lymph node (LN) dissection without any fatal complications, or compromising oncologic principles. We previously described a novel method of robotic thyroidectomy with ND using a gasless transaxillary approach for metastatic thyroid cancer, and here, we firstly introduce a less invasive robotic procedure which has been modified from the original one, which we refer to as the transaxillary single-incision robotic ND.

Keywords: Robotic neck dissection (ND); transaxillary; single incision; thyroid cancer

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Introduction

The movie director Christopher Nolan has been famous for the creative trials in his film, and the movie "Interstellar" made by him has been a box office hit in 2014. He made again the innovative concepts—transcending time and space—in this movie, and it made profound impression to the cinema audiences.

Robotic surgical system was firstly introduced in 1999, and substantially overcame optic (2-D representation) and instrumental limitations of conventional endoscopic procedures, and facilitated minimally invasive surgery (1-5). However, some of thoracic and abdominal surgeries can only be performed by the robotic surgical system at that time.

The first introduction of robotic thyroidectomy has similar impact and impression to the head and neck surgeons and patients who acutely want to remove the conspicuous scars on the neck. Because, the application of robotic surgery in head and neck achieved in a hard way due to the lack of a pre-existing working space, relatively bulky robotic arms in deep, narrow operative fields, and the hypervascularities of target organs, which are invariably surrounded by critical nerves and major vessels (6,7).

In the head and neck area, well-differentiated thyroid cancer is the most common malignancy, and the incidence of early stage cancer of the thyroid has markedly increased due to the various health-screening programs. Furthermore, the proportion of thyroid cancer in young women who are particularly sensitive to cosmesis is increasing. Accordingly, the needs and trials on robotic or minimally invasive techniques in thyroid surgery have continuously grown with the aim of avoiding prominent cervical scars, and many of early satisfactory results have already been reported for these techniques (8-11).

Even though the technical dexterity of the robotic

surgical system for thyroidectomy has been proved through various routes, there are still hot debating about the necessity and suitability of robotic thyroidectomy considering the cost-effectiveness of the procedure and the monopoly of robotic company (6-11). Furthermore, although robotic thyroidectomy has excellent cosmetic benefits and little discomfort on anterior neck area, it is still widely invasive technique comparing to the conventional open procedure.

However, in terms of robotic neck dissection (ND), the situation is somewhat different from robotic thyroidectomy. Papillary carcinoma of the thyroid (PTC)—the most common type of differentiated thyroid cancer—usually has a mild biologic course, but nevertheless, it frequently metastasizes to local cervical lymph nodes (LN). In cases of metastasis to the lateral neck nodes (LNM) from PTC, bilateral total thyroidectomy with ipsilateral ND is the treatment of choice. Although conventional open ND is the safest and most efficient type of surgical treatment, extensive surgical dissection and long incision scar on the neck are inevitable. In view of the wide surgical extent and cosmetic problems of open ND, minimally invasive and remote site approaches to the ND has been facilitated. Accordingly, we have applied robotic techniques to thyroidectomy and ND procedures, and the dexterous robotic technology enables more precise and meticulous dissection during the complex procedure required for ND. Recently, the technical feasibility and safety of robotic ND and functional benefits of robotic ND over the conventional open ND have been serially reported, and the technique has been found to be capable of complete compartment-oriented dissection (12-14).

In this chapter, we firstly describe in detail of robotic ND using single incision method for the management of thyroid cancer with LNM.

Preoperative diagnosis

Well-differentiated thyroid cancer should be diagnosed in all patients by preoperative fine needle aspiration biopsy (FNAB). High-resolution staging ultrasonography (US) and computed tomography (CT) of the neck can be performed for preoperative disease staging. Comprehensive preoperative evaluation should be performed to rule out any advanced disease with thyroid cancer to avoid unexpected difficult situation.

All patients with clinically palpable lateral neck nodes or a lateral LN with a suspicious ultrasound appearance by preoperative staging US should undergo US-guided FNAB.

The presence of metastasis to a lateral neck node can be determined by US-guided FNAB histology or by measuring thyroglobulin (Tg) levels in FNAB wash out fluid (FNA-Tg >10 ng/mL, > mean + 2 SD of FNA-Tg measured in node negative patients, or > serum-Tg) from lateral neck LNs.

Indication

The eligibility criteria for robotic ND are as follows: (I) well-differentiated thyroid cancer with clinical LNM (cases with a minimum numbers of metastatic LNs in the lateral neck); (II) a primary tumor size of ≤4 cm; or (III) minimal invasion of the anterior thyroid capsule and strap muscle by the primary cancer.

The role of the robotic procedure for the management of cancer of the thyroid with LNM remains controversial. For experienced surgeons, this approach may be well suited for cases with limited LNM from well-differentiated thyroid cancer (WDTC), but its role in cases of more locally advanced cancer is uncertain, and thus, robotic ND is clearly contraindicated in such cases.

The exclusion criteria which should be applied are: (I) definite tumor invasion to an adjacent organ [recurrent laryngeal nerve (RLN), esophagus, major vessels, or trachea]; (II) multiple LN metastases in multiple levels of the lateral neck; (III) LN metastasis on the substernal area or area below the clavicle; or (IV) peri-nodal infiltration at a metastatic LN.

Extent of dissection

The role of prophylactic central ND in PTC remains the subject of considerable debate. However, therapeutic lateral ND in PTC patients with clinically determined LNM is always necessary.

Most commonly used surgical approaches in cases with LNM from PTC are bilateral total thyroidectomy with central compartment ND and concurrent modified radical ND [type III, sparing sternocleidomastoid muscle (SCM), spinal accessory nerve, and the internal jugular vein (IJV)].

In terms of extent of the dissection, the submental, submandibular, parotid, and retroauricular nodes are virtually never dissected, and levels IIB and VA LNs are not routinely dissected either in cancer of the thyroid with LNM, because its rarely metastasizes to levels I or IIB, or VA.

However, if an enlarged or suspicious cervical LN is encountered by palpation or by preoperative US in these

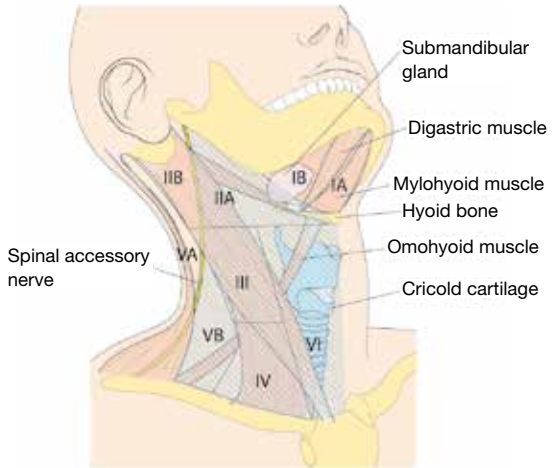

Figure 1 The anatomic landmarks used to divide the lateral and central LN compartments into levels I-VI; the area with a deviant crease line is where LN dissection is made during MRND. LN, lymph nodes; MRND, modified radical neck dissection.

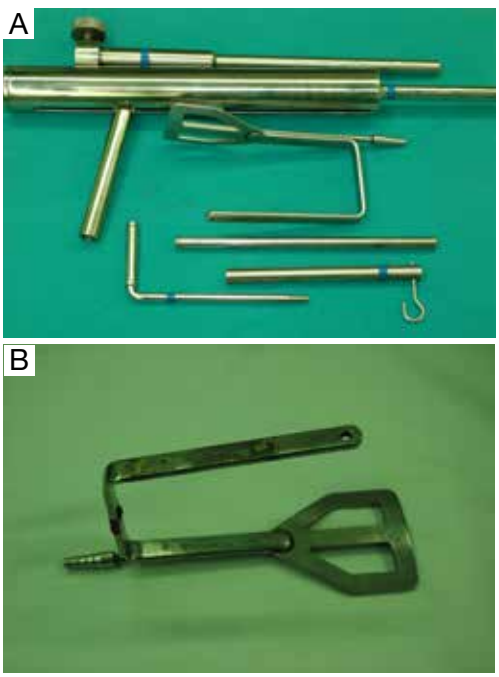

Figure 2 Special set of Chung's retractor for ND. (A) Wide and long blade of external retractor; (B) table mount and suspension devices.

areas, these compartments are also included in *en bloc* dissection. Thus, the usual extents of surgical dissection for ND in differentiated thyroid cancer with LNM are levels IIA, III, IV, VB, and VI, which applies to robotic and open ND procedures as well (*Figure 1*).

Special equipment and preparation materials

For the patient position, arm board (lesion side) which can be attached to the operating table and soft pillow (for neck extension) should be prepared. During the development of working space, electrocautery with regular and extended-sized tip, vascular Debakey or Russian forceps (extended length), two army-navy retractors, right-angled retractors, and breast lighted retractors are used. Laparoscopic clip appliers can be used for the ligation of external jugular vein during this procedure. After placing the wide and long blade of external retractor (special set of Chung's retractor for robotic ND) (*Figure 2A*,*B*), for maintenance of the working space, actual robotic procedures are started. For the robotic ND, da Vinci S or Si system (Intuitive, Inc., Sunnyvale, CA, USA) can be used. Three robotic instruments (5-mm Maryland dissector, 8-mm ProGrasp forceps, and 5-mm Harmonic curved shears) and dual channel camera (30 degree, used in the rotated down position) are needed. For the energy device, Harmonic curved shears is preferred (*Table 1*).

Surgical technique

Patient preparation

With a patient in a supine position under general anesthesia, the neck is slightly extended by inserting a soft pillow under the shoulder, and turning the face away from the lesion. The lesion-side arm is stretched out laterally and abducted about 80 degrees from the body (for optimal expose of the axillar and lateral neck areas). The landmarks for dissection are; the connecting line of sternal notch and the SCM bifurcation medially, the anterior border of trapezius muscle laterally, and the submandibular gland superiorly (*Figure 3*).

Development of working space

A 10-12 cm linear skin incision is placed in the axilla along the anterior axillary fold and the lateral border of the pectoralis major. A subcutaneous skin flap is made over the anterior surface of the pectoralis muscle from axilla to the clavicle and the sternal notch. After crossing the clavicle, a subplatysmal skin flap is made. The flap is dissected medially to the anterior border of SCM clavicular head. Laterally, the trapezius muscle is identified and dissected upwards along its anterior border. The spinal accessory nerve is identified and traced carefully along its course until it passes on the undersurface of

Table 1 For the robotic total thyroidectomy and ND, the instruments and materials needed additionally are summarized below

Procedure	Instruments or materials
Patient position	• Arm board • Soft pillow
Development of working space	• Electrocautery with regular and extended-sized tip • Vascular Debakey or Russian forceps (extended length) • Army-navy retractor ×2 • Right-angled retractors ×2 • Breast lighted retractor ×2 • Endoscopic clip appliers
Maintenance of working space	• Chung's retractor (special set of retractor for ND) • Table mount and suspension device (Marina Medical, Sunrise, USA)
Robotic procedure	• 5 mm Maryland dissector • 8 mm ProGrasp forceps • 5 mm Harmonic curved shears • Dual channel 30 degree endoscope (used in the rotated down position) • Endoscopic graspers and forceps • Endoscopic suction irrigator

ND, neck dissection.

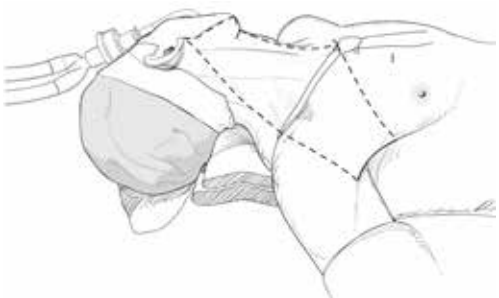

Figure 3 Patient position and superficial landmark for flap dissection.

the SCM muscle. The subplatysmal skin flap is elevated upwards to the Erb's point, and after exposure of this point, the dissection proceeds underneath of the posterior surface of the SCM muscle toward the submandibular gland superiorly. After subplatysmal flap dissection, the posterior half of clavicular head of the SCM is transected

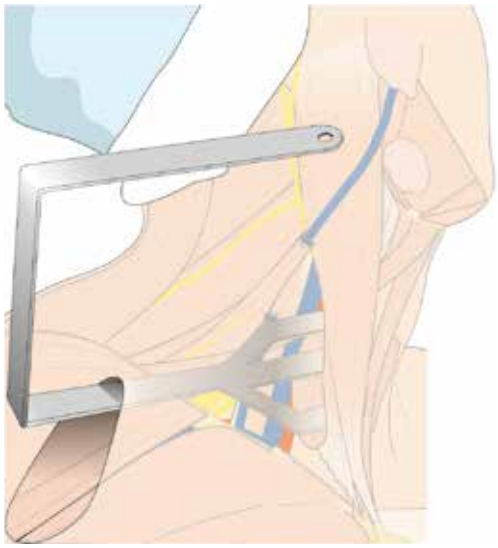

Figure 4 External retractor insertion; initial position of retractor for thyroidectomy and neck dissection of levels III, IV, VB.

at the level of clavicle-attachment point (to completely expose the junction area between the IJV and subclavian vein). The external jugular vein is ligated where it crosses the SCM muscle, and the dissection proceeds underneath of SCM and goes upward until the submandibular gland and the posterior belly of digastric muscle are exposed. The superior belly of omohyoid muscle is divided at the level of thyroid cartilage, and IJV and lateral border of strap muscles are carefully separated. Thyroid gland is then exposed and detached from the strap muscles until contralateral lobe is fully exposed. For the Flap dissection, special retractor (breast lighted retractor) and long vascular Debakey forcep are very helpful. Especially, the blade end of breast lighted retractor is thin and slightly hooked shape, so it is extremely beneficial for lifting up strap muscle during thyroid exposure. It also can be connected with light cable, so deep area dissection from the skin incision (such as submandibular gland exposure or contralateral thyroid gland exposure) can be easily performed without head light.

After flap dissection, the patient's face is returned to the front direction for bilateral total thyroidectomy. A long and wide retractor blade (Chung's retractor) designed for ND is inserted through the axillary incision and lift up the skin flap and SCM & strap muscles (*Figure 4*). The entire thyroid gland and levels IIA, III, IV, VB, VI area are fully exposed by elevating the two heads of the SCM muscle and the strap muscles.

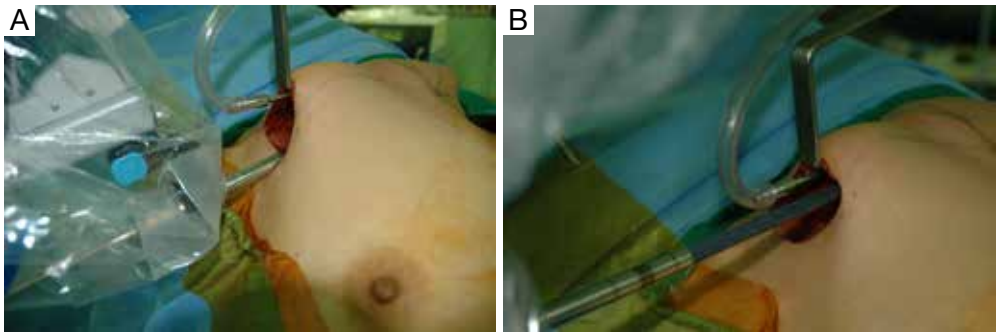

Figure 5 (A) Position of the camera: located in the center of the axillary incision and the external third joint should be placed in the lowest part of the incision and the camera tip should be directed upward; (B) position of the ProGrasp forceps: located as close as possible to the ceiling of the working space.

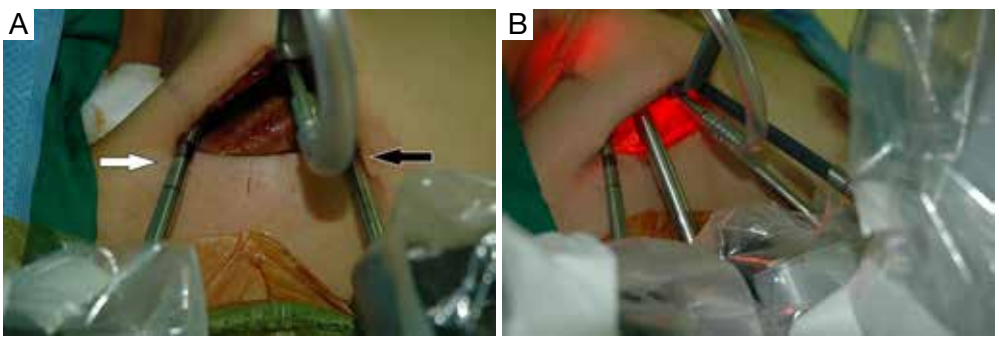

Figure 6 (A) External view of the Maryland dissector and harmonic curved shears: Maryland dissector (white arrow) and harmonic curved shears (black arrow) should be as far apart as possible; (B) all the robotic instruments are introduced through the axillary skin incision.

Docking and instrumentation

The patient cart is placed on the lateral side of the patient (opposite side to the skin incision). The operating table should be positioned slightly oblique with respect to the direction of the robotic column to allow the straight line between the robotic column and the surgical approach route (direction of retractor insertion).

Previously, we described a novel method of robotic ND using a gasless, transaxillary approach, which requires two skin incisions; an axillary incision for camera, 1st and 2nd robotic arm access and an anterior chest wall incision for the 3rd robotic arm (12,13). However, according to the procedure described here, all four robotic arms are inserted through an axillary single incision. To prevent interference between robotic arms, we offer several tips and rules as to where to place the ProGrasp forceps and how to introduce the robotic arms at appropriate angles and inter-arm distances.

For the Rt. Side approach, a 12 mm trocar for the camera and a 30° dual channel endoscope are located in the center of the axillary incision. The camera is inserted in the upward direction (the external 3rd joint should be placed in the lowest part (floor) of the incision entrance, and the camera tip should be directed upward). An 8 mm trocar for the ProGrasp forceps is then positioned at the right of camera, parallel with the suction tube of the retractor blade. At this point, the ProGrasp forceps must be located as close as possible to the ceiling of the working space (the retractor blade) (*Figure 5A*,*B*). The 5 mm trocar of a Maryland dissector is then positioned on the left of the camera (at the left edge of the incision), and the 5 mm trocar for the Harmonic curved shears at the right side of the camera (at the right edge of the incision). Instruments should be as far apart as possible, and inserted upward direction (the same way of camera insertion) (*Figure 6A*,*B*).

Robotic total thyroidectomy with central compartment ND

The procedure used is same with that of two-incision

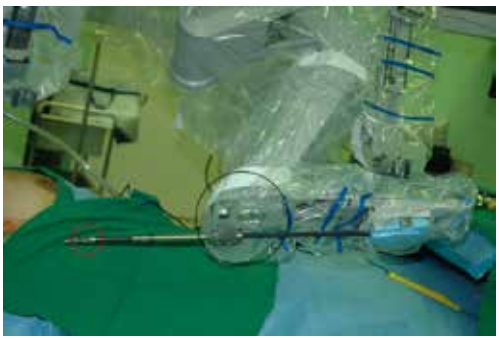

Figure 7 Parts of the ProGrasp forceps are showing; red circle indicates endowrist and black circle is external 3rd joint of the ProGrasp forceps.

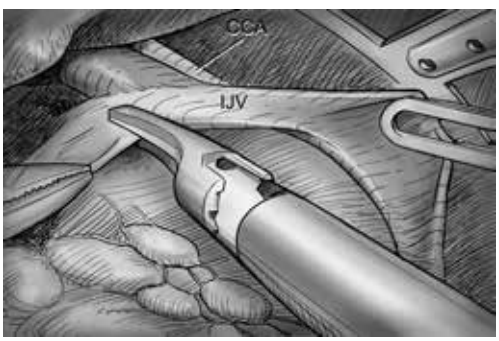

Figure 8 Level III/ IV dissection. The IJV is drawn medially using the ProGrasp forceps, soft tissues and lymph nodes are pulled lateral direction by Maryland dissector and detached from the anterior surface of the IJV to the posterior aspect of IJV until the CCA and vagus nerve are identified. CCA, common carotid artery; IJV, internal jugular vein.

robotic thyroidectomy & ND, except for the use of the ProGrasp forceps. Previously, we used movements of the endowrist and the external joint of the ProGrasp forceps to achieve tissue traction (*Figure* 7). However, during the single-incision approach, tissue should be drawn mostly using endowrist motion of the forceps and its external joint should be moved as little as possible. Because all four robotic arms are inserted through the same incision, minimizing the movements of the external joints of the robotic arms is best for prevention of collisions. We use a Harmonic curved shears for vessel ligation and dissection during the entire procedure. After applying traction to the thyroid upper pole in the medio-inferior direction with the ProGrasp forceps, the superior thyroidal vessel is identified and individually divided Harmonic curved shears. The ProGrasp forceps is used to pull the upper pole steadily, and is repeatedly repositioned in accord with gradual upper pole dissection. The superior parathyroid gland is identified and preserved by detaching the thyroid gland from the cricothyroid muscle. The entire dissection is performed carefully so as not to injure the RLN insertion site. Central compartment node dissection (CCND) is performed after thyroid superior pole dissection. The RLN should be identified before central LN dissection. After tracing the whole running course of RLN, the thyroid can be detached from the trachea completely. In the Berry ligament region, great caution is required to prevent direct or indirect thermal injury of the RLN by the Harmonic curved shears. After Rt. Lobectomy of the thyroid gland, contralateral lobectomy of the thyroid is performed by subcapsular dissection manner, while safely preserving the parathyroid glands and the RLN. In some cases, to achieve better exposure of the contralateral tracheo-esophageal groove, the operating table can be tilted to 10-15 degrees (left side up). After specimen extraction, ND procedure can be followed.

