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INTERVENTIONAL PULMONOLOGY

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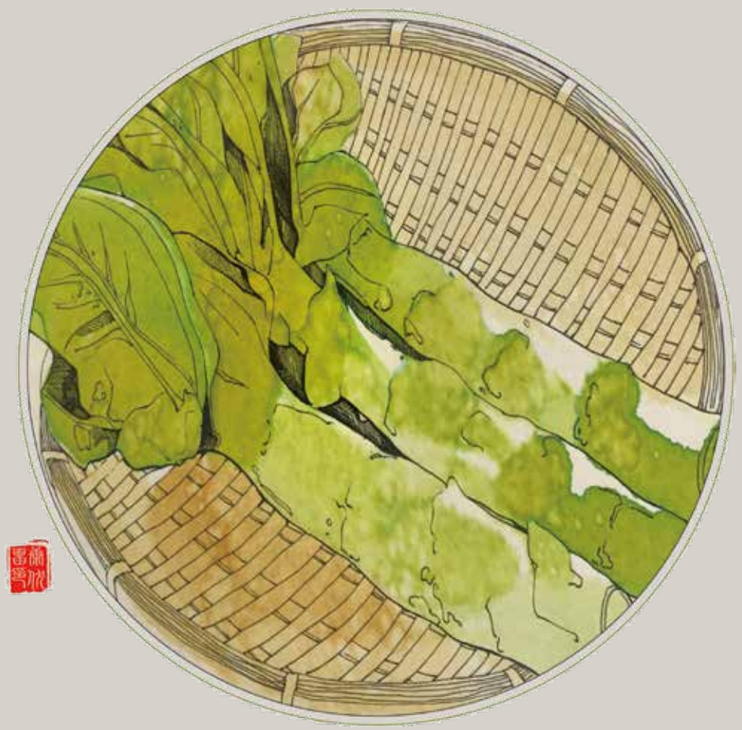

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AME Publishing Company

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# Interventional Pulmonology (FIRST EDITION)



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We are pleased to announce that the "AME Research Time Medical Book Series" launched by AME Publishing Company has been published as scheduled.

Finishing my medical degree after 4 years and 3 months of study, I decided to leave the path toward becoming a doctor only after 3 months of training. After that, I had been muddling through days and nights until I started engaging in medical academic publishing. Even 10 years after graduation, I had not totally lost the affection for being a doctor. Occasionally, that subconscious feeling would inadvertently arise from the bottom of my heart.

In April 2011, Mr. Tiantian Li, the founder of DXY.cn, and I had a business trip to Philadelphia, where we visited the Mütter Museum. As part of The College of Physicians of Philadelphia, the museum was founded in 1858 and has now become an exhibition hall of various diseases, injuries, deformities, as well as ancient medical instruments and the development of biology. It displays more than 20,000 pieces of items including pictures of wounded bodies at sites of battle, remains of conjoined twins, skeletons of dwarfs, and colons with pathological changes. They even exhibited several exclusive collections such as a soap-like female body and the skull of a two-headed child. This museum is widely known as "BIRTHPLACE OF AMERICAN MEDICINE". Entering an auditorium, we were told by the guide that the inauguration ceremony of the Perelman School of Medicine at the University of Pennsylvania would take place there every year. I asked Mr. Li, "If it was at this auditorium that you had the inauguration ceremony, would you give up being a doctor?" "No," he answered.

In May 2013, we attended a meeting of the British Medical Journal (BMJ) and afterwards a gala dinner was held to present awards to a number of outstanding medical teams. The event was hosted annually by the Editor-in-Chief of the BMJ and a famous BBC host. Surprisingly, during the award presentation, the speeches made by the BMJ never mentioned any high impact papers the teams had published in any prestigious journals over the past years. Instead, they laid emphasis on the contributions they had made on improving medical services in certain fields, alleviating the suffering of patients, and reducing the medical expenses.

Many friends of mine wondered what AME means.

AME is an acronym of "Academic Made Easy, Excellent and Enthusiastic". On September 3, 2014, I posted three pictures to social media feeds and asked my friends to select their favourite version of the AME promotional leaflet. Unexpectedly, we obtained a perfect translation of "AME" from Dr. Yaxing Shen, Department of Thoracic Surgery, Zhongshan Hospital, Shanghai, who wrote: enjoy a grander sight by devoting to academia (in Chinese, it was adapted from the verse of a famous Chinese poem).