Robotic ND

After total thyroidectomy with central compartment ND, lateral ND is started at the level III/IV area around the IJV. The IJV is drawn medially using the ProGrasp forceps, soft tissues and LNs are pulled in the lateral direction using the Maryland dissector and detached from the anterior surface of the IJV to the posterior aspect of IJV until the common carotid artery and vagus nerve are identified. Smooth, sweeping lateral movements of the Harmonic curved shears can establish a proper plane and delineate vascular structures from specimen tissues (*Figure 8*). Skeletonization of the IJV progresses upward from the level IV to the upper level III area. During this procedure, the superior belly of omohyoid muscle is cut at the level of thyroid cartilage. Packets of LNs are then drawn superiorly using the ProGrasp forceps, and LNs are meticulously detached from the junction of the IJV and subclavian vein. Careful dissection is performed to avoid injury to the thoracic duct. Difficulty may be experienced in this point. Especially for the right side ND, reaching the straight Harmonic curved shears to the deepest point of level IV can be hindered by the prominent clavicle. In these cases, the remote center in the shears' robotic arm should be re-positioned higher than previous status, and the introduction angle of the Harmonic curved shears should be increased. However, two instruments (ProGrasp forceps

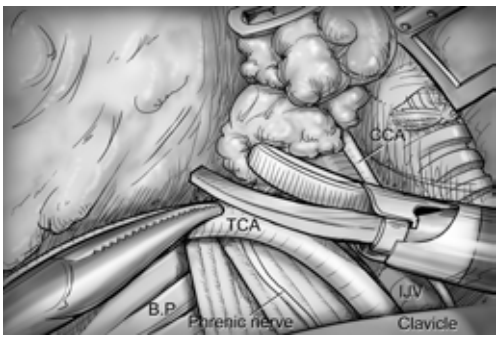

Figure 9 Levels IV, V dissection. Transverse cervical artery (a branch of the thyrocervical trunk) is skeletonized by detaching levels IV, V lymph nodes identifying anterior scalene muscle, phrenic nerve and brachial plexus. CCA, common carotid artery; IJV, internal jugular vein; TCA, transverse cervical artery; BP, brachial plexus.

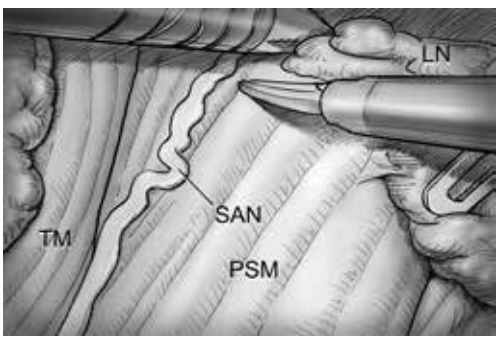

Figure 10 Level V dissection. After clearing level IV area, the dissection proceeds upward along the anterior border of TM while preserving the SAN. PSM, posterior scalene muscle; SAN, spinal accessory nerve; TM, trapezius muscle; LN, lymph nodes.

and Harmonic curved shears) are concurrently inserted at the same side (right side of the camera), so, there is too little space to raise the remote center of shears' arm up. The best solution is changing the position of Harmonic curved shears with Maryland dissector, and using the straight harmonic instrument on the left side to the camera enables it to reach the deepest area of level IV without any disturbance. The second-best choice is shifting the 3rd robotic arm for ProGrasp forceps to the left side of camera during this procedure, and re-positioning of the robotic instrument (Maryland in 3rd arm, ProGrasp in the 2nd arm, and Harmonic in the 1st arm) can make some space for elevating the remote center of shears' arm. For the left side ND, these problems are seldom encountered. In general,

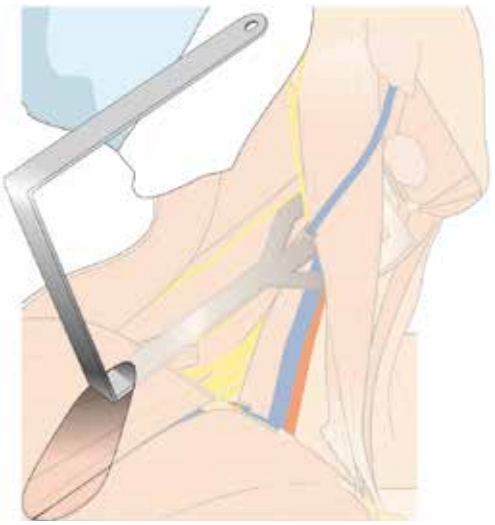

Figure 11 Repositioned external retractor for level II dissection.

the transverse cervical artery (a branch of the thyrocervical trunk) courses laterally across the anterior scalene muscle, anterior to the phrenic nerve. Using this anatomic landmark, the phrenic nerve and transverse cervical artery can be preserved without injury or ligation (*Figure 9*). Further dissection is followed along the subclavian vein in a lateral direction. After clearing level IV area, the inferior belly of omohyoid muscle is cut at the point where it meets trapezius muscle. The distal external jugular vein (which can join the IJV or subclavian vein) is ligated with Weck® Hem-o-lok® Clips at the inlet to the subclavian vein. Dissection then proceeds upward along the anterior border of trapezius muscle while preserving the spinal accessory nerve (*Figure 10*). After finishing levels III, IV, and VB node dissections, re-docking is needed to improve the operation view for the dissection of the level II LN. The external retractor is firstly removed, and patient face should be turned the opposite side of ND for the better exposure of lateral neck. After then, the retractor is re-inserted to the direction of submandibular gland (*Figure 11*). The second docking procedure is performed in the same manner as the first docking, and thus, the operative table should be repositioned more obliquely with respect to the direction of the robotic column to allow alignment between the axis of the robotic camera arm and the direction of retractor blade insertion. Drawing the specimen tissue inferolaterally, the soft tissues and LNs are detached from the lateral border of the sternohyoid muscle, submandibular gland, anterior surfaces of carotid arteries, and the IJV. Level IIA dissection proceeds to the posterior belly of digastric muscle and the

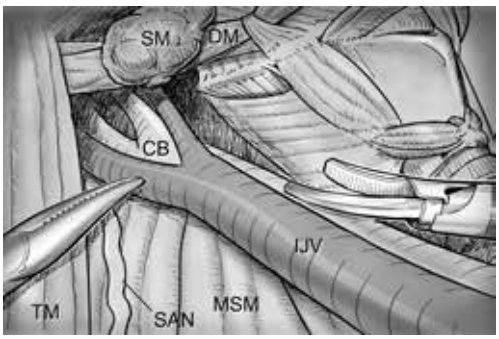

Figure 12 Level II dissection. The level IIA dissection proceeds to the posterior belly of digastric muscle and the submandibular gland superiorly. SM, submandibular gland; DM, digastric muscle (posterior belly); CB, bifurcation of common carotid artery; IJV, internal jugular vein; MSM, middle scalene muscle; SAN, spinal accessory nerve; TM, trapezius muscle.

submandibular gland superiorly (*Figure 12*). After removal of the specimen, the operating field is irrigated, and fibrin glue is sprayed around the area of the thoracic duct and minor lymphatics. A closed suction drain (3 mm in size) is inserted just under the axillary skin incision, and the wound is closed cosmetically. The incision scar in the axilla is completely covered when the arm is in its natural position.

Postoperative management

Post-operative pain can be controlled by the usual medication regimen for pain control.

The routine period of drain placement after the operation is usually different from each surgeon according to their own experience and preference. However, if the drainage amount is less than 50 mL per day, the drain can be safely removed without any risk of post operative seroma.

Complications

The complications after robotic ND are similar to those after conventional open ND.

Hypoparathyroidism (transient/permanent), recurrent (inferior) laryngeal nerve injury, superior laryngeal nerve injury can occur after central compartment ND, and chyle leakage, nerve injuries [spinal accessory, ramus mandibularis, sympathetic (Horner's syndrome), phrenic, brachial plexus], hemorrhage/seroma, and wound infection can occur after lateral ND.

Through the 3-D camera in magnified view, critical nerves and thoracic ducts are more vividly identified and preserved during robotic ND than during open methods. Furthermore, multi-articulated instruments and a stable robotic platform reduce the risks of major vessel or thoracic duct injury.

If the surgeon is experienced with the manipulation of robotic instruments and with the open ND procedure, robotic ND has no technique-specific complication.

Conclusions

The dexterities of cutting-edge robotics have markedly advanced endoscopic and minimally invasive surgery. Using this technology, the most exacting procedures in the head and neck area can be managed using an endoscopic approach with excellent cosmesis. Already, satisfactory early surgical outcomes and excellent technical feasibilities have been reported for the management of thyroid cancer with LNM by robotic ND. Furthermore, robotic ND using the transaxillary approach can allow complete compartment-oriented LN dissection without injury to any major vessel or nerve and without compromising surgical oncologic principles.

With advances in instrumentation and more experience, robotic ND is sure to become as accepted alternative means of surgery in low risk thyroid cancer patients with LNM.

Acknowledgements

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References

1. Gutt CN, Oniu T, Mehrabi A, et al. Robot-assisted abdominal surgery.Br J Surg 2004;91:1390-7.
2. Lobe TE, Wright SK, Irish MS. Novel uses of surgical robotics in head and neck surgery. J Laparoendosc Adv Surg Tech A 2005;15:647-52.
3. Miyano G, Lobe TE, Wright SK. Bilateral transaxillary endoscopic total thyroidectomy. J Pediatr Surg 2008;43:299-303.
4. Savitt MA, Gao G, Furnary AP, et al. Application of robotic-assisted techniques to the surgical evaluation and treatment of the anterior mediastinum. Ann Thorac Surg 2005;79:450-5; discussion 455.
5. Link RE, Bhayani SB, Kavoussi LR. A prospective comparison of robotic and laparoscopic pyeloplasty. Ann Surg 2006;243:486-91.

6. Kang SW, Jeong JJ, Yun JS, et al. Robot-assisted endoscopic surgery for thyroid cancer: experience with the first 100 patients. Surg Endosc 2009;23:2399-406.
7. Kang SW, Jeong JJ, Nam KH, et al. Robot-assisted endoscopic thyroidectomy for thyroid malignancies using a gasless transaxillary approach. J Am Coll Surg 2009;209:e1-7.
8. Ryu HR, Kang SW, Lee SH, et al. Feasibility and safety of a new robotic thyroidectomy through a gasless, transaxillary single-incision approach. J Am Coll Surg 2010;211:e13-9.
9. Holsinger FC, Sweeney AD, Jantharapattana K, et al. The emergence of endoscopic head and neck surgery. Curr Oncol Rep 2010;12:216-22.
10. Lee S, Ryu HR, Park JH, et al. Excellence in Robotic Thyroid Surgery: A Comparative Study of Robot-Assisted versus Conventional Endoscopic Thyroidectomy in Papillary Thyroid Microcarcinoma Patients. Ann Surg 2011;253:1060-6.
11. Lee J, Yun JH, Nam KH, et al. Perioperative clinical outcomes after robotic thyroidectomy for thyroid carcinoma: a multicenter study. Surg Endosc 2011;25:906-12.
12. Kang SW, Lee SH, Ryu HR, et al. Initial experience with robot-assisted modified radical neck dissection for the management of thyroid carcinoma with lateral neck node metastasis. Surgery 2010;148:1214-21.
13. Kang SW, Lee SH, Park JH, et al. A comparative study of the surgical outcomes of robotic and conventional open modified radical neck dissection for papillary thyroid carcinoma with lateral neck node metastasis. Surg Endosc 2012;26:3251-7.
14. Lee J, Kwon IS, Bae EH, et al. Comparative analysis of oncological outcomes and quality of life after robotic versus conventional open thyroidectomy with modified radical neck dissection in patients with papillary thyroid carcinoma and lateral neck node metastases. J Clin Endocrinol Metab 2013;98:2701-8.

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Video-assisted surgery for thyroid cancer patients

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Background: Today is well known that endoscopic thyroidectomy could reach the same level of completeness as a conventional operation. We have been using minimally invasive video assisted thyroidectomy (MIVAT) as our favorite minimally invasive access to thyroid diseases from the late nineties.

Methods: Our experience with MIVAT is represented by 2,413 cases between 1998 and 2014: in particular 821 patients were operated with a total thyroidectomy for a papillary carcinoma (34.0%). Furthermore 967 patients underwent a MVAT for the presence of an undetermined lesion (40.0%).

Results: The conversion rate was very low: 24 patients (1.0%), mainly due to: unexpected posterior tracheal invasions (nine patients), involvement of lymph nodes not evident at echography (four patients), esophageal infiltration (three patients), strap muscles infiltration (three patients) and finally in five cases the presence of serious thyroiditis that had escaped to ultrasonographic evaluation.

Conclusions: The minimally MIVAT to treat malignant thyroid tumors has today a very clear indication for malignancies.

Keywords: Thyroid cancer; minimally invasive surgery; minimally invasive video assisted thyroidectomy (MIVAT)

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Introduction

In the early phase of endoscopic surgery of the neck only benign diseases seemed to be viable for such an approach, in particular as far as thyroid and parathyroid glands were concerned. In fact the first endoscopic endocrinological operation in the neck was a parathyroidectomy (1) for a parathyroid hyperplasia. Likewise all the endoscopic accesses proposed for thyroid, either in the cervical area (2) or in an extra cervical region (3) implied the presence of a benign disease. Only few years later it was stated in some studies that an endoscopic thyroidectomy could reach the same level of completeness as a conventional operation (4). These studies encouraged many authors to use this access, in particular the minimally invasive video assisted thyroidectomy (MIVAT) to treat malignant thyroid tumors, at least low or intermediate risk differentiated carcinomas (5,6). In particular one of these studies clearly shows that in a prospective randomized controlled study it was demonstrated beyond any doubt that for these papillary carcinomas MIVAT had the same outcome as conventional surgery in terms of lymph-node recurrence after an adequate follow-up period. Certainly it is obvious that the demonstration of a similar mortality rate would necessitates of many more years of follow-up, but the 5-year follow-up which characterizes this study can be considered exhaustive in terms of lymph node recurrence and this was the conclusion of the paper: no statistically significant difference between patients that had undergone a MIVAT *vs*. patients that had undergone a conventional thyroidectomy.

Material and methods

We have been using MIVAT as our favorite minimally invasive access to thyroid diseases from the late nineties (2), at least until we started our experience also with robot via the axillary approach in 2013.

Our experience with MIVAT is represented by 2,413 cases between 1998 and 2014: one of the main indications was low risk papillary carcinoma, but another significant indication was Thy3 or undetermined follicular nodules.

In particular 821 patients were operated with a total

Table 1 Preoperative diagnosis

Classification	N (%)	Preoperative diagnosis	N (%) (n=2,413)
Benign disease	600 (24.9)	Multinodular goiter	445 (18.5)
		Graves' disease	97 (4.0)
		Toxic multinodular goiter	16 (0.7)
		Plummer adenoma	42 (1.7)
Indeterminate lesions	967 (40.0)	Follicular nodule	834 (34.6)
		Oxyphilic cells nodule	133 (5.5)
Malignancies	846 (35.1)	Papillary carcinoma	821 (34.0)
		Medullary carcinoma	7 (0.3)
		Ret + carriers	15 (0.6)
		TGD carcinoma	3 (0.1)

Table 2 Surgical procedures

Variables	N (%) (n=2,413)
Total thyroidectomy	1,818 (75.3)
Emithyroidectomy	542 (22.5)
Total thyroidectomy + central neck compartment dissection	31 (1.3)
Completion thyroidectomy	22 (0.9)

thyroidectomy for a papillary carcinoma (34.0%), seven patients (0.3%) were affected by medullary carcinoma, all those cases were clinically negative (no suspicious lymph nodes at preoperative US examination) and were diagnosed by means of routine calcitonin blood measurement, 15 patients were RET + carriers (0.6%) who underwent prophylactic thyroidectomy and three patients were affected by TGD carcinoma, all of those diagnosed as incidentally specimen findings.

Furthermore 967 patients underwent a MVAT for the presence of an undetermined lesion (40.0%) (*Table 1*). Of course only a small percentage of the latter proved to be carcinomas (mainly papillary) at final histology, but if we consider these two groups as malignant or potentially malignant patients we must conclude that almost ¾ of the cases of MIVAT are carried out in patients that do not show a benign disease.

We could say that this is an operation that, moving from its prudential onset, has today a very clear indication for malignancies.

Results

In only 22 patients we had to go back for a completion thyroidectomy after final histology: this happened in patients that had undergone a lobectomy for a follicular nodule or hurtle cells nodule referred as Thy3 lesions which had turned out to be a follicular variant of papillary carcinoma (FVPC). We operated via the same central access and repeating a MIVAT in all cases. The conversion rate was very low: 24 patients (1.0%), mainly due to: unexpected posterior tracheal invasions (nine patients), involvement of lymph nodes not evident at echography (four patients), esophageal infiltration (three patients), strap muscles infiltration (three patients) and finally in five cases the presence of serious thyroiditis that had escaped to ultrasonographic evaluation.

In 31 cases a central compartment clearance was associated to total thyroidectomy (3.9%) (*Table 2*).

The mean duration of the operation was 41 minutes. The main complication is represented by unilateral recurrent laryngeal nerve palsy (1.2%) discovered by postoperative direct laryngoscopy performed for each patient with no regard to dysfonia. Surprisingly the definitive hypoparathyroidism, assessed when six months postoperative PTH value and serum calcemia were less than 13 pg/mL and 8.0 mg/dL respectively, was very low in the series (0.4%). Both wound infection and hemorrhage showed very low rate (respectively: 0.01% and 0.08%) (*Table 3*).

Mean hospital stay was 1.5 days after the operation, but in the last 1,300 cases patients are discharged on first post operative day.

Discussion

It can be assumed that, although MIVAT still represents

Table 3 Complications	
Variables	N (%)
Unilateral nerve palsy	30 (1.20)
Hemorrhage	2 (0.08)
Hypoparathyroidism	10 (0.40)
Wound infection	3 (0.01)

an ideal indication for the simplest cases, in particular for small thyroids (7-9), and benign diseases more easily reflect this situation (9), malignancies are now currently treated via MIVAT as our series and others' papers (10) clearly show. This change was certainly driven by the sound demonstration of the oncologic completeness of the operation (5), but was also implemented by the excellent post operative results: the reasonable rate of recurrent nerve palsy and the very low incidence of hypoparathyroidism (*Table 3*) have done the operation attractive for many surgeons also in USA (7). These data are not surprising when considering that, among the inclusion criteria for MIVAT, the nodule, the gland size and the absence of clear lymph node involvement are an important limit: so only T2N0 patients are enrolled for this operation: as a consequence dissection and preservation of parathyroid and recurrent nerve turned out to be simpler and more successful than in more advanced cases. Basically we prefer not to treat via MIVAT patients with an evident involvement of lymph nodes, but when necessary, as it can be seen in *Table 2*, a central compartment clearance is always possible.

The conversion rate is certainly very low: 1% of all cancers (*Table 3*) and basically it reflects the limits of pre-operative ultrasonography: in fact all the underscored diagnoses which provoked the conversion to open surgery can be considered as echography drawbacks.

Finally the more favorable post operative course which characterizes the operation (11), in particular in terms of post operative distress offers the possibility of discharging most of the patients on the same day of surgery, as widely practiced in USA (12), unlike our cohort where we had to keep patients hospitalized for at least one night, by law.

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References

1. Gagner M. Endoscopic subtotal parathyroidectomy in patients with primary hyperparathyroidism. Br J Surg 1996;83:875.
2. Miccoli P, Berti P, Conte M, et al. Minimally invasive surgery for thyroid small nodules: preliminary report. J Endocrinol Invest 1999;22:849-51.
3. Ikeda Y, Takami H, Niimi M, et al. Endoscopic thyroidectomy by the axillary approach. Surg Endosc 2001;15:1362-4.
4. Miccoli P, Elisei R, Materazzi G, et al. Minimally invasive video-assisted thyroidectomy for papillary carcinoma: a prospective study of its completeness. Surgery 2002;132:1070-3; discussion 1073-4.
5. Miccoli P, Pinchera A, Materazzi G, et al. Surgical treatment of low- and intermediate-risk papillary thyroid cancer with minimally invasive video-assisted thyroidectomy. J Clin Endocrinol Metab 2009;94:1618-22.
6. Lombardi CP, Raffaelli M, De Crea C, et al. Video-assisted versus conventional total thyroidectomy and central compartment neck dissection for papillary thyroid carcinoma. World J Surg 2012;36:1225-30.
7. Terris DJ, Angelos P, Steward DL, et al. Minimally invasive video-assisted thyroidectomy: a multi-institutional North American experience. Arch Otolaryngol Head Neck Surg 2008;134:81-4.
8. Liu J, Song T, Xu M. Minimally invasive video-assisted versus conventional open thyroidectomy: a systematic review of available data. Surg Today 2012;42:848-56.
9. Miccoli P, Minuto MN, Ugolini C, et al. Minimally invasive video-assisted thyroidectomy for benign thyroid disease: an evidence-based review. World J Surg 2008;32:1333-40.
10. Lai SY, Walvekar RR, Ferris RL. Minimally invasive video-assisted thyroidectomy: expanded indications and oncologic completeness. Head Neck 2008;30:1403-7.
11. Del Rio P, Berti M, Sommaruga L, et al. Pain after minimally invasive videoassisted and after minimally invasive open thyroidectomy--results of a prospective outcome study. Langenbecks Arch Surg 2008;393:271-3.
12. Terris DJ, Moister B, Seybt MW, et al. Outpatient thyroid surgery is safe and desirable. Otolaryngol Head Neck Surg 2007;136:556-9.

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Robotic facelift thyroid surgery

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Abstract: Techniques for thyroid surgery have advanced dramatically over the past two decades, driven by a better understanding of thyroid physiology, anatomy, and perioperative management strategies. Improvements in surgical technology have permitted surgeons to perform minimally invasive surgery associated with less dissection, decreased pain, smaller anterior cervical incisions, and most importantly a faster recovery. The advent of robotic surgical technology has allowed the development of remote access thyroidectomy for select patients who wish to avoid a visible cervical incision completely. The robotic facelift thyroidectomy (RFT) approach also offers the advantage of outpatient surgery without the need for postoperative drainage. A growing body of evidence supports the safety and efficacy of the approach, and as a result the technique is now being performed at several centers around the world.

Keywords: Thyroidectomy; robotic; facelift; retroauricular; endocrine surgery

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Introduction

Though the traditional Kocher transcervical approach for thyroidectomy has passed the test of time, there has been increasing interest in limiting the cosmetic impact of the resultant large transverse incision at the base of the neck. The use of advanced energy devices such as the harmonic scalpel (Ethicon Endosurgery Inc., Cincinnati, USA) have allowed the development of minimally invasive approaches by which thyroid glands with small nodules could be removed through incisions as small as 1.5 to 2 cm in length. Miccoli is credited with the development of the minimally invasive video assisted thyroidectomy (MIVAT) which utilizes an endoscope, modified retractors, and advanced energy devices to safely perform thyroid surgery through tiny incisions (1). These approaches obviate the need for postoperative drainage and permit safe outpatient surgery in selected patients.

Concurrent with these developments, other surgeons experimented with remote access techniques designed to completely remove any visible incision from the base of the neck. These techniques emerged primarily in Asian centers, where there is a higher risk of hypertrophic scarring and a cultural emphasis on the cosmetic appearance of the anterior neck (2,3). Initial attempts used endoscopes through small incisions placed on the anterior chest, breast, or axilla, or combinations of these sites (4-7). Many of these early remote access techniques for thyroid surgery necessitated CO_2 insufflation to maintain the operative space, involved multiple incisions on the breast or chest, and were constrained by 2-dimensional endoscopic visualization and rigid endoscopic instruments. These logistical constraints limited their popularity outside of Asia. The ability to perform thyroid surgery without any visible cervical incision became more feasible with the introduction of the daVinci surgical robot (Intuitive Surgical, Sunnyvale, USA), which allowed the development of a gasless transaxillary approach (8).

As surgeons in the United States began to implement this approach, concerns emerged over the safety of the technique in patients with a larger Western body habitus (9-13). The approach also required placement of drains and necessitated hospital admission, which represented a step backwards from advances made in minimally invasive thyroid surgery during the prior decade. An alternate

robotic remote access approach, the robotic facelift thyroidectomy (RFT), was developed to help overcome the concerns and limitations of robotic axillary thyroidectomy in the Western patient population (14,15).

History of procedure

Reports of significant complications not generally associated with thyroid surgery, such as esophageal perforations and brachial plexus injuries emerged with application of the robotic axillary approach into Western practices, so the quest for a better means of eliminating the anterior cervical incision in thyroid surgery continued (9,12,16,17). Experiments evaluating endoscopic access routes to the thyroid compartment in a pig model had indicated that a superiorly-based approach offers improved access to the thyroid, yet required incisions located in cosmetically unfavorable locations (18). Modified facelift approaches had been used in head and neck operations such as parotidectomy and excision of superiorly located neck masses in order to avoid the visible neck incisions associated with more traditional approaches (19,20). These retroauricular approaches were associated with higher patient satisfaction due to improved cosmesis. The concept of retroauricular thyroid surgery combined the improved access of a superiorly based approach with the cosmetic advantages of a modified facelift incision. The key to the feasibility of this approach was the incorporation of the surgical robot, which allowed adequate visualization and intricate dissection through the extended length of the dissection pocket.

Development of the RFT approach began with cadaver dissections in order to assess the feasibility of the procedure (21). After the relevant anatomy was defined, the anticipated surgical approach was performed on seven cadavers. Morphometric analysis of these specimens revealed that the RFT approach required 38% less dissection than the robotic axillary approach.

Terris *et al*. reported the first use of the RFT approach in patients in 2011, with a series of 14 patients undergoing 18 RFT procedures (22). One patient had a total thyroidectomy through bilateral incisions and three patients had a second contralateral RFT procedure to address malignancies identified at the initial surgery. The mean operative time was 155 minutes, and there were no conversions to an anterior cervical approach. The first patient treated with this technique received a drain and was admitted, but all subsequent procedures were performed without drains in the outpatient setting. There were two seromas and one patient with transient vocal fold weakness in this series, and all of these resolved spontaneously without intervention. All patients reported temporary hypesthesia of the great auricular nerve (GAN) distribution which resolved within several weeks. Permanent vocal fold weakness and hypoparathyroidism did not occur.

Advantages/disadvantages

Remote access thyroidectomy approaches offer the distinct advantage over anterior cervical approaches of completely eliminating a visible neck scar. RFT is our preferred remote access approach for a variety of reasons. The anatomy and vector of dissection is familiar to head and neck surgeons and the brachial plexus is not at risk for injury as it is with the robotic axillary approach (10,12,15). The decreased area of dissection in the RFT approach compared to the axillary approach permits outpatient surgery without drains (14,21). Though the procedure was developed for a unilateral thyroid lobectomy, surgeons have developed robotic techniques to perform total thyroidectomy, bilateral central neck dissection, and an ipsilateral modified neck dissection through a unilateral retroauricular incision (23). While this approach is feasible, it has only been evaluated in a small series of 4 patients. Even in the most experienced hands, this approach took a considerable amount of time and planning, and is still considered experimental.

Despite these advantages, the technique is not without limitations. Transient hypesthesia in the distribution of the GAN is universal, and though it is temporary, patients need to be counseled appropriately because this does not occur through the conventional anterior approach. One main disadvantage of the RFT approach is the increased operative time over a conventional lobectomy (14). Another significant disadvantage in the United States is the additional cost of the procedure. Studies of the robotic transaxillary approach suggest that increased operative time, coupled with the capital expense of the robotic system and the specialized equipment required may significantly increase the cost of thyroid surgery (17,24). While compensation for robotic procedures is significantly higher than conventional approaches in Asia, there is no increased reimbursement in the United States (13).

Patient selection

Stringent patient selection criteria for RFT have been

Table 1 Selection criteria for robotic facelift thyroidectomy

Patient factors
Highly motivated to avoid cervical scar
No morbid obesity
No prior neck surgery
American Society of Anesthesiologists class 1 or 2
Disease factors
Unilateral surgery recommended for initial treatment
Largest nodule ≤4 cm
No thyroiditis
No pathologic lymphadenopathy
No substernal extension
No extrathyroidal extension

Reprinted with permission from (22).

created to maximize the likelihood of surgical success while minimizing the risk of complications (*Table 1*) (22). Candidates for the procedure should be healthy and able to tolerate general anesthesia for several hours. Patients should not be morbidly obese in order to avoid difficulty retracting an excessively thick skin flap, yet patients who are extremely thin are also challenging because elevating a thin skin flap requires very delicate dissection. There should be no prior history of neck surgery, as previous scarring can compromise flap integrity. Diabetes is not a contraindication to the robotic facelift approach, but strict glucose control in the perioperative period is imperative so that risks of wound healing complications are minimized. Finally, the patient must be highly motivated to avoid a visible cervical scar, understands the limitations and risks of the approach, and accept the unlikely chance that conversion to an anterior approach may be required.

In addition to favorable patient characteristics, the thyroid condition being addressed must also be appropriate for the approach (22). The thyroid disease should be one that is normally treated with unilateral surgery, such as an enlarging or symptomatic benign nodule, a follicular lesion, or follicular lesion of undetermined significance which is being removed for diagnostic purposes. The nodule size should not exceed 4 cm in greatest dimension, and there should be no thyroiditis or history of thyroid compartment surgery in the past. The thyroid lobe should have no substernal extension, and there should be no evidence of a high-grade malignancy such as extrathyroidal extension or pathologic lymphadenopathy.

Patient counseling

Proper preoperative counseling is crucial to patients' satisfaction of a successful surgical outcome. Patients must understand that RFT carries the standard risks of surgery through the anterior approach, with the added side effect of transient hypesthesia of the region supplied by the GAN. It is also important that they understand that RFT is not minimally invasive surgery, and that the longer operative time, more extensive dissection, and longer recovery period make it more invasive than conventional thyroid surgery. All patients must consent to conversion to an anterior cervical approach in the rare event that it is required. Patients should also understand that, in most instances, the contralateral thyroid lobe cannot be addressed with a unilateral RFT approach. Should the final pathology reveal malignancy, a second RFT on the opposite side or an anterior cervical approach may be required for completion surgery. Finally, patients need to appreciate that this is not a "scarless" procedure; the scar is merely hidden discreetly behind the ear and hairline when it is fully healed rather than at the base of the central neck.

Procedure

The procedure for RFT has been previously described in detail and is summarized in the following text (14,22). A natural neck crease is marked while the patient is sitting upright in the preoperative holding area in the event that an anterior cervical approach is necessary. When the patient is placed on the operating table, he or she should be positioned just off-center of the middle of the table toward the operative side, with the top of the head level with the top of the operating table.

General anesthesia is induced with the aid of a short-acting muscle relaxant, and general anesthesia is maintained with a propofol drip. The patient is subsequently intubated with an electromyographic (EMG) endotracheal tube (ETT) to permit intraoperative laryngeal nerve monitoring. A GlideScope (Verathon Inc, Bothell, USA) is useful during intubation so that all members of the operative team can confirm proper positioning of the EMG electrodes on the ETT. A straight extension is placed on the anesthesia circuit to limit tension and the tubing is then taped to the operating table to prevent inadvertent extubation during the operation. A 3-way stop-cock valve on the end tidal CO_2 return tubing prevents kinking of this small caliber tube. The bed is rotated 180°, and the patient's arms are tucked

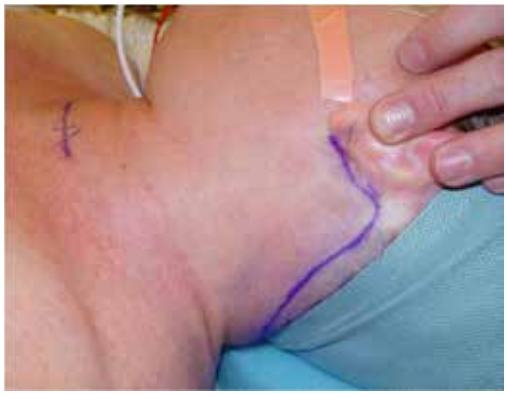

Figure 1 The robotic facelift thyroidectomy incision is placed approximately 1 cm posterior to the hairline. Reprinted with permission (22).

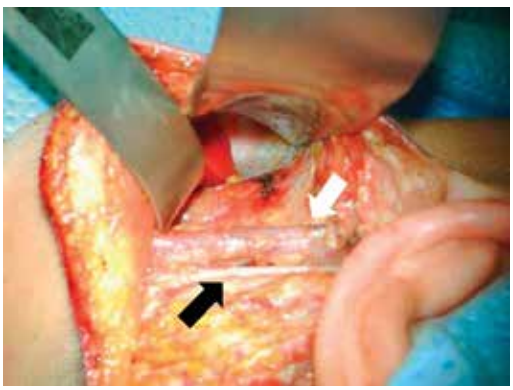

Figure 2 The great auricular nerve (black arrow) and external jugular vein (white arrow) are identified and preserved. Reprinted with permission (22).

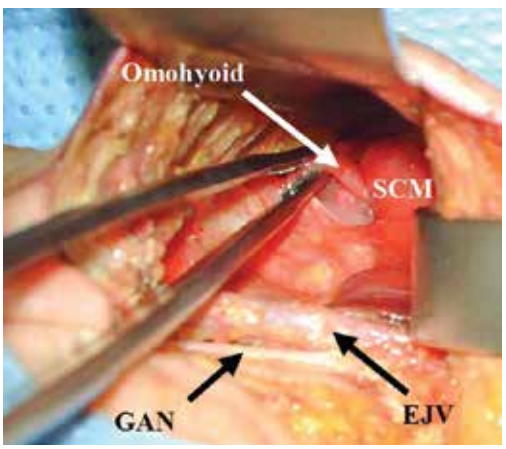

Figure 3 Dissection pocket in RFT. RFT, robotic facelift thyroidectomy; SCM, sternocleidomastoid muscle; GAN, great auricular nerve; EJV, external jugular vein. Reprinted with permission (14).

at their sides and secured with wide silk tape. A formal safety strap that attaches to the table is not used above the patient's waist because the strap interferes with placement of the retractors on the operating table rails. The patient's head is turned 20° to 30° away from the operative side, and the head is supported with soft towels.

The occipital hairline is shaved one cm posteriorly and the facelift incision is marked behind the hairline so that it will be concealed once the hair re-grows. The incision begins near the inferior extent of the lobule in the postauricular crease, and is carried superiorly and then posteriorly into the shaved region of the occipital hairline in a gentle curve (*Figure 1*). The incision is carried posteriorly and inferiorly as far as necessary to allow adequate exposure.

The incision is infiltrated with 0.25% bupivacaine with 1:200,000 epinephrine and the neck is prepped and draped in sterile fashion. The skin is incised with a scalpel and the diathermy is used to develop a subplatysmal flap. The sternocleidomastoid muscle (SCM) is identified, and dissection continues anteriorly and inferiorly along the SCM. The first important structure identified is the GAN. Dissection superficial to the GAN reveals the external jugular vein (EJV) and subsequently the anterior border of the SCM (*Figure 2*). Ideally, the EJV is preserved, but it may be divided if necessary to improve exposure. The table is placed in reverse Trendelenberg position and rotated away from the surgeon to allow visualization as dissection continues down the anteromedial border of the SCM to the clavicle.

The muscular triangle bordered by the SCM, the omohyoid and the sternohyoid is defined (*Figure 3*). The omohyoid, sternohyoid and sternothyroid muscles are then retracted ventrally, and the superior pole of the thyroid gland is exposed (*Figure 4*). The strap muscles are then elevated off of the thyroid lobe, and the superior pedicle is isolated. The modified Chung retractor (Marina Medical, Sunrise, USA) is secured on the contralateral side of the operating table and then positioned so that the strap muscles are retracted ventrally. A Singer hook (Medtronic, Jacksonville FL) attached to a Greenberg retractor (Codman & Shurtleff, Inc., Raynham, USA) secured to the ipsilateral side of the operating table retracts the SCM laterally and dorsally and provides a stable operative field (*Figure 5*). A modified approach has been described which involves splitting the sternal and clavicular heads of the SCM to provide a similar exposure (25).

The robotic console is positioned on the contralateral side of the patient, with the pedestal angled 30° away

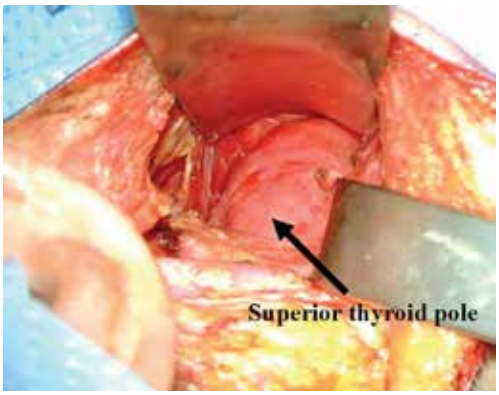

Figure 4 The operative pocket from a right remote access robotic facelift thyroidectomy, with the strap muscles retracted to reveal the superior aspect of the thyroid gland. Reprinted with permission (14).

Figure 5 The operative pocket with retractors in place.

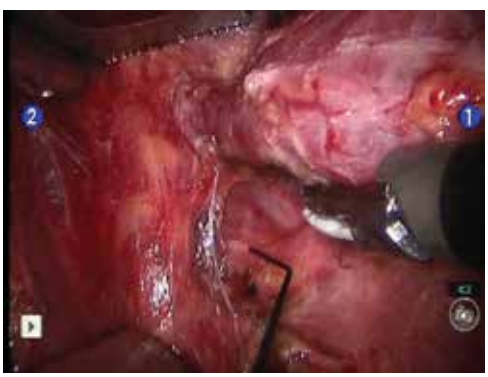

Figure 6 The recurrent laryngeal nerve is visualized at the tip of the nerve stimulating probe during RFT. Reprinted with permission (14). RFT, robotic facelift thyroidectomy.

from the operating table. Fine adjustments, if necessary, are more easily completed by moving the operating table rather than by moving the robot console. A 30° endoscopic camera is positioned on the robotic arm with the camera facing downward, and then advanced along the long axis of the modified Chung retractor into the surgical field. The camera arm is nearly completely extended in order to avoid collisions with the other two robotic arms. A Harmonic device (Ethicon Endosurgery Inc., Cincinnati, USA) is placed in the dominant robotic arm and a Maryland grasper is placed in the other.

The robotic portion of the procedure begins with the division of the superior pedicle with the Harmonic device. The superior thyroid pole is retracted inferiorly and ventrally to expose the inferior constrictor muscle. This muscle is dissected inferiorly to its lower border, and the superior laryngeal nerve is avoided. The superior parathyroid gland is identified on the posterior aspect of the thyroid and dissected so that the blood supply is preserved. The recurrent laryngeal nerve (RLN) is then identified as it courses under the inferior constrictor (*Figure 6*). The ligament of Berry is exposed, and then transected with the Harmonic device. The isthmus is divided, and the middle thyroid vein is ligated. The inferior parathyroid gland is identified, and then dissected away from the thyroid gland with its blood supply intact. Lastly, the inferior thyroid vasculature is transected with the Harmonic device, any remaining attachments between the thyroid lobe and the surrounding tissue are lysed and the specimen is removed from the field. The robotic arms are removed and the robotic cart is taken away from the operating table. Surgicel (Ethicon, Inc., Somerville, USA) is placed into the thyroid bed, and the incision is re-approximated using buried interrupted deep dermal 4-0 Vicryl sutures (Ethicon, Inc., Somerville, NJ) without the use of a drain. The skin edges are sealed with Dermaflex tissue adhesive (Chemence Medical Products, Inc., Alpharetta, USA) and 1/4 inch Steri-Strips (3M Corporation, St. Paul, USA) are placed horizontally along the incision. Deep extubation from anesthesia is preferable to minimize coughing or straining which might cause a hematoma.

Results

More than 70 RFT procedures have been performed in our center. In our most recent peer-reviewed publications, 22 RFT procedures in 18 patients were reported (14,22,26). All procedures were completed on an outpatient basis without

drainage in all but the first patient of the series. One incidence of transient vocal fold weakness and two seromas occurred, and all resolved without intervention. There have been no episodes of hypocalcemia and no conversions to an anterior cervical approach. Similar experiences have been repeated in at least 6 centers, with more than 300 procedures accomplished with complication profiles similar to those described in our reports.

A direct comparison of RFT and robotic axillary thyroidectomy techniques has been performed (15). The mean operative time for the first ten RFT procedures was 156.9 minutes and was 196 minutes for a group of five axillary approach procedures. Though the case volume was small in this series, the data suggested a shorter learning curve with the RFT approach. All patients treated with robotic axillary thyroidectomy were managed with drains as inpatients, while all but the first RFT patient were discharged on the day of surgery without drains. All patients with the axillary approach experienced chest wall numbness, where those in the RFT group had hypesthesia of the skin in the GAN distribution. No major or permanent complications have been described with the RFT approach to date.

Conclusions

The RFT is a safe and viable alternative to conventional thyroid surgery for selected individuals who wish to avoid a cervical scar. RFT is preferred over robotic axillary thyroidectomy, because it allows outpatient surgery without the need for a drain. As this technique is implemented on a broader scale, strict adherence to patient selection criteria is recommended for optimal outcomes. Training programs for the RFT have not been validated, and this approach should only be performed by experienced high volume endocrine surgeons in specialized centers at the current time. As higher clinical volumes of this procedure reach the literature, a more comprehensive understanding of the potential and limitations of this procedure will become available.

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References

1. Miccoli P, Berti P, Conte M, et al. Minimally invasive surgery for thyroid small nodules: preliminary report. J Endocrinol Invest 1999;22:849-51.
2. McCurdy JA Jr. Considerations in Asian cosmetic surgery. Facial Plast Surg Clin North Am 2007;15:387-97, vii.
3. Duh QY. Robot-assisted endoscopic thyroidectomy: has the time come to abandon neck incisions? Ann Surg 2011;253:1067-8.
4. Ohgami M, Ishii S, Arisawa Y, et al. Scarless endoscopic thyroidectomy: breast approach for better cosmesis. Surg Laparosc Endosc Percutan Tech 2000;10:1-4.
5. Ikeda Y, Takami H, Niimi M, et al. Endoscopic thyroidectomy by the axillary approach. Surg Endosc 2001;15:1362-4.
6. Shimazu K, Shiba E, Tamaki Y, et al. Endoscopic thyroid surgery through the axillo-bilateral-breast approach. Surg Laparosc Endosc Percutan Tech 2003;13:196-201.
7. Choe JH, Kim SW, Chung KW, et al. Endoscopic thyroidectomy using a new bilateral axillo-breast approach. World J Surgr;31:601-6.
8. Kang SW, Lee SC, Lee SH, et al. Robotic thyroid surgery using a gasless, transaxillary approach and the da Vinci S system: the operative outcomes of 338 consecutive patients. Surgery 2009;146:1048-55.
9. Kandil EH, Noureldine SI, Yao L, et al. Robotic transaxillary thyroidectomy: an examination of the first one hundred cases. J Am Coll Surg 2012;214:558-64;discussion 564-6.
10. Landry CS, Grubbs EG, Warneke CL, et al. Robot-assisted transaxillary thyroid surgery in the United States: is it comparable to open thyroid lobectomy? Ann Surg Oncol 2012;19:1269-74.
11. Perrier ND. Why I have abandoned robot-assisted transaxillary thyroid surgery. Surgery 2012;152:1025-6.
12. Kuppersmith RB, Holsinger FC. Robotic thyroid surgery: an initial experience with North American patients. Laryngoscope 2011;121:521-6.
13. Dionigi G. Robotic thyroidectomy: Seoul is not Varese. Otolaryngol Head Neck Surg 2013;148:178.
14. Terris DJ, Singer MC, Seybt MW. Robotic facelift thyroidectomy: II. Clinical feasibility and safety. Laryngoscope 2011;121:1636-41.
15. Terris DJ, Singer MC. Qualitative and quantitative differences between 2 robotic thyroidectomy techniques. Otolaryngol Head Neck Surg 2012;147:20-5.
16. Perrier ND, Randolph GW, Inabnet WB, et al. Robotic thyroidectomy: a framework for new technology assessment and safe implementation. Thyroid 2010;20:1327-32.

17. Inabnet WB 3rd. Robotic thyroidectomy: must we drive a luxury sedan to arrive at our destination safely? Thyroid 2012;22:988-90.
18. Terris DJ, Haus BM, Nettar K, et al. Prospective evaluation of endoscopic approaches to the thyroid compartment. Laryngoscope 2004;114:1377-82.
19. Terris DJ, Tuffo KM, Fee WE Jr. Modified facelift incision for parotidectomy. J Laryngol Otol 1994;108:574-8.
20. Roh JL. Retroauricular hairline incision for removal of upper neck masses. Laryngoscope 2005;115:2161-6.
21. Singer MC, Seybt MW, Terris DJ. Robotic facelift thyroidectomy: I. Preclinical simulation and morphometric assessment. Laryngoscope 2011;121:1631-5.
22. Terris DJ, Singer MC, Seybt MW. Robotic facelift thyroidectomy: patient selection and technical considerations. Surg Laparosc Endosc Percutan Tech 2011;21:237-42.
23. Byeon HK, Holsinger FC, Tufano RP, et al. Robotic total thyroidectomy with modified radical neck dissection via unilateral retroauricular approach. Ann Surg Oncol 2014;21:3872-5.
24. Cabot JC, Lee CR, Brunaud L, et al. Robotic and endoscopic transaxillary thyroidectomies may be cost prohibitive when compared to standard cervical thyroidectomy: a cost analysis. Surgery 2012;152:1016-24.
25. Saeed A, Alsaleh N, Moulthrop T, et al. Modified Approach for Robotic Retroauricular Thyroidectomy: Preclinical Simulation and a Surgical Case. Surg Innov 2014. [Epub ahead of print].
26. Terris DJ, Singer MC. Robotic facelift thyroidectomy: Facilitating remote access surgery. Head Neck 2012;34:746-7.