AME is a young company with a pure dream. While having a clear focus on research, we have been adhering to the core value of "Patients come first". On April 24, 2014, we developed a public account on WeChat (a popular Chinese social media platform) and named it "Research Time". With a passion for clinical work, scientific research and the stories of science, "Research Time" disseminates cutting-edge breakthroughs in scientific research, provides moment-to-moment coverage of academic activities and shares little-known behind-the-scene stories. With global vision, together we keep abreast of the advances in clinical research; together we meet and join our hands at the Research Time. We are committed to continue developing the AME platform to aid in the continual forward development and dissemination of medical science.

It is said that how one tastes wine indicates one's personality. We would say how one reads gives a better insight to it. The "AME Research Time Medical Books Series" brings together clinical work, scientific research and humanism. Like making a fine dinner, we hope to cook the most delicate cuisine with all the great tastes and aromas that everyone will enjoy.

**Stephen Wang**
Founder & CEO,
AME Publishing Company

We are excited to bring you the first edition of *Interventional Pulmonology*. This extensive compilation of diagnostic and therapeutic interventions for pulmonary malignancies and airway challenges will appeal to thoracic surgeons and interventional pulmonologists globally. With continued advances in molecular testing and minimally invasive therapeutic and diagnostic approaches for lung cancer, a detailed resource is needed for proper management of patients with these often challenging problems. General thoracic surgeons in both academic and community settings need to know how to take an evidence-based approach to management of these problems.

Lee and colleagues summarize the accuracy and indications for current imaging modalities for evaluating the new patient with suspected lung cancer as well as the management options for those not deemed to be surgical candidates for confirmed lung cancer. The role of magnetic resonance imaging beyond evaluation of chest wall invasion or superior sulcus tumors surprises us as a modality more sensitive-albeit more costly- than PET-CT for detection of advanced disease. Lin and Chung then offer ablative and stent options for palliating patients with central airway tumors and updates us on the state of drug-eluting and biodegradable airway stents, while Semaan and Yarmus outline a safe approach to rigid bronchoscopy and stent placement.

Extensive content is provided by global experts on the current state of endobronchial ultrasound (EBUS) for mediastinal staging. Folch and colleagues provide a thorough review of options for mediastinal staging from EBUS to standard transbronchial aspiration with inclusion of the molecular tests necessary to expeditiously evaluate your patient with suspected lung cancer and guide your therapeutic algorithm. Righi and colleagues provide lovely immunohistochemical images of rapid on site evaluation (ROSE) samples form EBUS but remind us of the standardization challenges of the molecular testing from these aspirates, and medical oncologists Tuzi *et al.* outline the role of these tests for the recurrent or metastatic cases. Both Canneto and colleagues and Kupeli provide guidelines for safe implementation of a new EBUS program, while Leoni *et al.* review the controversies of bronchodilators in the high risk COPD patients undergoing EBUS. Czarnecka-Kujawa and Yasufuku remind us that in the era of EBUS there is still a role for mediastinoscopy and thoracic surgeons need to be comfortable performing the more invasive and riskier procedure.

In addition to EBUS thoracic surgeons should be familiar with navigational bronchoscopic approaches for diagnosis and therapy and Arias *et al.* remind us that these procedures are complementary for "one-stop shopping" for the lung nodule patient. Transthoracic biopsies have not been replaced by the bronchoscopic approaches and experienced surgeons or interventional radiologists should be able to offer with a minimal bleeding or pneumothorax rate. DiBardino *et al.* provide detailed tables of these complications rates from their literature review in the "TTNA biopsy of the lung" chapter.

We have provided a thorough summary of state-of-the-art staging and management options of our patients with confirmed or suspected lung cancer as provided by world experts. We hope you will enjoy this compilation and use it take to care for your patients safely and efficiently!

Virginia R. Litle

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Endoscopic procedures, ultrasound imaging or more generally speaking interventional pulmonology allows modern diagnostic and therapeutic interventions in neoplastic and inflammatory mediastinal and lung diseases. The mentioned methods have gained importance over the last decades including conventional transcutaneous ultrasound (TUS), endoscopic ultrasound (EUS), and endobronchial ultrasound (EBUS) including specific techniques, e.g., elastography and contrast enhanced ultrasound.

Tumour-staging and mediastinal lymph node staging affect the management of patients with both operable and inoperable lung cancer (e.g., surgery *vs.* combined chemoradiation therapy). Tissue sampling is often indicated for accurate nodal staging. Mediastinal nodes can be sampled from the airways (endobronchial ultrasound combined with transbronchial needle aspiration [EBUS-TBNA]) or the esophagus (endoscopic ultrasound fine needle aspiration [EUS-FNA]). EBUS and EUS have a complementary diagnostic yield and in combination virtually all mediastinal lymph nodes can be biopsied. Additionally endoscopic ultrasound has been accepted assessing the typical findings in patients suspected of sarcoidosis.

Recent international lung cancer staging guidelines clearly state that endosonography should be the initial tissue sampling test over surgical staging. The European Federation of Societies for Ultrasound in Medicine (EFSUMB) has been publishing guidelines on interventional ultrasound which are featured as well in this book.

The book is helpful for the experts and also for doctors that will start using these methods. Congratulation to the authors based on their long standing clinical and research expertise in this.

Christoph F Dietrich

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Pulmonary diseases are among the leading causes of death worldwide. Lung infections, lung cancer and chronic obstructive pulmonary disease together accounted for a huge death worldwide (1). In order to improve the status, new diagnostic and therapeutic techniques are required. Interventional pulmonology (IP) was born out of this circumstance and it is exactly the field which offers advanced, minimally invasive diagnosis and treatment options for pulmonary disease and thoracic abnormalities.

IP is a broad term encompassing all nonsurgical procedures relating to lung and mediastinum. It has advanced at an incredible rate over the last decade. The rapid development and complexity of new technologies require that IP physicians constantly maintain and update their skills (2). With this goal in mind and with an aim to share research findings and clinical solutions, this new book, *Interventional Pulmonology*, has gathered about 80 world-renowned experts to share the state-of-the-art research findings on IP.

The book opens with the training program of IP in USA as the demand for IP fellowship trained physicians has been increasing. Then Dr. Wai-Kit Lee and his colleagues give an overview of modern diagnostic and therapeutic interventional radiology in lung cancer, while Dr. Fu-Tsai Chung and Dr. Chun-Yu Lin present a general review on interventional bronchoscopy in diagnosis and management.

It is well known that IP diagnostic capabilities including endobronchial ultrasound, flexible bronchoscopy, rigid bronchoscopy, autofluorescence bronchoscopy, electromagnetic navigation bronchoscopy and pleuroscopy. Therefore, in the second section of the book, it mainly focuses on the interventional diagnostic technique. In the third section, it primarily reviews some interventional therapy techniques, such as airway stent placement, endobronchial laser photoresection, spray cryotherapy and thoracoscopy.

IP is a new and constantly evolving field that requires the physicians to perform the latest, most innovative procedures with the highest level of skill to best meet patients' needs. We hope that this book could be such a helpful literature for the IP physicians.

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In 2009 the *Journal of Thoracic Disease* (*JTD*) was established, and in a relatively short-time has become a significant resource for physicians worldwide who treat thoracic diseases. The journal was first indexed in PubMed in 2011, then, in the Scientific Citation Index in 2013 and subsequently received an impact factor in 2014. There have been tremendous advances and dissemination of new technologies among thoracic surgeons around the world over the last two decades. Similarly, the field of interventional pulmonology (IP) has also been evolving. New technologies to facilitate diagnosis and therapy of benign and malignant thoracic diseases have been introduced into practice along with an expansion of IP training programs. It is not unusual to have IP and thoracic surgeons as part of the same team in many centers.

Not surprisingly *JTD* has published several articles that are relevant to interventional pulmonologists and thoracic surgeons using these advanced bronchoscopic techniques. These articles are also useful to physicians who see patients with lung nodules in helping them to decide between different diagnostic modalities that may be available to them and where to refer patients to. AME has collected 19 of the most noteworthy articles published in *JTD*, and presents them in this new textbook "Interventional Pulmonology". Leading clinicians from around the world describe diagnostic approaches such as CT imaging, bronchoscopy, endobronchial ultrasound and navigation bronchoscopy. The limitations of transbronchial and transthoracic biopsy of lung nodules is discussed in the section on diagnostic techniques. There are discussions on the technique of EBUS, its value for molecular testing as well as a comparison of EBUS to mediastinoscopy which was previously the gold standard for lymph node staging.

The last section of papers describes interventional therapeutic techniques. There are discussions on the use of rigid bronchoscopy and silicone stenting for central airway obstruction, a nice overview of different airway stents and their indications for use. Lastly there is a discussion of the technique and results of spray cryotherapy for airway disease. I am hopeful that clinicians managing airway disease and lung cancer, will find this textbook to be a useful resource to keep on hand in their offices.