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Robotic transaxillary and retroauricular parathyroid surgery

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Abstract: Current advancement in robotic surgery has provided a safe, precise, 3-dimensional (3D) magnified dissection for parathyroid surgery without the need for CO_2 insufflation, and with a better cosmetic outcome due to an invisible scar in the axillary or retroauricular region. Preoperative imaging studies that assist in the localization of lesions have been key elements in patients' selection for targeted parathyroid surgery.

Keywords: Robotic-assisted; parathyroidectomy; retroauricular; transaxillary; remote access

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Introduction

Robotic-assisted transaxillary parathyroidectomy using the da Vinci Si surgical system (Intuitive Surgical, Sunnyvale, CA, USA) has been described recently in several case reports and small series, as well as robotic-assisted retroauricular parathyroidectomy, which our initial experiences demonstrated as a safe and effective technique for parathyroid lesions (1-4). The robotic-assisted approach, among other reported routes, permits a safe, precise, 3-dimensional (3D) magnified dissection without the need for CO_2 insufflation, and also has a better cosmetic result due to the invisible scar in the neutral position (5). Targeted parathyroidectomy has become the preferred procedure over bilateral neck exploration for primary hyperparathyroidism (PHPT) by most endocrine surgeons. When a parathyroid adenoma is localized preoperatively, it can be removed without visualizing the other glands. However, the indications will likely broaden as the procedure becomes more common. We and most parathyroid surgeons would definitively recommend against unilateral exploration or remote access techniques in patients with suspected multiglandular disease, since bilateral exploration can be performed safely through a very small cervical incision.

Parathyroidectomy for patients with PHPT is associated with a reported cure rate of 95-98% and a low rate (1-3%) of complications (6,7). Minimally invasive parathyroidectomy is being used more frequently, although it is generally not performed in patients with a large goiter or previous neck surgery (*Table 1*).

This review article will discuss some of the preoperative localizing imaging studies, intraoperative adjuncts and the two remote access approaches used for parathyroid surgery. An overview on our experience with the robotic-assisted transaxillary and retroauricular parathyroidectomy with the modifications required for the Western population will be discussed.

Preoperative localizing imaging studies

High-resolution ultrasound (US)

Of all the imaging modalities, US is the least expensive and least invasive, with no radiation or contrast exposure. A high-frequency linear transducer ideally in the range of 12-15 mHz is usually used. Parathyroid glands appear well circumscribed and most commonly oval in shape, but can be multilobed, elongated or bilobed. They are typically hypoechoic, in contrast to the hyperechoic thyroid follicular nodules and usually solid nodules (*Figure 1*). Other abnormalities include parathyroid cysts, which are usually thin walled structures

Table 1 Contraindications to remote access parathyroidectomy

Voluminous goiter
Previous neck surgery or irradiation of the neck
Parathyroid carcinoma
Suspected multiglandular disease
Equivocal preoperative localization studies
Neck mobility problems and cervical spine disease

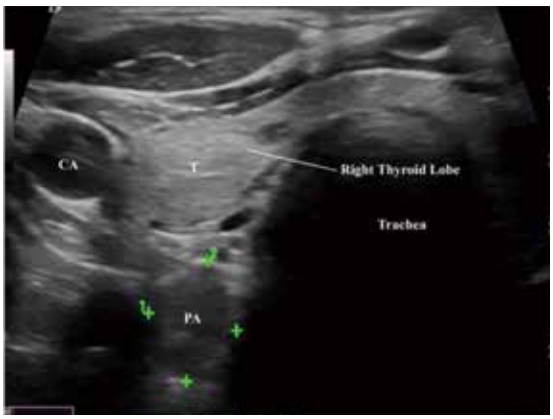

Figure 1 Transverse ultrasound of the neck shows a right inferior parathyroid adenoma. The lesion demonstrates a hypoechoic, well defined, oval shaped, homogenous shape, which is characteristic of a parathyroid adenoma. T, thyroid; CA, carotid artery; PA, parathyroid adenoma.

with posterior enhancement and lacking internal echoes. Some of the factors that can limit the accuracy of US imaging are (I) operator skill and experience; (II) obesity, (III) smaller gland size; (IV) concurrent thyroid pathology (i.e., thyroiditis, multinodular goiter); (V) reoperative cases or previous neck surgery; (VI) retrotracheal, retroesophageal and mediastinal glands; and (VII) multiglandular disease. Although intrathyroidal parathyroid adenoma is a not a very common pathology, presenting in 1-3% of cases (8), a surgeon must always keep that possibility in mind, as it may warrant a thyroid lobectomy. The sensitivity of US in the detection of a parathyroid adenoma is very wide, ranging from 27% to 95% (9,10). One of US's biggest disadvantages are that it is operator dependent, which most likely accounts for the wide range of the reported sensitivity. The combination of US and Sestamibi scan may increase the accuracy of localization of a single adenoma to 94-99% (10,11). The easy accessibility of US has led many

Table 2 Positive predictive values for various preoperative diagnostic modalities

% Ultrasound	% Sestamibi	% CT	% MRI	% PET
60-92	78-100	36-100	51-100	70-74

CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.

surgeons to use it in the operating room prior to surgery to help identify the parathyroid adenoma and its exact anatomical location, which helps in precisely localizing the incision. Lastly, US-guided fine needle aspiration (FNA) can confirm intrathyroidal parathyroid adenomas in selected cases of persistent or recurrent hyperparathyroidism after failed exploration. An elevated parathyroid hormone (PTH) washout concentration from the FNA biopsy can help in identifying parathyroid gland lesions, which aids in performing a minimally invasive surgical approach even with a negative cytology, thus allowing the success of a targeted surgical approach in difficult cases (12).

Nuclear imaging

Currently, nuclear Tc-99m sestamibi (MIBI) scan is one of the most accurate and reliable means of preoperative parathyroid imaging. MIBI can find glands that are deep in the neck, posteriorly located or ectopic in the chest or mediastinum, many of which cannot otherwise be seen on US (*Table 2*). These abnormal parathyroid tissues are identified by detection of the mitochondrial uptake of the radionuclide tracer in areas that are hyperfunctioning. Currently there are no parathyroid specific radionuclides, hence all the radionuclides that accumulate in the parathyroid also accumulate in the thyroid glands. When the tracer is injected, a set of images is usually taken at 15 minutes and another delayed set after 2 hours. The tracer initially becomes concentrated in the normal thyroid as well as abnormal parathyroid tissues, which would be shown in the first set of images. The concentration of the tracer decreases rapidly in normal thyroid tissue, leaving behind foci of relatively enhanced uptake in abnormal parathyroid tissues, characterizing the hyperfunctioning glands which will be detected on the set of images taken 2 hours post tracer injection.

It must be kept in mind that a lack of retention of the tracer does not exclude the diagnosis of PHPT, as small adenomas and hyperplasia can be missed. Hence, utilizing

MIBI and US in combination is recommended to localize parathyroid adenomas, a method reported to increase the sensitivity to 95% (11,13).

Computed tomography (CT)

CT is another noninvasive imaging study that is used to localize abnormal parathyroid glands. CT is usually utilized in localizing ectopic glands, such as those in the tracheoesophageal groove or anterior mediastinum (14). One of the advantages of CT is that it is less subjective than ultrasound. A more beneficial study that has been used is the four-dimensional computed tomography (4D-CT) scan.

4D-CT scan is similar to 3D-CT angiography except with the added dimension of changes in perfusion of contrast over time (15). 4D-CT has the ability to generate exquisitely detailed, multilane images of the neck, and allows the visualization of differences in the perfusion characteristics of hyperfunctioning parathyroid glands (i.e., rapid uptake and washout) compared with normal parathyroid glands and other structures in the neck. The 4D-CT is able to provide both anatomic and functional information in a single study that can be interpreted easily by the operating surgeon and serve an important role in localization before initial and/or re-operative parathyroid procedures. A recent study by Noureldine and Aygun *et al.* suggested that the 2-phase and 4-phase CT provide an equivalent diagnostic accuracy in localizing hyperfunctional parathyroid glands; in addition, the reduced radiation exposure to the patient may make 2-phase acquisitions a more acceptable alternative for preoperative localization (16).

Intraoperative adjuncts in parathyroid surgery

Radio guided parathyroidectomy (RGP)

RGP utilizes MIBI scan to help locate abnormal parathyroid glands prior to surgery. Patients are injected with the MIBI isotope approximately 1-2 hours prior to surgery. The gamma probe is then used to direct the incision site and localize the abnormal parathyroid glands during the surgery. After removal of the suspected adenoma, the gamma probe can be used again to confirm the high metabolic activity within the resected tissue as well as monitor the surgical bed to make sure no additional hyperactive glands are left behind. Some of the potential advantages of RGP include facilitation of a minimally invasive parathyroidectomy, shorter operating time, and the ability to verify a successful surgery. Absolute contraindications for RGP include pregnancy and allergy or sensitivity to MIBI.

Intraoperative PTH (IOPTH) assay

IOPTH monitoring has been advocated by some to minimize the possibility of persistent or recurrent hyperparathyroidism and improve the surgical success of minimally invasive parathyroidectomy. Demonstrating an appropriate reduction in IOPTH levels before the surgeon leaves the operating room, as well as assessing the adequacy of resection without the need to expose all the parathyroid glands, can confirm the patient's eucalcemic status. Some of the advantages that IOPTH assay has brought to the field of parathyroid surgery are minimizing operative time, diminishing the need for bilateral neck exploration, and improving cure rates. IOPTH is based on the short half-life of circulating PTH. PTH is cleared from the blood in an early rapid phase with a half-life variously reported as 1.5-21.5 min in patients with normal renal function (17). The criteria for successful removal of hypersecreting glands are subject to ongoing debate, and the different approaches are summarized in *Table 3*. If the criteria are met, the operation is completed and the incision is closed. If the PTH fails to decrease sufficiently, further neck exploration is required. Several studies have aimed to explore the optimal percent decrease in PTH for the highest predictive cure rate. A decline of more than 50% in PTH level from the highest pre-excision level is associated with a predictive cure rate of 94-97% of cases. Some have used the return of PTH levels to the normal range as the optimal drop for a successful operation, but this criterion can be somewhat problematic since some patients have a slightly elevated baseline level. Different criteria may be utilized with similar accuracy rates. When used correctly, we believe that IOPTH is the most accurate adjunct available to the surgeon performing parathyroid surgery.

Methods

Indication and patient selection

The main concern many young females have when undergoing neck surgery, assuming there are no complications, is the incision length, location, design and healing in the assessment of the overall quality of the surgery. Therefore, guiding principles that can serve as a framework for the safe implementation of these emerging

Table 3 Different available criteria for successful parathyroidectomy using IOPTH

Institute	And/or	Minute	% drop	Compared to	PTH levels
Miami		10	≥50%	Pre-incision	
				Pre-excision	
Vienna		10	≥50%	Pre-incision	
Rotterdam	Or	10	>70%		And PTH 100-200 ng/L
		10	>80%		And PTH >200 ng/L
Ann	And		50%	Baseline	
Arbor		5 or 10			12-75 pg/mL
Wisconsin		5, 10, or 15	≥50%	Pre-incision	
				T5 if higher	

IOPTH, intraoperative parathyroid hormone; PTH, parathyroid hormone.

Table 4 Ideal patients for remote access parathyroidectomy

Sporadic primary hyperparathyroidism
Signal gland disease as suggested in preoperative ultrasonography and/or sestamibi scan
BMI <30

BMI, body mass index.

technologies in parathyroid surgery should be considered to avoid any unnecessary harm (*Table 4*). Nonetheless, ideal patient selection criteria are not well established. The ideal candidates for this approach are thin or average sized [body mass index (BMI) <30 kg/m^2] young patients with concerns of a visible neck scar, or patients with a history of hypertrophic scar formation or keloids. With our extensive experience, we have been able to expand the selection criteria of our patients. Nevertheless, we still recommend being conservative with the selection criteria, especially during the beginning of the surgeon's learning curve, which is vital for the safety and efficacy for robotic-assisted parathyroid procedures. This approach is usually deferred in patients with a previous history of neck surgery or irradiation of the neck. Patients should also be screened for contraindications that affect patient positioning during this procedure such as neck mobility problems and cervical spine disease.

Special equipment and room setup

One of the advantages of the robotic-assisted approach is its facilitation of an endoscopic neck surgery while maintaining a three-instrument approach. It also gives the surgeon the ability to retract, view target surgical anatomy, and still have two arms to operate, while maintaining traction and countertraction. The robotic wristed instruments permit the surgeon to reduce physiological tremors and increase the surgeon's operative free dexterity of movement. Three robotic instruments (Maryland dissector, ProGrasp forceps and Harmonic curved shears) and a dual-channel camera are needed. By placing the camera through the axillary/retroauricular incision and using an endoscope with 30-degree down orientation, principles from the conventional cervical approach can be applied safely to this endoscopic technique. During development of the working space, electrocautery, a vascular DeBakey forceps and various retractors (army-navy, right-angled and lighted breast retractors) are used for subcutaneous flap dissection and elevation (*Table 5*).

It is important for the surgeon to determine the best way to organize the operating room prior to the procedure. The operating table should be positioned where the anesthesiologist has access to the patient's airway. We highly recommend the use of a laryngeal nerve monitor. The patient cart is covered with sterile drapes and positioned on the contralateral side of the operating table. The patient cart is initially kept away from the operating table during the development of the working space to allow space for the surgical assistant to work across the table and retract the thyroid.

Operative technique, transaxillary approach

Step 1: patient positioning

It is essential that the patient is properly positioned for

Table 5 Equipment needed for the robotic-assisted transaxillary/retroauricular approach

Development of the working space
Electrocautery with a short, regular and long tip
Vascular DeBakey
Army-navy retractors
Right-angled retractors
Breast lighted retractors*
Table devices
Chung's retractor, or Marina retractor (Marina Medical, Sunrise, FL, USA)
Laparoscopic suction irrigator
Laparoscopic clip appliers for hemostasis
Endo Peanut 5-mm device
Robotic instrumentation
5-mm Maryland dissector
8-mm ProGrasp forceps
5-mm Harmonic curved shears
30-degree endoscope (used in the rotated down position)
Robotic arrangement
Arm 1—Maryland dissector
Arm 2—Harmonic shears
Arm 3—ProGrasp forceps
Endoscope—30-degree rotated down

*, transaxillary approach only.

surgical exposure. Patients with limited shoulder range of motion are not good candidates for this approach. The arm and shoulder should be at the same vertical height, with proper padding of the forearm and elbow to prevent neuropraxia or stretch injury.

The patient is positioned supine under general anesthesia and intubated with an Nerve Integrity Monitor (NIM) endotracheal tube (Medtronic Xomed, Jacksonville, FL, USA) to allow intraoperative monitoring of recurrent laryngeal nerve (RLN) function. The neck is then slightly extended and the arm ipsilateral to the lesion (ipsilateral to the larger parathyroid gland) is placed cephalad and flexed above the head (modified Ikeda's arm position) (*Figure 2*). Additionally, we routinely perform monitoring for the median and ulnar nerves using somatosensory evoked potentials (SSEP) (Biotronic, Ann Arbor, MI, USA) to avoid neuropraxia (*Figure 3*). However, many other robotic surgeons do not use SSEP and were able to avoid this serious complication by careful positioning of the arm. Other surgeons place

Figure 2 Patient is positioned supine under general anesthesia and intubated with an NIM endotracheal tube. NIM, Nerve Integrity Monitor.

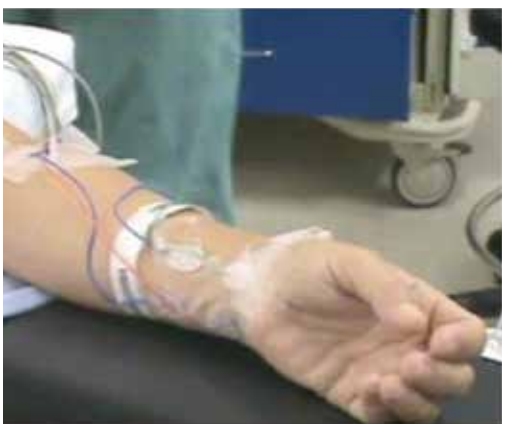

Figure 3 Ulnar and median nerves are routinely monitored using somatosensory evoked potentials (SSEP).

the ipsilateral arm on an arm board. In our opinion, this would increase the dissection distance from the axilla to the thyroid bed. Professor Chung initially described rotating the ipsilateral arm to the lesion nearly 180 degrees cephalad, then placed on an arm board and padded. However, this was not very well tolerated in the Western population. Using this modified Ikeda's arm position shortens the distance between the axilla and the thyroid space.

Intraoperative ultrasound examination is recommended by many robotic surgeons prior to the surgical incision, to further aid the surgeon in determining the exact location of the parathyroid lesion and to examine the relationship of the internal jugular vein to the thyroid gland in the

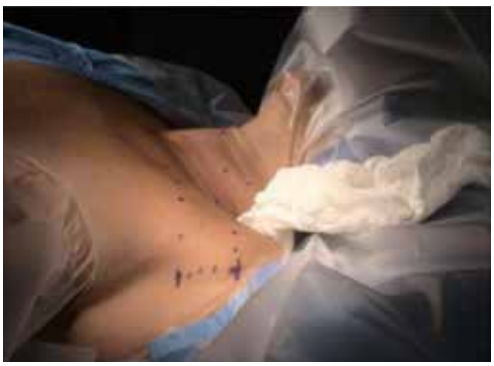

Figure 4 Landmarks for the robotic trans-axillary incisions.

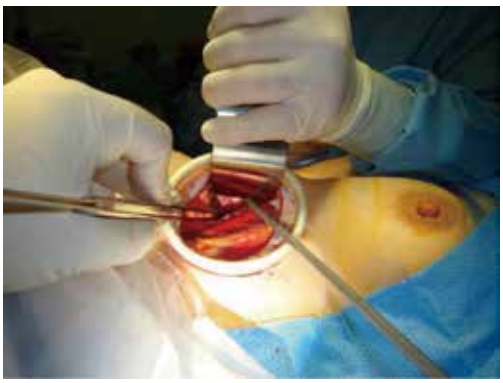

Figure 5 Subcutaneous plane is developed superficial to the pectoralis major muscle fascia and the heads of the SCM are identified (The plane can be developed using electrocautery or ultrasonic Harmonic scalpel). SCM, sternocleidomastoid.

anteroposterior plane.

During parathyroid surgery, Blood is drawn for a baseline rapid PTH serum level prior to prepping or palpating the neck.

Step 2: skin incisions

The location of the incision is determined by drawing a transverse line from the sternal notch laterally to the axilla, which marks the inferior limit of the incision. The inferior limit of the incision is directed posteriorly towards the patient's back to ensure the incision will be well hidden. A 60-degree oblique line is drawn from the thyrohyoid membrane to the axilla, which marks the superior limit of the incision (*Figure 4*). The anterior chest and neck are prepped and draped. Following infiltration with 10 mL of 1% lidocaine with 1 in 200,000 adrenaline, a 5-6 cm incision is made with a scalpel from the intersection of the oblique line and the anterior axillary line as the superior limit and the intersection of the transverse line with the anterior axillary line as the inferior limit. Attention to detail in incising and handling the skin reduces cicatrix hypertrophy. For less experienced surgeons, the use of breast fold trocar will provide an easier operative technique. An additional small 0.8-cm skin incision can be made in the anterior chest wall, in the medial fold of the breast and 2-cm superior to the patient's nipple. A trocar is used, and one of the robotic arms can be docked to the cannula and can assist in the manipulation, retraction and dissection of the thyroid gland. However, with experience, all instruments can be placed through a single axillary incision.

Step 3: establishing the working space

Dissection is then carried out using a monopolar electrocautery to create a subplatysmal plane anterior to the pectoralis fascia up to the clavicle. A wound protector (Alexis wound retractor system from Applied Medical, CA, USA) can be used to protect the axillary wound edges from any heat generated by the electrocautery or Harmonic scalpel and to expand the incision. Retractors can be used to maintain proper visualization as the dissection is carried out. An extended-tip Bovie is needed to aid in the dissection.

The clavicle is then identified and followed medially, which naturally leads to the dissection of the sternocleidomastoid (SCM) muscle (*Figure 5*). The surgeon should then develop a wide access to the midline of the neck through the axilla. This could be challenging in the obese population. When elevating the skin, the surgeon can avoid "buttonholes" into the skin by having an assistant pull the skin away from the tunnel. When using the lightened skin retractor, dissection should be carried out deep and lateral to the retractor to minimize the risk of skin injury. In general, the working space should be carried out from the clavicular head to just above the omohyoid muscle, which correlates with the superior pole of the thyroid lobe.

The triangulated window between the sternal head of the SCM (medially) and the clavicular head of the SCM (laterally) is then identified. Once these muscles are lifted, the surgeon will find the thyroid lobe covered by the adherent sternothyroid muscle. The uppermost fibers of the sternothyroid muscle are then dissected off the superior pole of the gland, as in open surgery. Using the Harmonic scalpel helps to develop a reasonable space between the sternal heads of the SCM, and the strap muscles are then lifted anteriorly by inserting and suspending the Chung

retractor, creating the working space and exposing the anterior surface of the thyroid gland.

After suspending the retractor apparatus, the anesthesiologist should reconfirm adequate padding of the neck and shoulders. If the surgeon prefers, the second chest wall incision is made at this point. It is important to note that placing the chest wall trocar after the placement of the retractor apparatus will confirm the proper positioning of the chest wall retractor below the Chung retractor. However, placing the trocar prior to placing the Chung retractor would risk covering the entry of the chest wall retractor under the Chung retractor.