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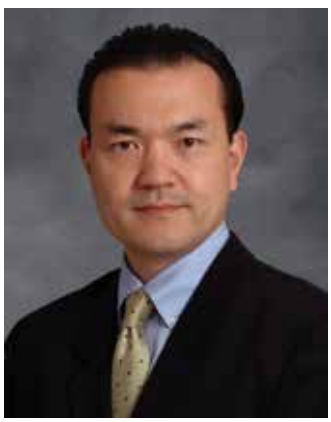
## Preface

Since the first successful removal of an airway foreign body performed by Gustav Killian on March 30, 1897 using an esophagoscope, bronchoscopy has evolved significantly. Chevalier Jackson led the development of the current rigid bronchoscope in early twentieth century. The development of the flexible bronchoscopy by Shigeto Ikeda opened up further advancements in the field of bronchoscopy. In the past decade, the emergence of new technologies including endobronchial ultrasound (EBUS) and navigational bronchoscopy have expanded the role of bronchoscopy and interventional pulmonology in the management of thoracic oncology.

In this new book entitled "*Interventional Pulmonology*", various diagnostic and therapeutic procedures performed by thoracic surgeons, interventional pulmonologists and bronchoscopists are reviewed with contributions from the experts in the field. The different technical aspects of new technologies as well as old technologies are reviewed in detail. For diagnostic procedures, EBUS-TBNA has emerged as the new standard for assessment of the mediastinum and the hilum. Bronchoscopists are now challenged to not only get tissue diagnosis but also to obtain sufficient amount of tissue for various molecular analysis. EBUS may have replaced the Gold standard of invasive mediastinal staging "Mediastinoscopy", but mediastinoscopy still has a role. Traditional transbronchial needle aspiration has its role in interventional pulmonology. The gold standard for biopsy of peripheral lung nodules is still transthoracic needle aspiration. However, new technologies including navigational bronchoscopy is an alternative approach though limitations exist.

Rigid bronchoscopy continues to be a key therapeutic procedure for interventional pulmonologists. Central airway obstruction is managed by the traditional rigid bronchoscope similar to that used by Killian. However, improvements have been made both in the devices available as well as the technique. Stenting and ablative devices, both hot and cold, are also available for use during an intervention. In the near future, these ablative devices will be applied to transbronchial therapeutics for peripheral lung tumors.

It is an exciting time for interventional pulmonology with emergence of new technology for diagnostics and therapeutics. This book will serve as a guide for many bronchoscopists interested in the field. Again, I congratulate the editors and the authors on the completion of this excellent book.



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In the era of precision medicine and personalized therapy, interventional pulmonology has become an essential diagnostic, therapeutic and follow-up tool in lung cancer patient management and the improvement of more and more effective and safe techniques will allow even more precise approaches, particularly in case of advanced tumor stages that preclude surgical solutions. Furthermore, the multidisciplinary management of lung cancer disease has brought different lung specialists face to face to reach together the best approach for staging, diagnostic and therapeutic purposes, valuating chorally the most accurate and minimally invasive technique for patient care and benefit. Along this path, the use of conventional or EBUS-TBNA has grown up, maximizing both effective staging in early diseases and diagnostic yield for mediastinal advances stages. On the other hand, transthoracic FNA or percutaneous biopsy can lead to a more precise diagnosis in peripheral parenchymal lesions being also useful for ablation of peripheral localizations in the control of oligo-metastatic tumor spread.

The great improvement of biomarker-driven personalized therapies in non small cell lung cancer has risen the need of tumor profiling looking for specific markers predictive of response to therapies, spurring requests by medical oncologists of biopsies and re-biopsies for molecular profiling assessment also along patient's treatment history. In this scenario tumor tissue has reached a fundamental role in diagnosis and therapy of advanced patients. In these cases, since the obtained diagnostic cytological or bioptical specimens are often the only available material is of utmost importance to plan tissue analyses that will guide the most adequate personalized patient treatment. All the immunohistochemical and molecular biomarkers could be tested in these small samples with efficient results, comparable to surgical tissues, to warrant adequate and precise tumor profiling reports.

Finally, interventional pulmonology could be useful also for therapeutic purposes in endobronchial obstructive lesions or tracheal stenosis. In this field, tacking advantage of endobronchial stents in conjunction with other endoscopic therapy, such as the modern cryoprobe, different situations can be solved, including ablation of benign and malignant neoplasms, ablation of granulation tissue, treatment of infections, nerve ablation for chronic pain, bronchoscopic biopsies and even cosmetic surgery.

In this book, a valuable collection of studies is put together to highlight major issues about interventional pulmonology, to make aware the reader throughout all relevant aspects of this fascinating discipline.

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# Modern diagnostic and therapeutic interventional radiology in lung cancer

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**Abstract:** Imaging has an important role in the multidisciplinary management of primary lung cancer. This article reviews the current state-of-the-art imaging modalities used for the evaluation, staging and post-treatment follow-up and surveillance of lung cancers, and image-guided percutaneous techniques for biopsy to confirm the diagnosis and for local therapy in non-surgical candidates.