Operative technique, retro-auricular approach

Step1: patient positioning

Patients are placed supine on the operating room table. The head is turned to the side contralateral to the side of the diseased gland. Patients are intubated using a NIM endotracheal tube size 6.0 (Medtronic Xomed, Jacksonville, FL, USA) to allow intraoperative monitoring of RLN function.

Step 2: skin incisions

A small portion of postauricular hair is shaved for the extension of the planned incision lines into the hair-bearing skin. The retroauricular incision is then marked out just posterior to the earlobe, extending into the postauricular crease and adjacent to the occipital hairline at a position that will be covered completely by the ear and hair at rest.

Step 3: establishing the working space

The flap is created superficial to the platysma using a Metzenbaum scissor. Care is taken to preserve the greater auricular nerve. Dissection in the plane superficial to the platysma is performed until the head of the sternocleidomastoid muscle is visualized.

The space between the strap muscles and the SCM is created with electrocautery or Harmonic scalpel (Ethicon, Somerville, NJ, USA).

The working space is created all the way to just above the omohyoid muscle, which correlates with the superior pole of the thyroid lobe.

A specially designated retractor (Marina Medical, Sunrise, FL, USA) is then secured to the table mount lift and placed under the strap muscles to allow continuous exposure of the surgical field, maximizing access to the parathyroid gland. The flap creation time is approximately 30 minutes.

Step 4: docking of the da Vinci Si surgical robot

At this time, the da Vinci Si system (Intuitive Surgical, Inc., Sunnyvale, CA, USA) is docked using the 30° scope, Maryland dissector, and a Harmonic scalpel (The camera is positioned in the center of the field, a Maryland grasper is placed in the nondominant hand, and the Harmonic is placed in the dominant hand). Nerve dissection at the cricothyroid membrane entrance, and stimulation at its most consistent location just proximal to the inferior margins of the inferior constrictor muscle, is performed by the assistant at the bedside to confirm nerve integrity. The docking time is approximately 7 minutes.

Docking of the da Vinci Si surgical robot

The Intuitive Surgical Model Si robot (Intuitive, Sunnyvale, CA, USA) is docked from the contralateral side of the operative field, with the 30-degree down looking endoscope, Harmonic scalpel, and Maryland forceps entering via the axillary/Retro-auricular incision. For less experienced surgeons, the Harmonic curved shears are placed in the robotic arm corresponding to the surgeon's dominant arm; however, this is not an issue with more experienced surgeons. Professor Chung recommends having the Harmonic scalpel in the patient's "right-hand" position, regardless of the side of the lesion. Nevertheless, because the Harmonic scalpel does not have the same freedom of motion as other instruments, some surgeons move the Harmonic between the other robotic arms to improve visualization or the angle of approach. This maneuver is used more often when operating from the patient's right-hand side. Currently, Intuitive has a vessel sealer with wristed movements which some surgeons are using during robotic thyroid surgery. However, this vessel sealer is significantly larger in size than the Harmonic Shears.

Placement of the instruments deserves special attention to allow optimal visualization and avoid collision of the instruments during the operation. The camera should be positioned high inside the wound, to provide a 30-degree downward view angle onto the thyroid bed.

Parathyroid dissection

The army-navy retractor is used to retract the SCM clavicular head inferiorly. The thyroid gland is turned medially, then the plane between the parathyroid and the thyroid gland is identified and very meticulous circumferential dissection of the parathyroid from the

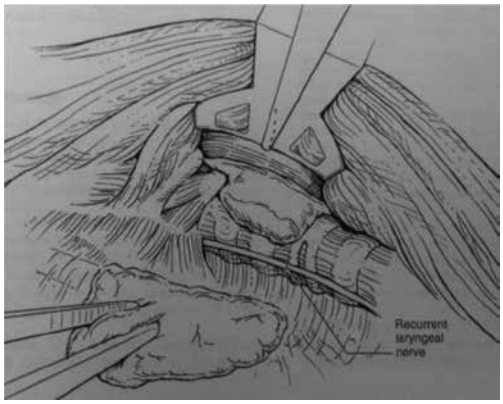

Figure 6 Identification of the recurrent laryngeal nerve in the tracheosophageal groove.

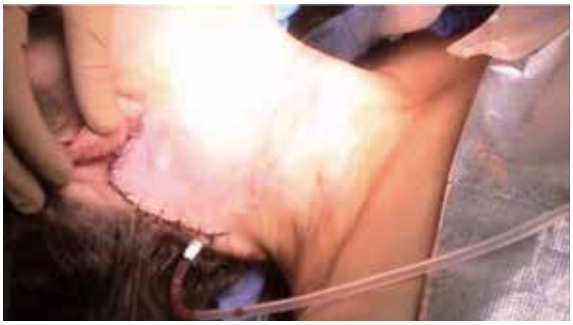

Figure 7 Closure of the skin at the hairline with interrupted 5-0 Prolene sutures and staples.

thyroid gland is performed using a Maryland dissector. Adventitious tissue between the thyroid and parathyroid gland is dissected using the Harmonic scalpel. A gamma probe is brought into the field by the assistant and is used to confirm the location of the parathyroid gland. Identification of the inferior thyroid pedicle with dissection RLN in the tracheoesophageal groove is then undertaken to minimize the risk of injury to either structure (*Figure 6*). The nerve monitor stimulation is then brought to the field by the assistant to confirm the integrity of the RLN. After separating the parathyroid gland medially and circumferentially, the pedicle of the parathyroid is then identified and dissected at the base using the Harmonic scalpel. An endocatch bag is then brought into the field by the assistant, and the parathyroid gland is placed in the bag and removed safely through the retroauricular incision. A gamma probe is then used to confirm the absence of any residual parathyroid tissue.

Curative resection is established with the aid of IOPTH monitoring. We routinely place a drain protruding through the retroauricular incision. Interrupted subdermal closure is performed with 3-0 Vicryl suture. The skin at the hairline is closed with interrupted 5-0 Prolene sutures and staples (*Figure 7*). For patients who underwent concomitant neck lift surgery, the flap is created bilaterally using the above-mentioned approach. At the end of surgery and after the robot is undocked, excision of extra skin on both sides is performed prior to surgical site closure.

Postoperative management

Robotic-assisted transaxillary/retro-auricular parathyroidectomy is usually performed as an outpatient procedure. Patients are discharged on anti-inflammatory pain medication with narcotics only for breakthrough discomfort. Postoperative management is similar to that of the open approach. The drain is removed at the patient's postoperative visit, usually 2 or 3 days after surgery. Due to the large working space, the risk of airway compression from hematoma postoperatively is lower when compared to that of the open approach. Therefore, some surgeons feel comfortable discharging their patients the same day of surgery with an advanced cold and compression regime, which helps with pain and swelling. Others will keep their patients overnight for observation. Many patients do not require any pain medication in their postoperative recovery.

Parathyroidectomy patients are supplemented with calcitriol 0.25 mcg twice daily and elemental calcium 1 g twice daily unless signs or symptoms of hypocalcemia present. No laboratory studies are required following intraoperative verification of serum PTH normalization. The patient's first outpatient follow-up is 3-4 days postoperatively for pathology review, wound inspection and further instruction on wound care. Duration and extent of vitamin D and calcium supplementation are based on preoperative bone mineral density determination and interdisciplinary management with an endocrinologist.

Patients can be discharged on the same day of surgery.

Conclusions

Due in part to the social stigmatization of young females with visible scars, the remote endoscopic technique was implemented, refined and later enhanced with the advancement in robotic technology. The introduction of robotic technology into thyroid and parathyroid surgery has

gained wide popularity in Asia, Europe and North American practice. Different approaches have been described recently, including axillary and the retroauricular region, resulting in a lack of visible neck scars. In order to maximize the utilization of these approaches, multiple preoperative scans must be performed in order to help localize the diseased gland for a targeted parathyroidectomy. Remote access has been shown to be a feasible and safe approach for parathyroidectomy in select patients.

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References

1. Noureldine SI, Lewing N, Tufano RP, et al. The role of the robotic-assisted transaxillary gasless approach for the removal of parathyroid adenomas. ORL J Otorhinolaryngol Relat Spec 2014;76:19-24.
2. Katz L, Abdel Khalek M, Crawford B, et al. Robotic-assisted transaxillary parathyroidectomy of an atypical adenoma. Minim Invasive Ther Allied Technol 2012;21:201-5.
3. Landry CS, Grubbs EG, Morris GS, et al. Robot assisted transaxillary surgery (RATS) for the removal of thyroid and parathyroid glands. Surgery 2011;149:549-55.
4. Foley CS, Agcaoglu O, Siperstein AE, et al. Robotic transaxillary endocrine surgery: a comparison with conventional open technique. Surg Endosc 2012;26:2259-66.
5. Mohamed SE, Li X, Khadra H, et al. Different surgical approaches in parathyroid adenoma resections. Gland Surg 2013;2:227-9.
6. Udelsman R, Donovan PI, Sokoll LJ. One hundred consecutive minimally invasive parathyroid explorations. Ann Surg 2000;232:331-9.
7. Macfarlane DP, Yu N, Leese GP. Subclinical and asymptomatic parathyroid disease: implications of emerging data. Lancet Diabetes Endocrinol 2013;1:329-40.
8. Temmim L, Sinowatz F, Hussein WI, et al. Intrathyroidal parathyroid carcinoma: a case report with clinical and histological findings. Diagn Pathol 2008;3:46.
9. Roy M, Mazeh H, Chen H, et al. Incidence and localization of ectopic parathyroid adenomas in previously unexplored patients. World J Surg 2013;37:102-6.
10. Liu ST, Li P, Feng L, et al. Diagnosis and surgical treatment of parathyroid neoplasms. Zhonghua Yi Xue Za Zhi 2013;93:2062-4.
11. Lumachi F, Zucchetta P, Marzola MC, et al. Advantages of combined technetium-99m-sestamibi scintigraphy and high-resolution ultrasonography in parathyroid localization: comparative study in 91 patients with primary hyperparathyroidism. Eur J Endocrinol 2000;143:755-60.
12. Abdelghani R, Noureldine S, Abbas A, et al. The diagnostic value of parathyroid hormone washout after fine-needle aspiration of suspicious cervical lesions in patients with hyperparathyroidism. Laryngoscope 2013;123:1310-3.
13. Kasai ET, da Silva JW, Mandarim de Lacerda CA, et al. Parathyroid glands: combination of sestamibi-(99m) Tc scintigraphy and ultrasonography for demonstration of hyperplasic parathyroid glands. Rev Esp Med Nucl 2008;27:8-12.
14. Ismail M, Maza S, Swierzy M, et al. Resection of ectopic mediastinal parathyroid glands with the da Vinci robotic system. Br J Surg 2010;97:337-43.
15. Chazen JL, Gupta A, Dunning A, et al. Diagnostic accuracy of 4D-CT for parathyroid adenomas and hyperplasia. AJNR Am J Neuroradiol 2012;33:429-33.
16. Noureldine SI, Aygun N, Walden MJ, et al. Multiphase computed tomography for localization of parathyroid disease in patients with primary hyperparathyroidism: How many phases do we really need? Surgery 2014;156:1300-6; discussion 13006-7.
17. Xing M, Westra WH, Tufano RP, et al. BRAF mutation predicts a poorer clinical prognosis for papillary thyroid cancer. J Clin Endocrinol Metab 2005;90:6373-9.

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Single incision robotic transaxillary approach to perform parathyroidectomy

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Introduction

The recent development of robotic systems provided a safe, precise, 3D magnified dissection without the need for CO_2 insufflation and has a better cosmetic result due to the invisible axillary scar in the neutral position (1). In the past two decades, significant improvements in the accuracy and reliability of preoperative localization studies have facilitated further evolution in surgical management of primary hyperparathyroidism (2). Targeted parathyroidectomy is the current preferred procedure for PHPT by most endocrine surgeons (3,4).

Herein, we are presenting a video for a patient with a typical parathyroid adenoma that required, enblock resection of parathyroid adenoma with the adjacent thyroid lobe. The robotic transaxillary approach provided a remote access to avoid a visible neck scar.

Procedure steps

Patient positioning and placement of NIMS endotracheal tube

The patients' neck was slightly extended, and the arm ipsilateral to the lesion was placed cephalad and flexed above the head as described by Ikeda (5-7). This optimized exposure of the axilla and created a short distance from the axillary skin to the thyroid gland, through which dissection was performed.

The patient was intubated under general anesthesia with a NIMS endotracheal tube (Medtronic Xomed, Jacksonville, FL, USA) to allow intraoperative monitoring of the RLN function. Appropriate placement of the NIMS endotracheal tube was confirmed by direct laryngoscopy and by visualization of the electromyographic wave form on the NIMS monitor.

Creation of a working space

The thyroid was identified by palpation and a vertical line was drawn from the midline of the thyroid to the sternal notch, demarcating the medical boundary of dissection. The inferior limit of dissection was drawn from the sternal notch to the ipsilateral axilla in a transverse manner. The superior limit of dissection was drawn in an oblique manner from the cricoid to the axilla.

Approximately two inches incision was then made with a #15 blade. Monopolar electrocautery under direct vision was then used to dissect above the pectoralis fascia. A flap was raised in the direction of the thyroid until the sternal and clavicular heads of the sternocleidomastoid muscle were visualized, opened and a retractor is used to elevate and retract the sternal head exposing the strap muscles. A wound protector was placed to protect the axillary wound edges from any heat generated by the electocautery or the harmonic scalpel. The triangular window between the sternal and clavicular heads was entered using the Harmonic Scalpel (Ethicon, Somerville, NJ, USA), allowing identification of the carotid sheath and omohyoid muscle. The strap muscles are then elevated off the thyroid gland providing exposure from the sternal notch to the superior pole and across the midline. Special retractor (Marina Medical, Sunrise, FL, USA) was placed under the strap

muscles and secured to the table mount lift to maintain an adequate working space without CO_2 gas insufflations.

Docking of the surgical robot system

The da Vinci Si robot was docked from the side of the bed contralateral to the operative field. The robotic instruments used were the Pro Grasp forceps (Intuitive Surgical, Sunnyvale, CA, USA), Maryland Dissector (Intuitive Surgical, Sunnyvale, CA, USA) and Harmonic scalpel (Ethicon, Somerville, NJ, USA). The 30 degree endoscope is used in a downward facing orientation. The robotic arms were equipped with the Maryland dissector, the Pro Grasp forceps and the Harmonic scalpel. The Maryland dissector and Harmonic scalpel should be as far apart as possible.

The gland was then grasped by the Pro grasp and rotated medially. The middle thyroid vein was then dissected with the Maryland dissector and divided using the harmonic scalpel.

Identification and accurate dissection of the RLN

Dissection of RLN was performed in tracheoesophageal groove and location of the RLN with identification confirmed via intraoperative nerve monitoring. Then the inferior thyroid pedicle was dissected and divided using the harmonic scalpel. The superior pedicle was also dissected and divided using the harmonic scalpel.

Resection of parathyroid adenoma and closure

The thyroid gland was at that point turned medially and with cautious dissection the parathyroid adenoma identified. The adenoma was then circumferentially dissected and excised enblock with the thyroid lobe. Intraoperative PTH monitoring was performed to ensure a successful operation. The wound was irrigated and excellent homeostasis was achieved. A Jackson-Pratt drain was coursed through the axilla and sutured to the skin. The wound was closed with absorbable running sutures.

Comments

Patients who might have multiglandular disease are not good candidates for this surgery.

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References

1. Lee D, Nam Y, Sung K. Single-incision endoscopic thyroidectomy by the axillary approach. J Laparoendosc Adv Surg Tech A 2010;20:839-42.
2. Palazzo FF, Delbridge LW. Minimal-access/minimally invasive parathyroidectomy for primary hyperparathyroidism. Surg Clin North Am 2004;84:717-34.
3. Tolley N, Arora A, Palazzo F, et al. Robotic-assisted parathyroidectomy: a feasibility study. Otolaryngol Head Neck Surg 2011;144:859-66.
4. Miccoli P, Bendinelli C, Berti P, et al. Video-assisted versus conventional parathyroidectomy in primary hyperparathyroidism: a prospective randomized study. Surgery 1999;126:1117-21; discussion 1121-2.
5. Ikeda Y, Takami H, Niimi M, et al. Endoscopic thyroidectomy and parathyroidectomy by the axillary approach. A preliminary report. Surg Endosc 2002;16:92-5.
6. Kandil EH, Noureldine SI, Yao L, et al. Robotic transaxillary thyroidectomy: an examination of the first one hundred cases. J Am Coll Surg 2012;214:558-64; discussion 564-6.
7. Kandil E, Abdelghani S, Noureldine SI, et al. Transaxillary gasless robotic thyroidectomy: a single surgeon's experience in North America. Arch Otolaryngol Head Neck Surg 2012;138:113-7.

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Guideline

Clinical guidelines on intraoperative neuromonitoring during thyroid and parathyroid surgery

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Introduction

Recurrent laryngeal nerve (RLN) injury is one of the most severe complications of thyroid surgery. Hoarseness due to unilateral RLN injury and breathing disorders and even asphyxia due to bilateral RLN injury can impose serious impacts on the patient's life. It is estimated that the incidence of RLN injury during thyroid surgeries ranges 0.3-18.9% (1-5), making RLN protection a great concern among thyroid surgeons. Intraoperative neuromonitoring (IONM) combines both the functional and anatomic techniques and has the following features: intra-operative navigation and rapid identification of the RLN distribution; predicting nerve variation and protecting of the functional integrity of RLN; clarifying the mechanism and lowering the incidence of RLN injury; and easy to perform. It is a helpful adjunct for complicated surgeries (6,7).

With an attempt to help the surgeons thoroughly understand IONM and carry out this technique in a standardized and reasonable manner, the Chinese Thyroid Association established the Clinical Guidelines on IONM during Thyroid and Parathyroid Surgeries (China Edition).

Basic principles of IONM

Application of IONM in thyroid surgeries was initially proposed by Shedd in 1966 and by Flisberg in 1970. Based on the principle of electrophysiology, the motor nerve is stimulated by electricity during the surgery, and then the nerve impulses are formed and transferred to the dominant muscles to produce myoelectric signals, forming waves and alerts in electromyography (EMG), which will help the surgeons to judge the functional integrity of nerves (8,9) (*Figure 1*).

Clinical significance and technical advantages of IONM

For doctors who are transforming from generalist to specialist, junior doctors, and surgeons who are facing a complicated thyroid surgery, IONM undoubtedly is a good aid (10-12).

Facilitates the identification and locating of RLN

Before RLN exposure, the nerve can be accurately located at its distribution area using the cross method, which enables the doctor to rapidly determine the anatomic range of RLN as well as its rare anatomic variations such as non-recurrent RLN (13).

Facilitates the exposure and dissection of RLN

During the dissection of RLN, continuous monitoring together with naked-eye observation enables the

differentiation between the monitored nerve and its surrounding non-nerve tissues and the accurate tracing of the nerve and its functional branches. Also, the intra-operative navigation is also helpful for the complete resection of lesions.

Facilitates the judgment of the functional integrity and injury mechanisms of nerves

Electrophysiological monitoring provides quantitative indicators for judging the functional integrity of nerves, can accurately locate the "injury point" of a nerve (14) (*Figure 2*), and help the operator to analyze the injury mechanism and timely recognize and resolve the injury during surgery. Thus, it can markedly reduce the incidence of RLN injury.

Indications of IONM (15-18)

IONM is a preferred option in the following patients, while its application in the other patients should be upon the doctor's recommendation: (I) the mass is located at the dorsal side of the thyroid, with suspected recent capsular hemorrhage or thyroid cancer; (II) in patients with hyperthyroidism, pre-operative ultrasound indicates large gland and rich blood supply; (III) in patients with malignant thyroid tumor, neck lymph node dissection is required, especially in patients with swollen central lymph nodes; (IV) patients receiving a second thyroid surgery but with disordered anatomic structures and severe adhesions; (V) patients with retrosternal goiter and/or large thyroid mass, along with suspected RLN dislocation; (VI) pre-operative imaging indicated the presence of transposition of viscera or subclavian artery variation, along with suspected non-recurrent RLN; (VII) patients with unilateral vocal cord paralysis, with the contralateral lobe requiring surgical treatment; (IX) patients requiring total thyroidectomy, in particular an endoscopic surgery; (X) patients requiring a surgery to repair RLN injury; (XI) patients requiring a parathyroid surgery; and (XII) patients with special requirements on sound and tone and thus requiring IONM.

Notably, (I) if intra-operative exploration shows that the thyroid cancer has completely infiltrated the RLN, nerve preservation will unavoidably result in residual tumor; thus, the invaded nerve must be resected to thoroughly remove the tumor. Under such circumstances, the post-operative hoarseness can not be avoided even after the application of IONM; (II) in patients with pre-operative vocal palsy, IONM

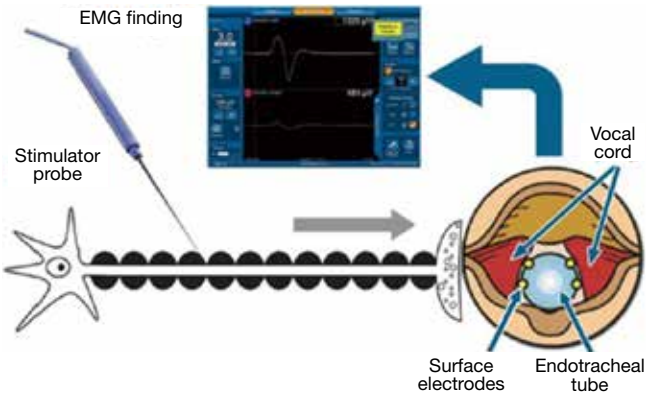


Figure 1 Basic principles of IONM. IONM, intraoperative neuromonitoring.

can be applied to search for the injury site, and nerve repair can be completed with the assistance of IONM; however, it is difficult to completely restore the nerve function.

Since it is impossible to predict all the complex cases before a thyroid or parathyroid surgery, the indications of IONM may be widened if condition allows. The same recommendation has also proposed in international literature: since it is difficult to predict RLN variation before surgery, IONM may be routinely applied if condition allows.

Essential monitoring devices of IONM

The IONM devices can be divided into recording side (recording electrode and its ground electrode) and stimulation side (stimulator probe and its loop electrodes) as well as EMG monitor, interface-connector box, anti-jamming silence detector, and patient simulators (19) (*Figure 3*).

Needle-like electrode and intubation surface electrode are two typical recording electrodes, with the latter being routinely recommended (20).