**Keywords:** Lung neoplasms; computed tomography (CT); positron emission tomography (PET)/CT; magnetic resonance (MR) ; biopsy; ablation

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## Introduction

Imaging has an important role in the multidisciplinary management of primary lung cancer, and is necessary to establish the diagnosis; localise, characterise and stage the tumour; map relevant nodal, vascular and bronchial anatomy for treatment planning; and for surveillance of treatment efficacy and development of metachronous tumours. Image-guided treatment of primary lung cancers can be performed in select cases. This article reviews the imaging modalities currently used for the evaluation of lung cancers, and discusses image-guided percutaneous interventional techniques for histopathologic diagnosis and local tumour treatment. Lung cancer screening is beyond the scope of this article.

## Imaging modalities

Computed tomography (CT) is the imaging modality of choice for the initial evaluation of suspected or proven lung cancers. Positron emission tomography (PET)/CT is the most accurate imaging modality for the staging of primary lung cancers. Magnetic resonance (MR) imaging is useful for evaluation of superior sulcus (Pancoast) tumours and suspected malignant invasion of the chest wall, mediastinum or spine. The current recommended imaging required for lung cancer staging is CT scan of the thorax and PET/CT from skull base to mid-thigh (1).

## Computed tomography

Advanced CT scanners permit a high-resolution, comprehensive evaluation of the entire chest in a single breath-hold lasting several seconds with an improved radiation dose profile to generate an isotropic dataset that allows detailed anatomical assessment as well as functional assessment of lung cancers. Radiation dose reduction is achieved by utilising automatic tube current modulation and iterative reconstruction techniques, which enable a CT examination to be performed either at a reduced dose with a similar image quality or at the same dose with improved image quality (2,3). Improved detection of

small lung tumours is achieved by rapid acquisition and new visualisation techniques. Rapid acquisition reduces respiratory and cardiac motion artefacts that allow more accurate depiction of lung nodules, especially in the lung bases and in the para-cardiac lung. New visualisation techniques, such as maximum intensity projection, volume rendering, stereographic display and computer-aided detection, enhance lung cancer detection and enable the reader to differentiate small lung nodules from vessels (4). Isotropic dataset acquisition permits easy multiplanar reconstructions, including high-resolution angiograms and three-dimensional reconstruction of vascular and bronchial anatomy, for surgical or percutaneous interventional planning.

### *Staging*

Despite recent advances in CT technology, lung cancer staging with CT remains suboptimal but is routinely performed because it remains excellent for local staging of T1 and T2 tumours, is able to delineate T3 and T4 tumours, guides selection of the most appropriate lymph nodes and the invasive technique for nodal sampling, and allows triage of patients to non-surgical therapy when unequivocal distant metastases are present. Limitations of CT for staging include accurate detection of early mediastinal and chest wall invasion, mediastinal staging and detection of small extrathoracic metastases. With regards to local tumour extent, differentiation between absent, minimal and gross T3 and T4 disease is of critical clinical significance as it determines whether the tumour is completely resectable and the surgical approach (5). The utility of thin-section CT has not significantly improved the detection of malignant invasion of the parietal pleura. One study of 90 patients using a 4-detector CT showed sensitivity, specificity and accuracy of 42%, 100% and 83%, respectively, for the detection of chest wall invasion (6). Another small study using a 4-detector CT showed the use of multiplanar reconstructions can improve the sensitivity, specificity and accuracy of CT to 86%, 96% and 95%, respectively, for the detection of chest wall invasion (7). With regards to malignant nodal involvement, a recent meta-analysis showed a pooled sensitivity and specificity of 55% and 81%, respectively, for the detection of malignant mediastinal lymph nodes when a widely accepted definition of normal-sized lymph nodes of a short-axis diameter of ≤1 cm on a transverse CT scan image is used to differentiate benign from malignant lymph nodes (8). These results show that nodal size criterion alone is insufficient for the accurate detection of nodal metastases because metastases to normal-sized lymph nodes are missed and enlarged lymph nodes can be reactive or hyperplastic in aetiology. Recent studies suggest that evaluation of nodal morphology and CT enhancement pattern can improve the accuracy of CT for the detection of nodal metastases in lung cancer (9,10). With regards to distant metastases, CT is inferior to PET/CT for detection of extrapulmonary metastases with an accuracy of 88% compared to 97% with PET/CT (11). To our knowledge, there has been no study that examined the accuracy of CT for lung cancer staging using CT scanners with more than 16-detector rows.

### *Post-treatment evaluation and surveillance*

There is currently no consensus on the optimal follow-up and surveillance programme for patients with proven lung cancers. CT has been recommended for the routine evaluation and surveillance of patients who have undergone therapy with curative-intent for non-small cell lung cancer (NSCLC), but routine imaging surveillance is not recommended in asymptomatic patients with advanced lung cancer who are not undergoing therapy (12-14). CT evaluation of response to treatment is usually dependent on morphologic changes in tumour and nodes. However, morphology is not a good indicator of early response to treatment and a positive response can be manifested as a delayed reduction in size or paradoxical increase in size (15). CT can be effective for post-treatment surveillance with one study showing CT detected 93% of new lung cancers and 61% of recurrences in a cohort of over 1,000 patients after resection of early-stage NSCLC (16).

### *New developments*

Recent advances in CT technology have allowed investigation of novel methods for the evaluation of lung cancers including nodule volumetry, nodule perfusion analysis, dual-energy applications and computer-aided detection. Quantitative analysis of lung nodules by assessment of a nodule's volume can be performed using semi-automated or automated segmentation tools that allow assessment of nodule stability or progression over time. The rate of growth of a nodule is a predictor of the likelihood of malignancy, and volumetric analysis can be used to predict tumour response to treatment (17). CT perfusion analysis of nodules may allow better characterisation of the nodule

 

in order to determine the likelihood of malignancy as well as earlier determination of treatment response compared to morphologic change in size (18,19). The likelihood of malignancy is considered low when contrast uptake is below 30 Hounsfield units (HU) (20). Dual-energy CT is a technique that allows differentiation of iodine from other materials, such as soft tissue and bone, due to iodine's stronger photoelectric absorption (21). This method allows visualisation of the degree and pattern of enhancement within a mass following contrast-enhanced CT. One study showed that the degree of enhancement within a pulmonary nodule can be used to differentiate benign from malignant tumours with a sensitivity, specificity and accuracy of 92%, 70% and 82%, respectively (22). In another study, moderate correlation was found between the maximum iodine attenuation and SUVmax in thoracic nodes in patients with NSCLC, but poor correlation in those patients with small cell lung cancer (23). The authors suggest that moderate correlation in NSCLC could be explained by moderate specificity of PET for determination of malignant nodes, and the difference in correlation seen with NSCLC compared to SCLC due to differing tumour biology such as angiogenic ability.

## Positron emission tomography

### *Solitary pulmonary nodule*

PET with F-18 deoxyglucose (FDG) is a useful technique for the characterisation of pulmonary nodules to distinguish between benign and malignant lesions. Two meta-analyses showed the sensitivity and specificity of FDG-PET for the diagnosis of malignant pulmonary nodules were about 96% and 80%, respectively (24,25). The significance of a PET-positive result is dependent on the clinical context and the prevalence of granulomatous and infectious disease, which are recognised causes of false positive PET results. False negative results can occur in small (<10 mm) nodules due to partial volume effect or the effect of respiratory blurring, or in some subtypes of lung malignancy with a low intrinsic FDG avidity, such as adenocarcinoma *in situ*. On a practical level, a PET-positive study often implies that biopsy or intervention is warranted to obtain pathological confirmation (26), while a PET-negative study may allow conservative approach and avoidance of unnecessary invasive procedures (27). There is evidence that the use of FDG-PET is cost-effective in the management of solitary pulmonary nodules (28,29).

### *Staging*

PET is the most accurate imaging modality for the assessment of nodal and distant metastases from lung cancer, which is vital for treatment planning. PET has been found to be more accurate than CT in the staging of mediastinal nodal disease in many clinicopathological studies, including two meta-analyses that showed the sensitivity and specificity of PET was 79-85% and 90-91%, respectively, compared to 60-61% and 77-79% for CT (30,31). The accuracy of nodal assessment is further increased with PET/CT, which has an excellent negative predictive value of 91% in the mediastinal assessment of early-stage disease (32,33). Despite the high accuracy of PET/CT in nodal staging, there remains a significant false positive rate that is more common with larger (>1 cm) nodes, which is often due to reactive or granulomatous nodal disease (34). With the increased availability of minimally invasive mediastinal nodal sampling procedures, such as endobronchial ultrasound and endoscopic ultrasound, it is imperative to obtain pathological confirmation of PET-positive nodes before denying surgery to patients with potentially curable disease (35,36). PET is the imaging modality of choice in the assessment for distant metastases of lung cancer due to its whole body imaging capability and high tumor-to-background contrast which allows superior detection of both osseous and soft tissue metastases (37-39). There is a significant incidence of unrecognised distant metastatic disease when staging with conventional CT and bone scintigraphy. One study showed distant metastases were only identified with PET in 7.5%, 18% and 24% of stage I, stage II and stage III disease, respectively (40). Up to 20% of patients who are thought to be operable when staged with conventional imaging are found to be inoperable following PET and, therefore, PET is considered essential prior to curative treatment to avoid unnecessary futile surgical intervention (41,42). PET/CT has been shown to be superior to stand-alone PET or CT in the detection of distant disease mainly due to the ability of PET/CT to obtain anatomical correlation to reduce false positive PET interpretation of physiologic uptake in normal structures (43). A recent meta-analysis showed PET/CT was significantly superior to PET, MR imaging and bone scintigraphy for the detection of bony metastases with a pooled PET/CT sensitivity and specificity of 92% and 98%, respectively (44). Given the high background FDG uptake in the brain, FDG-PET is not the optimal imaging modality for the exclusion of cerebral metastases, which should be