The stimulation probes can be divided into monopolar and bipolar types, with the monopolar Prass probe with ball tip is routinely recommended (21).

Standardized procedures of IONM

Non-standard application of IONM techniques will cause significant monitoring errors. The main aim of standardized IONM procedures is to guide and improve the quality of IONM techniques and avoid any adverse effect due to improper monitoring operations (22-24). The standard procedure of IONM is shown in *Table 1*.

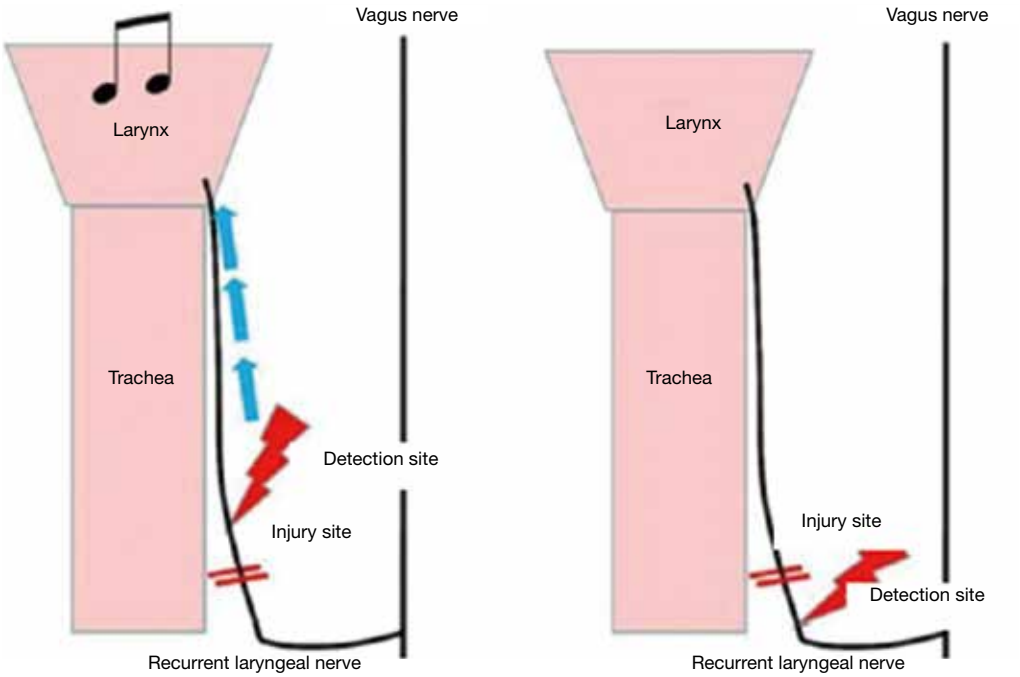


Figure 2 Locating nerve "injury site" by IONM. IONM, intraoperative neuromonitoring.

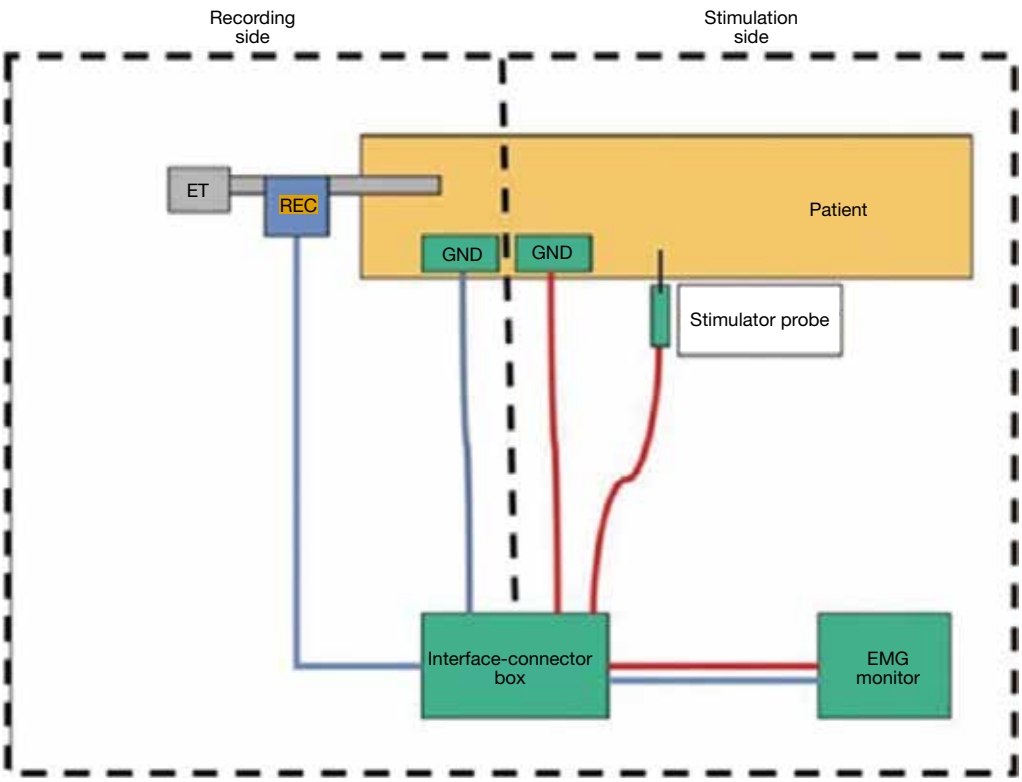


Figure 3 Basic monitoring equipment setup. ET, endotracheal tube; REC, recording electrodes; GND, ground electrodes; EMG, electromyography.

Table 1 The standard procedures of IONM

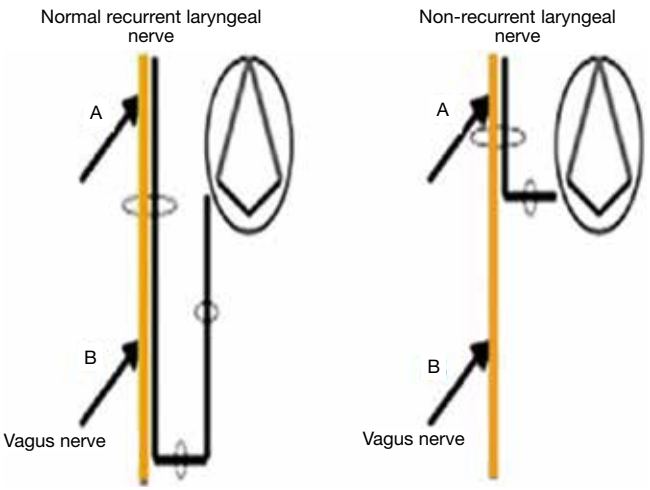
Procedures	Note
Record vocal cord movement before surgery	Use of fiberoptic laryngoscope
Recommended anesthesia method for IONM	Intermediate- or short-acting muscle relaxant is recommended for preoperative anesthesia induction. The dosage of intermediate-acting muscle relaxant is smaller than that used for routine anesthesia induction. 1x ED95 intermediate-acting non-depolarizing muscle relaxant is recommended; avoid adding muscle relaxant before the termination of intraoperative monitoring
Body position and tube placement	Anesthesia intubation is performed after positioning (intubation under video laryngoscope is recommended)
Device connections and checking	
The ground electrodes are routinely placed under the skin at the shoulders or xiphoid	
Confirm the monitoring system has been effectively established	
Check electrode impedance and differences in impedance values	Electrode impedance <5 kΩ, with deviations <1 kω
Check initial EMG	Initial fluctuations: about 10 μV
Set up event thresholds	Typically 100 μV
The current intensity of stimulator probe should be routinely set at 1-3 mA	
The monitoring device should be placed far away from electro-surgical devices and be connected with anti-jamming silence detectors	
The recording electrode positions should be confirmed during surgery	Directly detect, locate, and record the electrode depth at the antemedial laryngeal line using stimulator probe
IONM four-step method	
Step 1: V1 signal	Obvious bipolar EMG signal is obtained at the ipsolateral vagus nerve at the plexas thyreoidea inferior level (point B), confirming the successful establishment of the monitoring system. If signal is absent at point B, detect the vagus nerve at the plexas thyroid superior level (point A); the presence of signal at point A confirms the presence of non-recurrent laryngeal nerve (25) (*Figure 4*)
Step 2: R1 signal	Before the exposure of RLN, its EMG signal is located using the Cross method by applying the probe vertical to trachea at its traveling area and then parallel to trachea
Step 3: R2 signal	Continuous monitoring is applied during the dissection of RLN and the signal change is compared in a real-time manner. After the RLN is exposed, the most proximal end of the exposed part is detected for EMG signal
Step 4: V2 signal	After complete hemostasis is achieved at the surgical field, the EMG signal of the vagus nerve is detected before closing the incision
Signal analysis	
Basic EMG parameters	The biphasic waveform should be differentiated from the monophasic non-EMG artifacts

Table 1 *(continued)*

Table 1 *(continued)*

Procedures	Note
No obvious decrease in R2 and V2 signals	The basic EMG parameters include amplitude, latency and duration (26) (*Figure 5*); the RLN has intact function
Loss of R2 and V2 signals	If the RLN is injured during the surgical operation, detect the "injury site" and search for the injury cause*
Photo recording the exposed RLN during surgery	To confirm the RLN continuity (visual integrity)
Postoperative laryngoscopy	

*, If no "injury site" is detected, it is important to determine whether there is a "real" loss of signal. (I) stimulate the nerve and then observe the contact between endotracheal tube electrode and vocal cord via a laryngoscope; (II) detect signals at vagus nerve and RLN again before closing the incision. IONM, intraoperative neuromonitoring; RLN, recurrent laryngeal nerve.



Results of vagus nerve monitoring	Normal nerve signa	Non-recurrent nerve signal
B (plexas thyreoidea inferior)	With signal	Without signal
A (plexas thyreoidea superior)	With signal	With signal

Figure 4 Monitoring setup of non-recurrent laryngeal nerve.

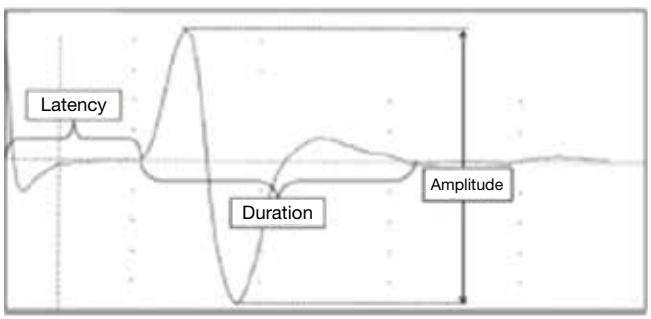


Figure 5 Basic parameters of the EMG wave of IONM. IONM, intraoperative neuromonitoring.

Causes and solutions of common IONM errors

The incidence of IONM error ranges 3.8-23.0% (27). IONM errors can bring great psychological pressure to the operator, delay the surgical process, and even cause the operator make wrong decision. Therefore, it is important to master the causes and solutions of common IONM errors, so as to ensure the surgery is performed in a safe and smooth manner. *Table 2* lists the causes and solutions of common IONM errors, and the troubleshooting process (28) is displayed in *Figure 6*.

The standard application of IONM can help 85% of beginners to smoothly locate the laryngeal nerves, provide quantitative indicators of nerve function for surgeons, assist the surgeons to deal with the complicate anatomic structures and skillfully keep away from the dangerous areas. Also, by using both eyes and ears (by listening to the alerts), the operators can accurately resect the tumor. Thus, IONM has become an effect adjunct for the golden standard of naked-eye protection. With "simple, effective, and practicable" as the basic principles, the Clinical Guidelines on IONM during Thyroid and Parathyroid Surgeries (China Edition) established by Chinese Thyroid Association elucidates the standardized operation procedures and decision-making steps of IONM. Before the application of IONM, the surgeons need to fully know neuromonitoring systems and thoroughly understand the Guidelines and receive corresponding training and verification in a standardized monitoring base.

Table 2 Causes and solutions of common IONM errors

Common IONM errors	Causes	Solutions
Electrode impedance is too high	The subcutaneous electrodes have not completely removed after its withdrawal from patients	Check whether the subcutaneous electrodes fall off and keep the electrode clean
Subcutaneous electrodes >10 kΩ	The impedance of the electrode itself is too high	Replace the electrodes and fix them with tape
Stimulator probe electrodes >25 kΩ	The electrode core does not connect well with the interface-connector box The interface-connector box does not connect well with the monitor	Check the connections of the interface-connector box
Recording electrodes	The recording electrode does not connect well with vocal cord	Adjust the tube depth and angle under fiberoptic laryngoscope
Single electrode impedance >5 kΩ	The surface electrode of endotracheal tube is displaced	Indwell the tube under conventional video laryngoscope
Impedance deviation>1 kΩ	Application of insulating lubricant before intubation	Avoid the application of insulating medium at the recording electrodes
Electrode impedance is zero	Two subcutaneous electrodes contact with each other	Re-indwell the subcutaneous electrodes, with the inter-electrode distance of >1 cm
Electrosurgical interference	The probe of anti-jamming detector is not connected	Circle the cable of the electrosurgical device, with the anti-jamming detector clipped on the twisted cable
After the establishment of standard monitoring system	Preoperative vocal cord palsy	Re-check the preoperative laryngoscopic records
Before thyroid surgery	The nerve detected by the operator is actually not a vagus nerve	Detect at 1 mA after confirming the exposure of vagus nerve
V1 signal is absent	The vagus nerve is injured during its exposure non-recurrent laryngeal nerve is present	Directly detect the carotid sheath at 3 mA to obtain the V1 signal If the signal of vagus nerve is absent at the plexas thyreoidea inferior level, re-check it at the plexas thyreoidea superior level
	Anesthesia induction is not performed as recommended	Wail until the muscle relaxant wears off or use a proper dose of a muscle relaxant antagonist
	Improper type or dosage of muscle relaxant The detection current is not high enough	Check the matching between the measured stimulation (as displayed on monitor) and the stimulation setup value Re-check the connections between the electrodes and the interface-connector box Check whether the fuse in the interface-connector box has been burned out

Table 2 *(continued)*

Table 2 *(continued)*

Common IONM errors	Causes	Solutions
	The frequency of stimulus pulse is too low	Stimulus pulse frequency: 4 times/s by default
	The setup of event threshold is too high	Routinely 100 μV; avoid changing this parameter value casually
	The selected monitoring mode, channel, and volume are improper	Re-check the monitoring mode, channel, and volume setup
	The duration of detection for nerve is too short	Each detection should be maintained at least 1s
	The probe is damaged, with insulation layer falling off	Avoid reuse
	The shunt of the nerve detection area is too large	Clear liquids at the detection area
	The muscle for detecting neurological effects is detached from the recording electrode	Re-check whether the electrodes are off
		The depth of the surface electrodes of endotracheal tube can be detected and located at the laryngeal anteromedian line
EMG signal is present while no nerve is detected	Consecutive “sequence” EMG response cannot be explained	Light anesthesia, with spontaneous activity of laryngeal muscle; the recording nerve or muscle is tracted by other nerve or muscle
	Artifacts occur in the non-neural traveling area	The surface electrode of endotracheal tube is placed too deeply
	The detection current is too large	Direct detect the nerve trunk (1 mA is recommended)
		Adjust according to the anatomic structures and EMG signals during the surgery
V1 signal is good, confirming the establishment of standard monitoring system, whereas there is the decrease of signal by >50% or LOS during the dissection of RLN	Intraoperative anesthesia or muscle relaxation status changes	Avoid adding muscle relaxant before the termination of monitoring
	Nerve transection injury	Check the nerve continuity
	Nerve injury not visible to the naked eye	Locate the injury site and analyze the possible injury mechanisms: traction injury, heat injury, suction injury, and/or thread-cutting injury
	Monitoring system failure	Re-check the electrode connections to ensure a good circuit performance
	Recording electrode displacement due to changes in head position or body position during the surgery	Use simulators to re-check the monitor and interface-connector box (e.g., fuse)
		Re-check the laryngoscope and adjust the endotracheal tube

RLN, recurrent laryngeal nerve.

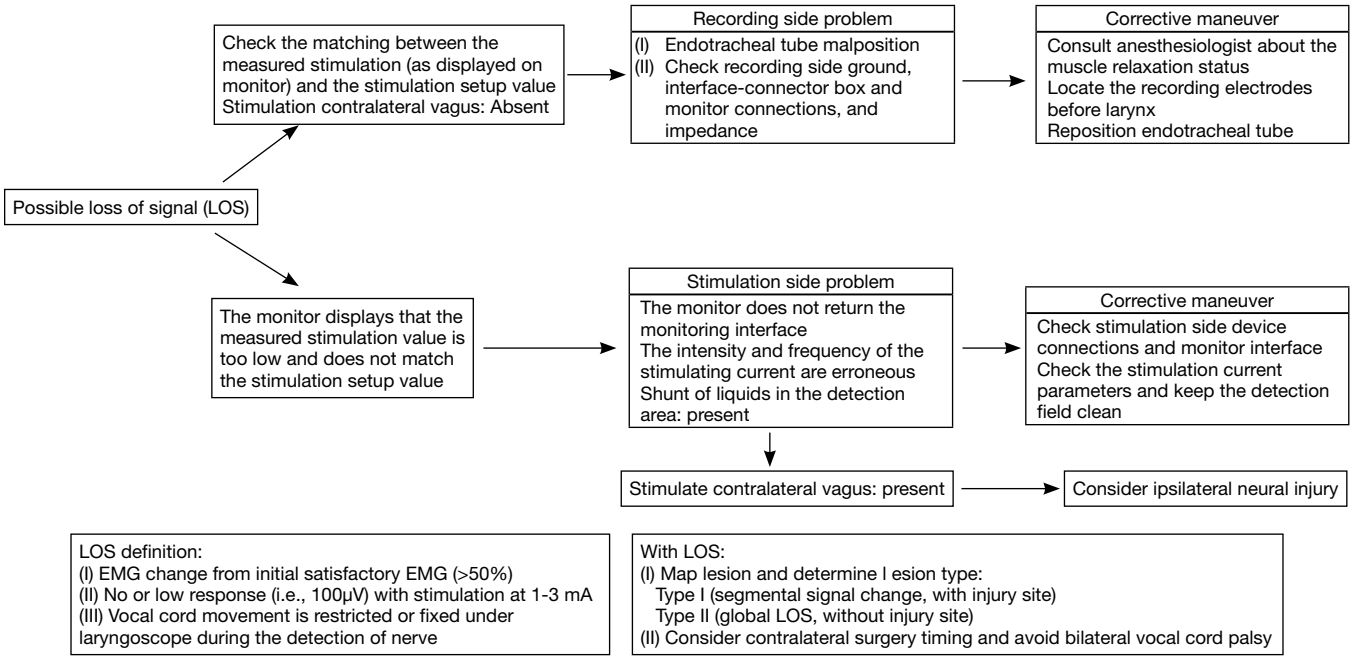


Figure 6 Algorithm for troubleshooting common IONM errors. IONM, intraoperative neuromonitoring.

With the assistance of IONM, an experienced surgeon will be able to further lower the incidence of RLN injury and improve the surgical safety and completeness, which can also be a new trend in laryngeal nerve protection during a thyroid surgery (29).

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Dralle H, Sekulla C, Haerting J, et al. Risk factors of paralysis and functional outcome after recurrent laryngeal nerve monitoring in thyroid surgery. Surgery 2004;136:1310-22.
2. Chiang FY, Wang LF, Huang YF, et al. Recurrent laryngeal nerve palsy after thyroidectomy with routine identification of the recurrent laryngeal nerve. Surgery 2005;137:342-7.
3. Chiang FY, Lee KW, Huang YF, et al. Risk of vocal palsy after thyroidecitomy with identification of the recurrent laryngeal nerve. Kaohsiung J Med Sci 2004;20:431-6.
4. Qu XC, Xiao Y, Huang T, et al. Exposure and injury prevention of recurrent laryingeal nerve during thyroid surgery. Chinese Journal of Cancer 2008;18:700-3.
5. Liu CP, Huang T. Causes and Treatment of Recurrent Laryngeal Nerve Injury during Thyroidectomy. Chin J Bases Clin General Surg 2008;15:314-7.
6. Dionigi G, Barczynski M, Chiang FY, et al. Why monitor the recurrent laryngeal nerve in thyroid surgery? J Endocrinol Invest 2010;33:819-22.
7. Liu XL, Sun H, Zheng ZL, et al. Application and advances in the monitoring of recurrent laryngeal nerve during thyroid surgeries. Chinese Journal of general surgery, 2009;18:1187-90.
8. Sun H, Liu XL, Lian LX, et al. Principles and application of the monitoring of recurrent laryngeal nerve. News and Reviews (Ear, Nose, and Throat) 2012;27:137-40.
9. Zhou G, Jiang KW, Ye YJ, et al. Intraoperative assessment of recurrent laryngeal nerve function by monitoring EMG of lateral cricoaryteoid muscle. Chinese Journal of General Surgery 2012;27:272-5.
10. Barczyński M, Konturek A, Cichoń S. Randomized clinical trial of visualization versus neuromonitoring of recurrent laryngeal nerves during thyroidectomy. Br J Surg 2009;96:240-6.
11. Dionigi G, Bacuzzi A, Boni L, et al. What is the learning

curve for intraoperative neuromonitoring in thyroid surgery? Int J Surg 2008;6 Suppl 1:S7-12.
12. Sun H, Liu XL, Zhang DQ, et al. Clinical application of recurrent laryngeal nerve protection and monitoring during thyroidectomy. Chin J Bases Clin General Surg 2010;17:768-71.
13. Chiang FY, Lu IC, Chen HC, et al. Anatomical variations of recurrent laryngeal nerve during thyroid surgery: how to identify and handle the variations with intraoperative neuromonitoring. Kaohsiung J Med Sci 2010;26:575-83.
14. Chiang FY, Lu IC, Kuo WR, et al. The mechanism of recurrent laryngeal nerve injury during thyroid surgery--the application of intraoperative neuromonitoring. Surgery 2008;143:743-9.
15. Sun H, Liu XL, Fu YT, et al. Application of intraoperative neromonitoring during complex thyroid operation. Chinese Journal of Practical Surgery 2010;30:66-8.
16. Qin JW, Hei H, Zhang ST, et al. Locating and protecting recurrent laryngeal nerve in minimally invasive video-assisted thyroidectomy. Cancer Research and Clinic 2010;12:804-5.
17. Wei T, Li ZH, Zhu JQ. Real-Time Monitoring of Recurrent Laryngeal Nerve During Thyroid Reoperation. Chin J Bases Clin General Surg 2010;17:772-4.
18. Wang P, Yan HC. Prevention and treatment of complications after complete endoscopic thyroidectomy. Journal of Laparoscopic Surgery 2012;17:806-9.
19. Randolph GW, Dralle H, International Intraoperative Monitoring Study Group, et al. Electrophysiologic recurrent laryngeal nerve monitoring during thyroid and parathyroid surgery: international standards guideline statement. Laryngoscope 2011;121 Suppl 1:S1-16.
20. Liu XL, Sun H. Principles and clinical application of intraoperative monitoring of recurrent laryngeal nerve. Chinese Journal of Practical Surgery 2012;32:409-11.
21. Sun H, Liu XL, Zhao T, et al. New methods for identifying recurrent laryngeal nerve during thyroid surgery. News and Reviews (Ear, Nose, and Throat) 2010;25:46-8.
22. Chiang FY, Lee KW, Chen HC, et al. Standardization of intraoperative neuromonitoring of recurrent laryngeal nerve in thyroid operation. World J Surg 2010;34:223-9.
23. Randolph GW, Kamani D. The importance of preoperative laryngoscopy in patients undergoing thyroidectomy: voice, vocal cord function, and the preoperative detection of invasive thyroid malignancy. Surgery 2006;139:357-62.
24. Liu XL, Sun H. Optimization and interpretation of intraoperative neuromonitoring of recurrent laryngeal nerve in thyroid operation. News and Reviews (Ear, Nose, and Throat) 2010;25:152-4.
25. Sun H, Liu XL, Zhao T, et al. Intraoperative neuromonitoring in identification of non-recurrent laryngeal nerve: experience of 6 cases. Chin J Endocr Surg 2010;4:402-4.
26. Dralle H, Sekulla C, Lorenz K, et al. Intraoperative monitoring of the recurrent laryngeal nerve in thyroid surgery. World J Surg 2008;32:1358-66.
27. Chan WF, Lo CY. Pitfalls of intraoperative neuromonitoring for predicting postoperative recurrent laryngeal nerve function during thyroidectomy. World J Surg 2006;30:806-12.
28. Sun H, Liu XL. The preservation method of the recurrent laryngeal nerve and superior laryngeal nerve in the thyroid surgery. Chinese Journal of Practical Surgery 2012;32:356-9.
29. Tian W, Luo J. Comparison of the guidelines on the management of thyroid nodules and differentiated thyroid cancer between China and the United States. Chinese Journal of Practical Surgery 2013;33:475-9.