 

evaluated by MR imaging when clinically indicated (45). The availability of both functional and structural information on PET/CT also facilitates the selection of stage critical lesions for biopsy to allow pathological confirmation. The use of PET and PET/CT is cost-effective in the staging of NSCLC (46-48) with a recent randomised clinical trial showing cost savings of 899 Euro per patient and 4,495 Euro per avoided thoracotomy (49). There is also a strong correlation between PET-stage and survival in both surgical and radical radiotherapy candidates which suggests that PET provides prognostically significant information (50,51).

### *Radiotherapy planning*

FDG-PET and PET/CT have been found to have a critical role in patient selection and target volume definition in patients with locoregionally advanced NSCLC considered for curative or radical radiotherapy. Radical radiotherapy is given with curative intent to non-surgical patients with gross locoregional tumour that can be encompassed by high-dose radiation in the absence of distant disease (52). A number of prospective studies investigating the utility of PET in the staging of potential candidates for radical radiotherapy found 25-30% of the patients were unsuitable for radical treatment owing to the presence of more advanced disease that was not shown on conventional imaging (53-55). PET-assisted radiotherapy treatment volume contouring has been found to be more accurate and significantly different from conventional treatment volumes, and a change in radiation volume was found in more than 30% of the patients (53,56,57). Survival benefit has also been shown with PET/CT-assisted radical radiotherapy. In one study, the 4-year survival of stage IIIA patients managed with PET/CT-assisted radical radiotherapy was 32%, which is superior to outcome with CT-assisted radical radiotherapy (58).

### *Post-treatment evaluation*

A prospective study of 73 patients comparing FDG-PET with CT for the assessment of response following radical radiotherapy and chemoradiation of NSCLC showed significantly more complete responders on PET (34 patients) than CT (10 patients). PET response was more predictive of survival duration than CT response, and was the only prognostic factor associated with survival duration on multifactor analysis (59). A more recent paper also reported a high metabolic tumour volume post definitive treatment for NSCLC was an independent poor prognostic factor (60). FDG-PET has also been found to provide prognostically significant response assessment in NSCLC patients undergoing induction chemotherapy. In a prospective study involving 31 patients with stage III unresectable disease, complete response on PET was more accurate than response on CT, and PET showed superior correlation with longer time to progression and overall survival (61). The ability of FDG-PET to provide superior prognostic information has also been reported in the setting of induction chemotherapy prior to surgical resection or chemoradiation, and there may be a role of PET in treatment selection and planning (62,63).

## Magnetic resonance imaging

Modern MR techniques have overcome the principal problem of magnetic field inhomogeneities due to the numerous air-soft tissue interfaces when imaging the lung as well as artefacts associated with cardiac and respiratory movement to produce diagnostic images. The utility of MR for the diagnosis, staging, radiotherapy planning and post-treatment evaluation in lung tumours is under-utilised and has been investigated at only a few centres. The sensitivity, specificity, positive predictive value and negative predictive value of MR for the detection of lung carcinoma and non-calcified lesions greater than 5 mm are close to 100% (64). Therefore, MR can potentially be used for lung cancer screening, but to our knowledge, there are no prospective trials investigating the utility of MR for this purpose (65,66). MR imaging with diffusion-weighted imaging (DWI) can be used to predict benignity of pulmonary lesions. One prospective study of 66 patients showed DWI had a sensitivity, specificity and positive predictive value of 95%, 73% and 87%, respectively, for the diagnosis of a malignant lesion (67).