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Guideline

Expert consensus statement on parathyroid protection in thyroidectomy

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Introduction

Thyroid cancer is the solid cancer with the most rapidly increasing incidence rate around the world. In 2012, the incidence rate of this condition has been the highest among malignancies in Korean women (1), ranking fourth in China (2). The most common pathological type is papillary thyroid carcinoma, accounting for about 80-85% of all thyroid cancers. Lymph node metastases are common in early papillary thyroid carcinoma, with a reported cervical metastasis rate of about 21-90% (3-5). Most investigators believe that the central zone is the first site of lymph node metastases, namely the sentinel lymph node (6,7). At present, surgery is the preferred treatment for thyroid cancer. Among others, total thyroidectomy with central lymph node dissection has become the most common surgical approach. The main complications are recurrent laryngeal nerve and parathyroid injury. The clinical application of neural monitors has played a positive role in intraoperative positioning and protection of the recurrent laryngeal nerve. Postoperative hypoparathyroidism due to parathyroid injury is still a challenge to thyroid surgeons. Parathyroid injuries include bruising, insufficient blood supply and mistaken incision. It is reported that the incidence rates of temporary and permanent hypoparathyroidism are 14-60% and 4-11% after thyroidectomy, respectively (8-15). A study showed that the incidence rates of transient and permanent hypoparathyroidism were 27.7% and 6.3% after total thyroidectomy, 36.1% and 7.0% after total resection with unilateral central lymph node dissection, and 51.9% and 16.2% after total thyroidectomy with bilateral central lymph node dissection, respectively (16). Temporary hypoparathyroidism may cause transient hypocalcemia symptoms, but will not have a large impact on the quality of life of patients. On the other hand, permanent

Table 1 Classification of recommendation

Class	Implications
A	Strongly recommended. With definite evidence. Can be applied to improve the prognosis, with more benefit than harm
B	Recommended. With good evidence. Can be applied to improve the prognosis, with more benefit than harm
C	Recommended. Based on expert opinions
D	Refuse to recommend. Based on expert opinions
E	Refuse to recommend. With good evidence. Can not improve the prognosis, with more harm than benefit
F	Strongly refuse to recommend. With definite evidence. Can not improve the prognosis, with more harm than benefit
I	Not recommended or not routinely recommended. With insufficient or contradictory evidence for recommending or refusing to recommend

hypoparathyroidism will cause permanent hypocalcemia symptoms, mostly limb numbness and spasms, seriously affecting the quality of life of patients, which is a main factor of medical disputes. Therefore, we should pay attention to the protection of the parathyroid gland during thyroid surgery.

To improve the safety and efficacy of thyroid surgery, and further reduce the incidence of postoperative hypoparathyroidism, the Chinese Thyroid Association of the Chinese Medical Association organized some experts to develop this Expert Consensus on Parathyroid Protection in Thyroidectomy. The consensus applies to all open and endoscopic thyroid surgery. The classification of recommendations is listed in *Table 1*.

Applied anatomy, physiological functions and types of the parathyroid

Applied anatomy

The parathyroid consists of endocrine gland. Most of them are flat oval bodies and in brown when alive. Then are similar to rice or flattened soybeans in a diameter of about 3-6 mm, which are wrapped in a thin layer of connective tissue. The number of parathyroid glands is indefinite. It is reported that 48-62% of the Chinese people have four of these glands, but there may be variation resulting in more or fewer than four, and investigators have even reported that about 15% just have two (17,18). Most parathyroid glands are tightly attached to the surface of the left and right thyroid lobes, often located in the fiber capsule between the natural and surgical coatings. The location of the upper parathyroid gland is relatively constant, 85% concentrated in the circle with a radius of 1 cm area with the lower corner of the thyroid cartilage as the center. The position of the lower parathyroid glands vary more often, with more than half of them located at the lower 1/3 of the junction of the posterior edge of the thyroid and the rest at the anterior of the thyroid, or inside the thymus, the mediastinum or the thyroid parenchyma. Most parathyroid glands have independent parathyroid arteries. There are usually three sources of blood supply to the upper parathyroid glands: (I) posterior branches of the upper thyroid artery, as the main blood supply source; (II) anastomotic branches of the upper and lower thyroid arteries; and (III) the lowest thyroid artery and the arteries at the larynx, trachea, esophagus, and so on. The major blood supply to the lower parathyroid glands derives mainly from the lower thyroid artery. The blood supply to the upper and lower parathyroid glands starts from the upper and lower thyroid arteries before they enter the thyroid tissue. Therefore, to ensure the parathyroid blood supply, the third-tier terminal blood vessels should be treated close to the natural thyroid capsule (true capsule), rather than ligating the trunk of the upper and lower thyroid arteries.

Recommendation 1: to effectively reserve parathyroid blood supply, the upper and lower thyroid arteries should be treated close to the natural thyroid capsule properly (class A).

Physiological function

Parathyroid glands secrete parathyroid hormone (PTH), whose main target organs are the bone and the kidney, with indirect intestinal effects as well.

The physiological function of PTH is to regulate calcium metabolism and maintain the balance of calcium and phosphorus. By acting on osteoclasts, it causes bone calcium to dissolve and release into the blood circulation, thus elevating blood calcium and phosphorus concentrations. When the calcium, phosphorus concentrations exceed the renal threshold, they will be excreted in the urine, leading to hypercalciuria and hyperphosphaturia. PTH can also inhibit renal tubular reabsorption of phosphorus, resulting in increased urinary phosphorus and decreased blood phosphorus. Therefore, in the case of postoperative hypoparathyroidism, hypocalcemia with hyperphosphatemia

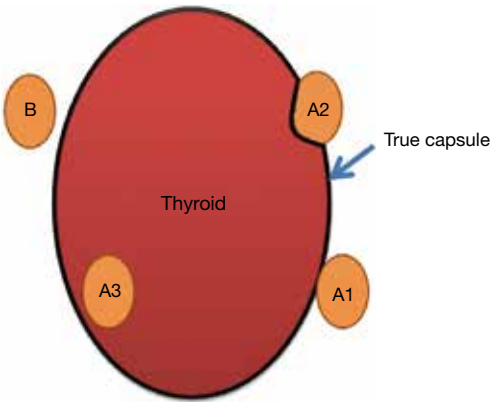

Figure 1 Positional relationship of parathyroid glands.

can occur, leading to numbness and even convulsions. Under normal circumstances, retaining one or more parathyroid glands with good blood supply will almost prevent serious permanent hypoparathyroidism after surgery (19). Thus, the overall policy for parathyroid protection in thyroidectomy should follow the "1+ X" principle. "1" means that we should treat every single parathyroid gland as the only (last) one, and treat and protect it carefully in the dissection; it also means that we have to identify at least one parathyroid gland in each thyroid surgery; "X" means that we are supposed to strive to protect more parathyroid glands during the surgery. That's because we have no idea how many parathyroid glands a patient may have, and even no idea as to which one is playing the major role. Meanwhile, we may encounter a patient who has only two parathyroid glands, and they may be located on the same side. Therefore, even if only one side is involved in the thyroid surgery, we should still pay attention to parathyroid protection.

Recommendation 2: parathyroid protection in thyroidectomy should follow the "1+ X" principle (class C).

Recommendation 3: at least one parathyroid gland with good blood supply should be reserved *in situ* as much as possible in each case of thyroid surgery (class A).

Types

Zhu *et al*. classified the parathyroid glands to two types, A and B, based on the positional relationship between the thyroid and the parathyroid, and the difficulty to reserve a gland *in situ* (*Figure 1*). Type A is the compact type, meaning that the thyroid and parathyroid glands are closely situated, making it relatively difficult to retain them *in situ*. This is further divided into three subtypes. Type A1: the parathyroid glands are attached to the surface of the thyroid (*Figure 2A*); type A2: the parathyroid glands are partially or fully embedded in the thyroid, but located outside the natural capsule (*Figure 2B*); type A3: the parathyroid glands are entirely within the thyroid tissue (*Figure 2C*) and inside the natural capsule, which is different from type A2. Type B is the non-compact type, meaning that there is a natural gap between the parathyroid and the thyroid, making it easier to retain *in situ*. It is also divided into three subtypes. Type B1: peripheral thyroid type (*Figure 2D*), including all type B parathyroid glands except B2 and B3; type B2: intra-thymus type (*Figure 2E*), in which the parathyroid glands are located in the thymus; type B3: blood supply from vessels of the thymus or mediastinum (*Figure 2F*). Therefore, in theory, it is easier to retain type B than type A, and type A1 than type A2, *in situ*. It is not possible to reserve type A3 *in situ*.

Recommended 4: typing of the parathyroid glands facilitates statistics and communication, and is also conducive to determine the degree of difficulty to reserve the parathyroid glands *in situ*. Therefore, in theory, it is easier to retain type B than type A, and type A1 than type A2, *in situ*. It is not possible to reserve type A3 *in situ* (class C).

Visual identification of parathyroid glands and tips

Visually identification

The parathyroid glands can be identified by the naked eye, positive development and negative development and other methods, but the most important thing is to learn how to visually identify them. Comprehensive judgments should be made based on the parathyroid anatomy, appearance and tolerance to ischemia, and so on. The parathyroid glands are usually not readily distinguishable from fat droplets, lymph nodes, ectopic thymus and thyroid. (I) Distinguishing between parathyroid glands and fat droplets. Since the majority of parathyroid glands are partially or completely wrapped in outer peripheral fat tissue, it is difficult to distinguish between the two. The defining aspects are: (i) color, parathyroid glands are usually yellowish brown or brown (depending on the amount of primary cells), while fat droplets are pale yellow; (ii) capsule, the fat tissue surrounding parathyroid glands has a complete capsule, which can be opened to expose yellowish brown or brown parathyroid glands with a scalpel. In contrast, fat droplets do not have such structure and do not contain brown tissue when dissected. (II) Distinguishing

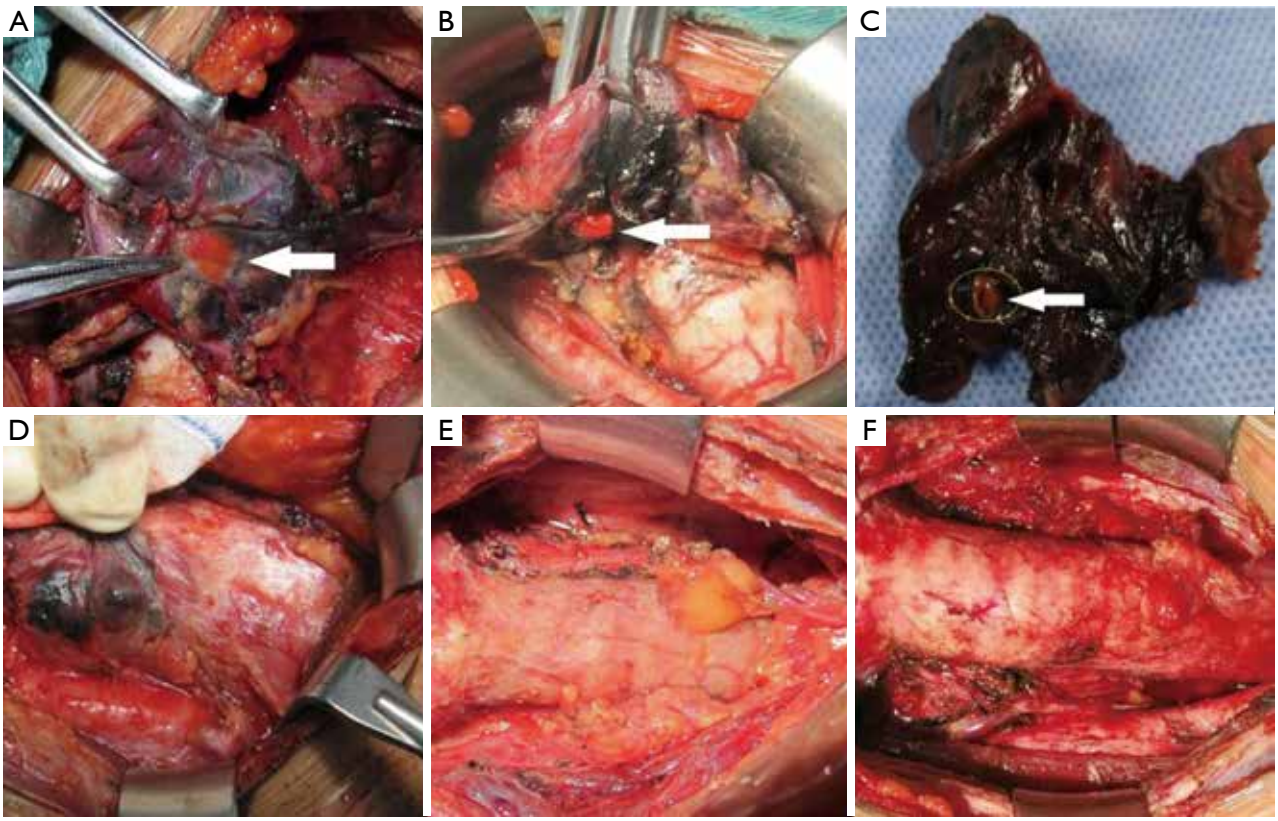

Figure 2 Types of parathyroid glands. (A) Type A1; (B) type A2; (C) type A3; (D) type B1; (E) type B2; (F) type B3. The white arrows indicate the parathyroid glands.

between parathyroid glands and lymph nodes. The defining aspects are: (i) color, parathyroid glands are brown or tan, while lymph nodes are pink (flesh) and some pale; (ii) thickness, this is one of key points in distinguishing between parathyroid glands and lymph nodes. In general, the thickness of the parathyroid is smaller compared with the length and width, usually at only 1-2 mm and rarely >3 mm, whereas lymph nodes are thicker with similar length and width; (iii) texture, the parathyroid is soft while lymph nodes are relatively hard, especially those with lymph node metastasis, followed by those complicated with Hashimoto's thyroiditis; (iv) appearance, parathyroid glands appear in good colors and moist, while lymph nodes appear to be poor and not moist; (v) surface, parathyroid glands have a more regular shape, smooth surface, with regular small structures, whereas lymph nodes may be irregular and less smooth with an uneven surface, which is more evident under a magnifying glass. (III) Distinguishing the parathyroid from scattered thymus and thyroid nodules. The defining aspects are: (i) color, parathyroid glands are brown or tan, while scattered thymus tissue is often crimson. The thyroid tissue is the same as the thyroid tissue *in situ*; (ii) shape, scattered thymus and thyroid nodules are often thick, with similar length and width; (iii) size, the maximum diameter of a normal parathyroid gland is generally <6 mm and rarely >8 mm, while scattered thymus and thyroid nodules are often about 10 mm. In addition, parathyroid glands are sensitive to blood supply changes. When the arteries are injured, they become lighter in color or even pale; when the veins are injured, they become purple due to venous congestion. On the other hand, lymph nodes, fat droplets and scattered thymus and thyroid tissue are not as sensitive to blood supply changes. Therefore, if a purple nodule is found during surgery which is not supposed to be present naturally, it should be highly suspected of a parathyroid gland with congestion. If it is not possible to distinguish between parathyroid tissue and the above, intraoperative frozen pathology should follow.

Recommendation 5: comprehensive judgments should be made based on visual inspection of the parathyroid anatomy,

appearance (color, tone, appearance, size and thickness) and tolerance to ischemia (class C).

Parathyroid positive development

With parathyroid positive development, a developer is used for parathyroid staining to make it easy to accurately identify parathyroid glands in surgery. The mostly reported positive parathyroid developer is methylene blue. Since Dudley identified the parathyroid glands using intravenous injection with methylene blue in neck dissection in 1971, there have been a large number of clinical reports of parathyroid exposure using preoperative peripheral intravenous injection with methylene blue in surgery. However, more and more studies show that, while pathological parathyroid tissue is prone to methylene blue staining, normal parathyroid tissue is not sensitive to staining, making this method not effective in practice. At the same time, methylene blue is not an approved developer and lymphatic tracer, and is associated with some side effects, such as heart disorders, slow movement disorders, neurotoxicity and mental disorders. Thus, in recent years, there have been few reports of methylene blue staining for intraoperative identification of parathyroid glands, especially normal parathyroid glands.

Recommended 6: methylene blue is not suitable for the identification of normal parathyroid glands in thyroid surgery (class D).

Nanometer carbon negative development for parathyroid identification and protection

Mechanism and clinical application

Carbon nanoparticle suspension injection (referred to as nano-carbon) is a suspension made of nanoscale carbon particles, with a particle diameter of 150 nm and a high tropism for the lymphatic system (20). Because the clearance between capillary endothelial cells is 20-50 nm, and the gap between capillary lymphatic endothelial cells is 120-500 nm with a hypoplastic base, the carbon nanoparticles injected into the thyroid tissue will not enter the blood vessels, but can quickly enter the lymph tubes or lymphatic capillaries after being swollen by macrophages. As they gather and deposit in the lymph nodes, the thyroid and its lymph drainage area will be dyed black (21). Compared with methylene blue and other developers, carbon nanoparticles are associated with strong lymphatic tropism, high tracing speed, high black dye rate, long duration, and high contrast with the surrounding tissue color.

Since the most parathyroid glands are located in the central area and do not accept thyroid lymphatic drainage, after injection of nano-carbon in the thyroid tissue, most lymphatic vessels and lymph nodes in the thyroid and its drainage area will be stained in black, but parathyroid glands will not, making them easily distinguishable from the former. Black staining of the thyroid facilitates the recognition of types A1, A2 and A3 parathyroid glands, while that of the central lymph nodes facilitates the recognition of type B1 glands. Zhu *et al.* (22) called it the technology of "nanometer carbon negative development for parathyroid identification and protection". So far, there have been tens of thousands of cases undergoing the nano-carbon technique and no adverse reaction has been reported. Zeng *et al.* (23) classified 80 patients of thyroid cancer randomly into the control group and the nano-carbon group to receive total thyroidectomy with central lymph node dissection or total thyroidectomy and modified neck dissection by the same team of surgeons, respectively. In the control group, 11 parathyroid glands were mistakenly removed, and 14 cases of temporary symptoms of hypocalcemia were noted. In contrast, no parathyroid glands were cut mistakenly in the nano-carbon group, and only one patient had transient postoperative hypocalcemia symptoms. Huang *et al.* (24) randomized 72 patients undergoing total thyroidectomy or total thyroidectomy with single or bilateral central lymph node dissection into the control and nano-carbon groups. The results showed hypocalcemia in 10 cases in the control group and only three in the nano-carbon group. A recent systematic review has also yielded similar results (25). Thus, carbon nanoparticles can help identify the parathyroid glands in thyroid surgery, conducive to the protection and prevention of postoperative hypoparathyroidism.

Recommendation 7: carbon nanoparticles can be used in thyroid surgery and is safe (class A).

Recommendation 8: nano-carbon negative parathyroid development technology helps identify and protect parathyroid glands during surgery and can reduce the incidence of postoperative hypoparathyroidism. Black staining of the thyroid helps identify types A1, A2 and A3 parathyroid glands, and central lymph node staining helps identify type B1 glands (class A).

Use methods and precautions

At present, most scholars recommend intraoperative injection with nano-carbon. This method can completely avoid the shortcomings of skin being dyed black, and hardly prolongs the operation length. The specific method is as below: (I) open the neck white line and the thyroid

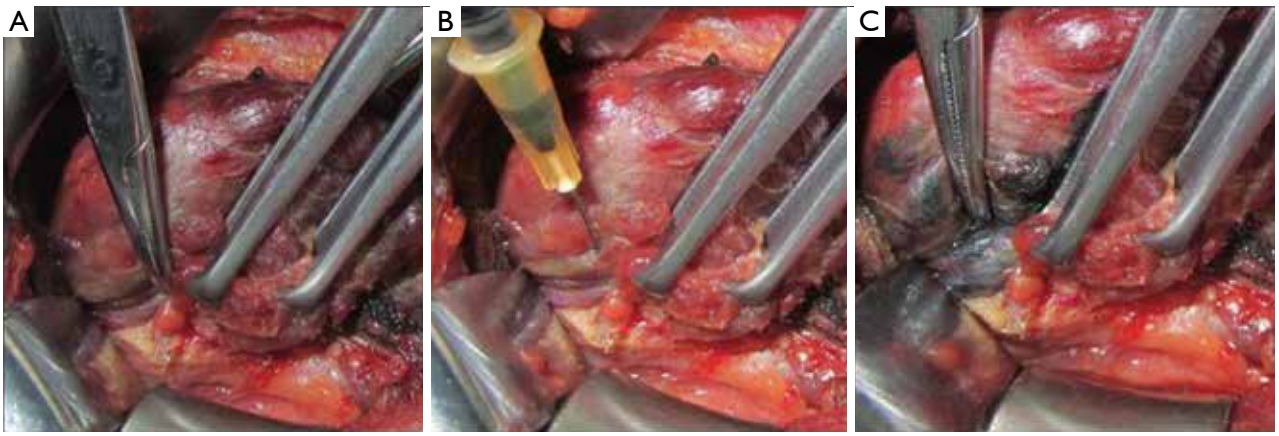

Figure 3 Additional injection of nano-carbon for the identification of parathyroid glands. (A) Before the additional injection; (B) during the additional injection; (C) after the additional injection. The white arrows indicate the parathyroid glands.

pseudocapsule, free the sternum thyroid muscle to both sides, revealing 1/3 of bilateral thyroid lobes. Be careful not to damage the integrity of the thyroid capsule, or carbon nanoparticles will spill and blacken the surrounding tissue, hindering the surgical field; (II) use a 1 mL for skin test syringe to draw carbon nanoparticles suspension to inject around the tumor tissue (upper and lower) slowly at 0.1-0.3 mL/side. Withdraw before the injection to avoid injecting vessels. For micro cancer, it is recommended to insert the syringe inside the thyroid for I° or less swollen thyroid, with approximately 0.1 mL on one side; and for enlarged thyroid of II° or above or Hashimoto's thyroiditis, it is recommended to inject at multiple points with about 0.1 mL each. For larger tumors without apparently normal thyroid tissue, the use of nano-carbon is not recommended; (III) after the needle is withdrawn, press the injection site with gauze for around 1 min to avoid spill of nano-carbon; (IV) wait 5 min before thyroid surgery. If lateral neck lymph node dissection is to be performed first, it is recommended to do it 20 min after injection.

Some surgeons choose to inject nano-carbon preoperatively, especially endoscopic thyroid surgeons. The specific method is as follows: (I) it is recommended to perform under ultrasound guidance; (II) apply local drape using sterile ultrasound probe and the coupling agent; (III) before inserting the needle, make sure there are carbon nanoparticles outside it to avoid skin staining. Refer to the intraoperative usage for the rest; (IV) when the needle is withdrawn to the subcutaneous part, continuously retreat to withdraw under a negative pressure to avoid skin staining.

Recommendation 9: according to the surgeon's habits, intraoperative or preoperative use of nano-carbon can be used. The preferred technique is the former and the injection volume of nano-carbon in unliateral thyroid tissue is 0.1-0.3 mL (class B).

Recommended 10: for larger tumors without apparently normal thyroid tissue, the use of nano-carbon is not recommended (class F).

Additional injection

Proper use of nano-carbon can help improve the intraoperative identification of parathyroid glands. When it is challenging to distinguish types A1 and A2 parathyroid glands from small undyed nodules on the thyroid surface, additional injection can be used to help. A small amount of nano-carbon is slowly injected into the unstained thyroid tissue around the nodules to be identified. If they are dyed black, they are thyroid nodules. Otherwise, it is highly possible that they are parathyroid glands (*Figure 3*).

Recommendation 11: additional injection can help identify nodules on the thyroid surface and types A1 and A2 parathyroid glands (class B).

Tips and strategies to protect parathyroid glands

Surgical techniques

Meticulous capsule dissection

Meticulous capsule dissection means that the third-tier blood vessels to and from the thyroid should be treated close to the natural thyroid capsule during thyroid resection.

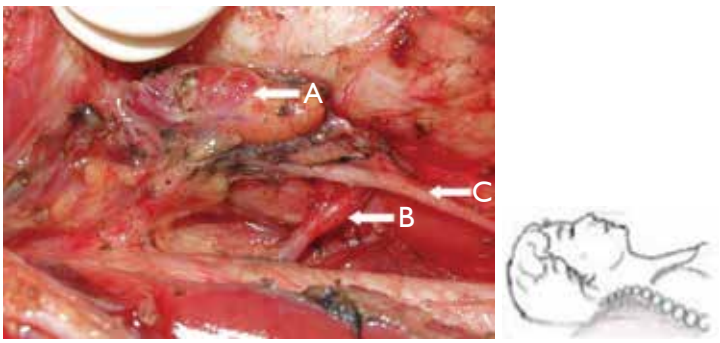

Figure 4 Reservation of main blood supply to parathyroid glands in central lymph node dissection. (A) The right superior parathyroid gland; (B) the inferior artery of the right parathyroid gland; (C) the right recurrent laryngeal nerve.

This is helpful in retaining types A1, A2 and B parathyroid glands *in situ* and the blood supply.

Recommendation 12: meticulous capsule dissection is helpful in retaining types A1, A2 and B parathyroid glands *in situ* and the blood supply (class A).

Reservation of main blood supply to parathyroid glands in central lymph node dissection

In the central lymph node dissection, the trunk and major branches of the lower thyroid artery should be carefully dissected and retained to ensure blood supply to the upper and lower parathyroid glands (*Figure 4*).

Recommendation 13: in the central lymph node dissection, the trunk and major branches of the lower thyroid artery should be retained as much as possible to ensure blood supply to the parathyroid glands (class A).

Reservations of thymus tissue in central lymph node dissection

Since types B2 and B3 parathyroid glands are closely related to the thymus, during the central lymph node dissection, if no thymic involvement is observed, the thymus tissue should be retained to avoid undesired removal of type B2 parathyroid glands and injury to blood supply to type B3 parathyroid glands.

Recommendation 14: in the central lymph node dissection, as long as the tumor does not involve the thymus, it should be retained to avoid undesired removal of type B2 parathyroid glands and injury to blood supply to type B3 parathyroid glands (class A).

Strategies of treating the lower corner area of the thyroid cartilage

The important anatomical structures in thyroid surgery are relatively concentrated in the lower corner area of the thyroid cartilage, such as the upper parathyroid glands (sometimes lower), the posterior branch of upper thyroid artery, upstream anastomotic branch of the lower thyroid artery, superior laryngeal nerve and recurrent laryngeal nerve. Thus, this is a high risk area in the surgery. Gong *et al.* (26) found that lymph node metastasis is rare in the lower corner area of the thyroid cartilage contralateral to the thyroid papillary carcinoma. Therefore, if the nano-carbon parathyroid negative development is used for identification and protection, for unilateral thyroid cancer, if no enlarged or positively stained lymph nodes are found in the lower corner of the contralateral thyroid cartilage, dissection of this area can be waived to reduce the incidence rate of injury to the parathyroid. This strategy is more important for repeat thyroid cancer surgery.

Recommendation 15: in the case of bilateral central lymph node dissection for unilateral thyroid cancer, if no enlarged or positively stained lymph nodes are found in the lower corner of the contralateral thyroid cartilage, dissection of this area can be waived to reduce the risk of postoperative hypoparathyroidism (class C).

Therapeutic central lymph node dissection in follicular thyroid carcinoma treatment

Since the central lymph node dissection increases the incidence of postoperative hypoparathyroidism, and follicular thyroid cancer is associated with only about 10% of lymph node metastasis, only therapeutic central lymph node dissection is done in the treatment of follicular thyroid carcinoma (14).

Recommendation 16: preventive central lymph node dissection is not performed in follicular thyroid carcinoma treatment (class A).

Proper use of advanced energy platform

Most advanced energy platforms inevitably produce heat during use, which may cause significant thermal damage to the surrounding tissue. Since parathyroid glands are sensitive to heat, operations close to them may damage the glands and their blood supply. Hence, when operating near the parathyroid glands, in the case of open surgery, a bipolar electrotome or thin suture can be used for vascular ligation; if an ultrasonic scalpel is used, the low configuration can be used while operating >3-5 mm away from the parathyroid glands and blood vessels with short continuous operation duration. When necessary, gauze with saline can be used to reduce the heat damage to the parathyroid.

Recommendation 17: rational use of advanced energy platforms can reduce intraoperative damage to parathyroid glands and blood supply (class C).

Careful search for parathyroid glands in specimens

Before sending the dissected thyroid and central tissue for pathological examination, routine caution should be given to identify parathyroid glands mistakenly cut. Since type A3 parathyroid glands are present in the thyroid tissue and cannot be identified or retained *in situ*, it is recommended that, when conditions permit, the thyroid tissue is dissected at an interval of 1-2 mm from front to rear longitudinally while paying attention to retain the backside continuity of about 1 mm thick to facilitate retention of the intact anatomical structure. Careful observation is needed of the presence or absence of type A3 parathyroid glands each cross section. During central tissue dissection, it is also needed to carefully check if any parathyroid glands are mistakenly cut. In general, it is required for fat tissue to be dissected to translucent to avoid missed parathyroid glands to the maximum extent.

Recommendation 18: it is necessary to routinely look for mistakenly cut parathyroid glands during surgery (class B).

Parathyroid autotransplantation

Parathyroid autograft transplant means to transplant the parathyroid glands that cannot be retained *in situ* or is mistakenly removed to other specific sites after pathological confirmation (1-2 mm specimen). Studies have shown that as long as the correct method of autologous transplantation is used, these grafts can survive and play a physiological function. Several studies have confirmed that in conventional thyroidectomy, 1 to 2 parathyroid autografts can almost avoid severe postoperative permanent hypoparathyroidism (27,28).

Particle entrapment

This is to cut parathyroid glands into particulates of <1 mm, decentralize and put them into the sternocleidomastoid muscle ("pocket"), and marked with non-absorbable sutures to help future recognition in the case of repeat operation. Caution should be made to completely stop the bleeding of the muscles to avoid hematoma, otherwise it may affect the survival of the implanted parathyroid tissue. In the event of serious localized invasion of the tumor and there is a high probability of recurrence, it is recommended to transplant the parathyroid tissue to the forearm or deltoid muscles. It should be noted that to improve graft survival, close placement of the parathyroid particles should be avoided. Multiple "pockets" (in the same or other muscles) can be made to reduce the risk of graft failure at a single site.

Homogenization injection

In homogenization injection, the parathyroid tissue is cut into pieces and fused into a syringe to inject into the forearm muscles at approximately 1 mL. The depth of injection should be carefully tapered by withdrawing while injecting to avoid concentrated grafts in one site, affecting their survival. The method is particularly suitable for use in a completely endoscopic thyroid surgery.

The parathyroid graft sites also include other muscles (such as the chest, trapezius) and subcutaneous tissue (such as the forearm, abdominal wall, etc.). In the thyroid surgery notes, the number and locations of parathyroid glands found, whether autologous transplant is conducted, and transplant number and locations should be recorded in detail to reduce damage to the parathyroid glands in repeat operations.

Recommendation 19: autologous transplantation of parathyroid glands mistakenly cut or unmaintainable *in situ* can effectively reduce the incidence of severe postoperative permanent hypoparathyroidism (class A).

Postoperative management

Postoperative serum PTH and calcium detection

Serum PTH and calcium levels are measured after day 1, day

3 and 1 month following the surgery to evaluate parathyroid functions. If serum PTH and calcium levels are still lower than normal or low calcium symptoms are present after a month, follow-up review of the serum PTH and calcium levels should be continued at a frequency depending on the circumstances.

Postoperative calcium supplementation

It is recommended to provide routine intravenous calcium after thyroid surgery, usually using 10% gluconate. A gradual transition to oral calcium supplementation or discontinuation is needed according to the patient's clinical symptoms, serum PTH and calcium levels. Oral calcium can be supplemented by vitamin D while appropriate.

Recommendation 20: serum PTH and calcium levels should be monitored after thyroid surgery, and calcium supplementation is needed based on clinical symptoms and findings (class B).

Conclusions

Under the general principles of "1+ X", the use of the meticulous capsule dissection technology, proper application of nano-carbon parathyroid negative development protection, careful identification of mistakenly cut parathyroid glands following detailed recognition and protection, autotransplant, postoperative management and other aspects are key to effective prevention of severe postoperative permanent hypoparathyroidism.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Jung KW, Won YJ, Kong HJ, et al. Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2012. Cancer Res Treat 2015;47:127-41.
2. Liu YQ, Zhang SQ, Chen WQ, et al. Trend of incidence and mortality on thyroid cancer in China during 2003 - 2007. Zhonghua Liu Xing Bing Xue Za Zhi 2012;33:1044-8.
3. Grebe SK, Hay ID. Thyroid cancer nodal metastases: biologic significance and therapeutic considerations. Surg Oncol Clin N Am 1996;5:43-63.
4. Mazzaferri EL. Management of a solitary thyroid nodule. N Engl J Med 1993;328:553-9.
5. Scheumann GF, Gimm O, Wegener G, et al. Prognostic significance and surgical management of locoregional lymph node metastases in papillary thyroid cancer. World J Surg 1994;18:559-67; discussion 567-8.
6. Qubain SW, Nakano S, Baba M, et al. Distribution of lymph node micrometastasis in pN0 well-differentiated thyroid carcinoma. Surgery 2002;131:249-56.
7. Gimm O, Rath FW, Dralle H. Pattern of lymph node metastases in papillary thyroid carcinoma. Br J Surg 1998;85:252-4.
8. Henry JF, Gramatica L, Denizot A, et al. Morbidity of prophylactic lymph node dissection in the central neck area in patients with papillary thyroid carcinoma. Langenbecks Arch Surg 1998;383:167-9.
9. Lee YS, Kim SW, Kim SW, et al. Extent of routine central lymph node dissection with small papillary thyroid carcinoma. World J Surg 2007;31:1954-9.
10. Pereira JA, Jimeno J, Miquel J, et al. Nodal yield, morbidity, and recurrence after central neck dissection for papillary thyroid carcinoma. Surgery 2005;138:1095-100, discussion 1100-1.
11. Sywak M, Cornford L, Roach P, et al. Routine ipsilateral level VI lymphadenectomy reduces postoperative thyroglobulin levels in papillary thyroid cancer. Surgery 2006;140:1000-5; discussion 1005-7.
12. Ito Y, Tomoda C, Uruno T, et al. Clinical significance of metastasis to the central compartment from papillary microcarcinoma of the thyroid. World J Surg 2006;30:91-9.
13. Goropoulos A, Karamoshos K, Christodoulou A, et al. Value of the cervical compartments in the surgical treatment of papillary thyroid carcinoma. World J Surg 2004;28:1275-81.
14. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167-214.
15. Cheah WK, Arici C, Ituarte PH, et al. Complications of neck dissection for thyroid cancer. World J Surg 2002;26:1013-6.
16. Giordano D, Valcavi R, Thompson GB, et al. Complications of central neck dissection in patients with papillary thyroid

carcinoma: results of a study on 1087 patients and review of the literature. Thyroid 2012;22:911-7.
17. Wang X, Li Y. Anatomical study on the parathyroid glands of Chinese adults. J Ningxia Medical College 2003;25:183-5.
18. Li ZH, Zhu JQ, Wei T, et al. Feature and clinical significance of parathyroid disposition in human body (anatomical research report of 50 cases). Chin J Bases Clin General Surg 2008;15:311-3.
19. Song CM, Jung JH, Ji YB, et al. Relationship between hypoparathyroidism and the number of parathyroid glands preserved during thyroidectomy. World J Surg Oncol 2014;12:200.
20. Yang F, Jin C, Yang D, et al. Magnetic functionalised carbon nanotubes as drug vehicles for cancer lymph node metastasis treatment. Eur J Cancer 2011;47:1873-82.
21. Hagiwara A, Takahashi T, Sawai K, et al. Lymph nodal vital staining with newer carbon particle suspensions compared with India ink: experimental and clinical observations. Lymphology 1992;25:84-9.
22. Zhu J, Wang Z, Wei T, et al. Application of Lymphatic Mapping to Recognize and Protect Negative Stained Parathyroid in Thyroid Carcinoma Surgery by Using Carbon Nanoparticles. Chin J Bases Clin General Surg 2013;20:992-4.
23. Zeng Y, Qian J, Cheng R, et al. Protective effect of lymphatic tracer on parathyroid glands in lymph node dissection in thyroid carcinoma. Chongqing Medicine 2012;41:1076-7.
24. Huang K, Luo D, Huang M, et al. Protection of parathyroid function using carbon nanoparticles during thyroid surgery. Otolaryngol Head Neck Surg 2013;149:845-50.
25. Li Y, Jian WH, Guo ZM, et al. A Meta-analysis of Carbon Nanoparticles for Identifying Lymph Nodes and Protecting Parathyroid Glands during Surgery. Otolaryngol Head Neck Surg 2015;152:1007-16.
26. Gong YP, Gong RX, Zhu JQ, et al. Clinical research strategy for cN0 thyroid papillary carcinoma central lymph node dissection. Zhonghua Wai Ke Za Zhi 2013;51:1081-4.
27. Ahmed N, Aurangzeb M, Muslim M, et al. Routine parathyroid autotransplantation during total thyroidectomy: a procedure with predictable outcome. J Pak Med Assoc 2013;63:190-3.
28. Testini M, Rosato L, Avenia N, et al. The impact of single parathyroid gland autotransplantation during thyroid surgery on postoperative hypoparathyroidism: a multicenter study. Transplant Proc 2007;39:225-30.

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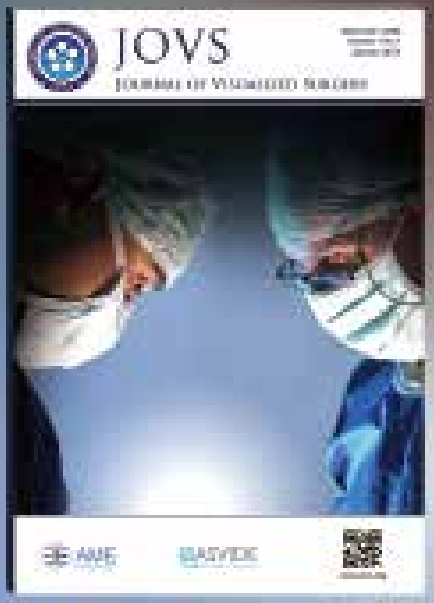

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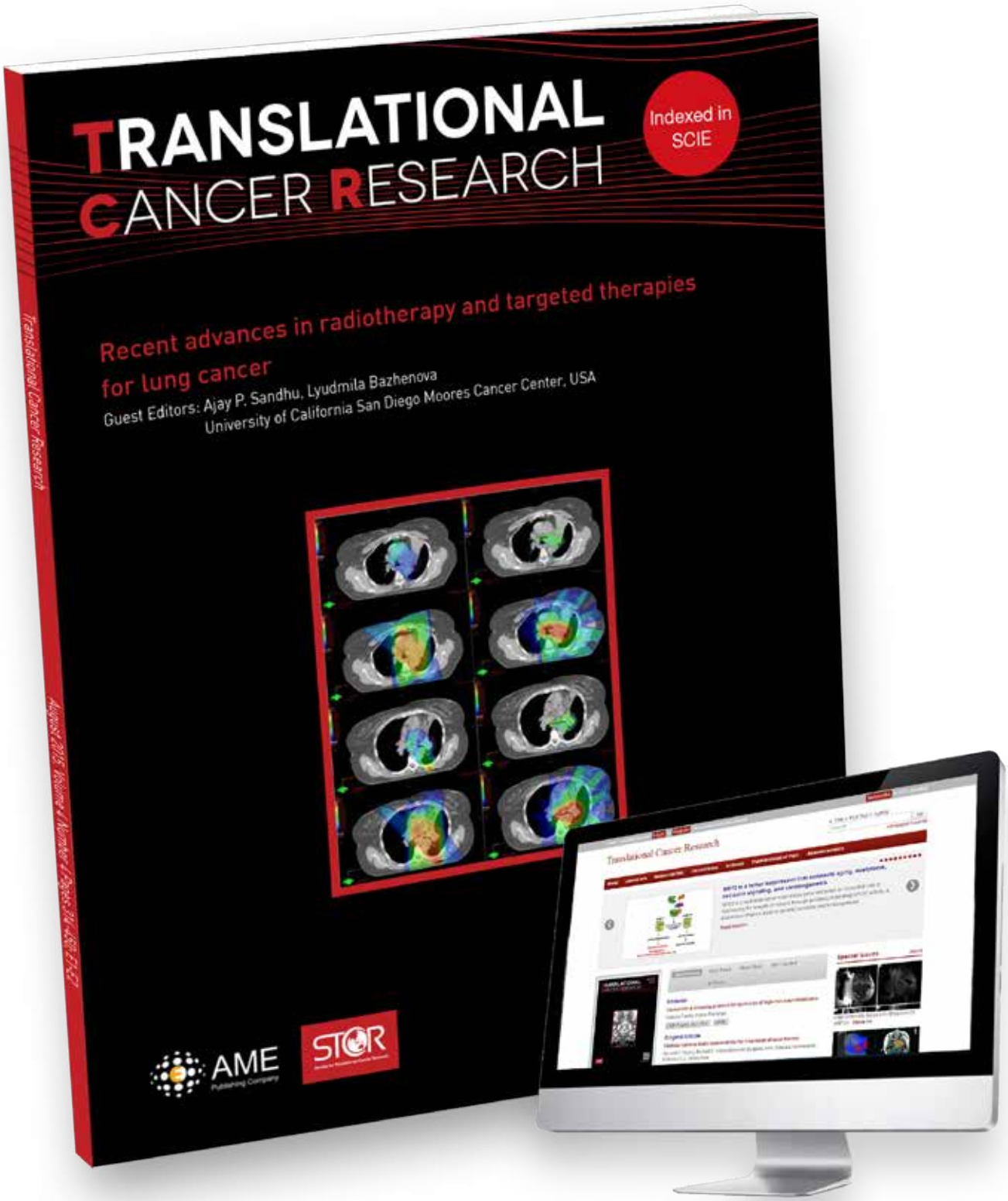
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