In current clinical practice, MR imaging is primarily used for the assessment of suspected chest wall or mediastinal invasion by lung cancer due to the superior soft tissue contrast resolution of MR. Comparative studies between MR and FDG-PET/CT have shown the two techniques to be equivalent for staging NSCLC (68-70). The strength of MR is in the detection of cerebral and hepatic metastases, while PET/CT is better at nodal staging. A recent prospective study showed MR imaging with DWI was superior to PET/CT for the detection and nodal assessment of NSCLC (71). MR also allows differentiation of viable tumour from necrotic tumour and atelectasis, and is helpful in radiotherapy planning (72). Post-treatment tumour response has been investigated using MR

 

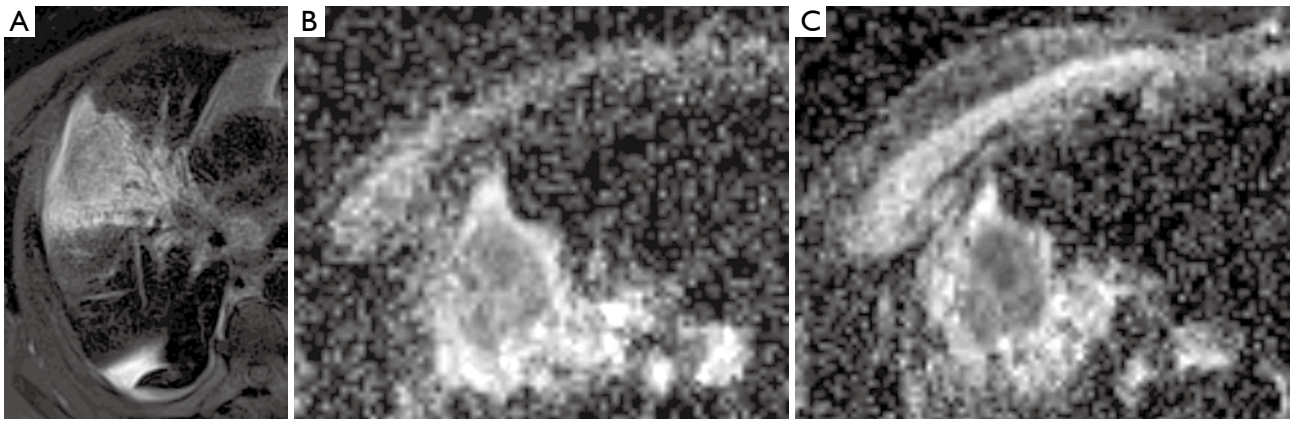


**Figure 1** A 71-year-old man with Stage III NSCLC in the right upper lobe. A. Axial T2-weighted MR image shows a heterogeneous T2 hyperintense mass with surrounding atelectasis; B, C. Axial ADC diffusion images before (B) and 24 hours after (C) starting chemotherapy show reduced ADC signal intensity in tumour following treatment.

techniques such as magnetization transfer, blood-oxygen-level dependent MR, and perfusion and diffusion imaging. Dynamic contrast-enhanced perfusion allows assessment of tumour angiogenesis, which has the potential to predict chemotherapy response in NSCLC patients, but its use is unproven for monitoring of anti-angiogenic therapy (73). MR perfusion can also be used for prediction of postoperative lung function (74). With regards to DWI, the apparent diffusion coefficient (ADC) measures the magnitude of diffusion of water molecules within tissue. Cell swelling or shrinkage is reflected in changes in ADC values. In general, an initial decrease in tumour ADC measurement performed within 30 days of treatment (*Figure 1*), and an increase in tumour ADC measurement 30 days following treatment were found to be predictive of a positive outcome, and our own unpublished data support similar findings (75,76).

## Image-guided percutaneous interventions

Image-guided percutaneous biopsy can be performed for confirmation of diagnosis and treatment planning. In non-surgical candidates, image-guided percutaneous therapy can be performed with curative-intent or for palliation, and these techniques include cryoablation, radiofrequency ablation and microwave ablation.

## Percutaneous biopsy

Percutaneous needle core biopsy is a minimally invasive procedure that can be used to confirm the diagnosis of lung malignancy. The most common complications are pneumothorax and bleeding. A higher risk of pneumothorax has been reported to occur with biopsy of smaller lesions and deeper lesions. Biopsy of lesions less than 2 cm in size is associated with an 11 times greater risk of pneumothorax than lesions greater than 4 cm, and this may be explained by the prolonged procedure time required to successfully biopsy smaller lesions (77). This study also showed that the risk of a pneumothorax is negligible for lesions abutting the pleura because the needle does not need to cross aerated lung, but there is a seven-fold increase in the rate of pneumothorax for biopsy of lesions less than 2 cm from pleura and a four-fold rate for lesions greater than 2 cm (77). Hence, the authors advocated a longer oblique needle path for biopsy of sub-pleural nodules to minimise pneumothorax risk, but a different study suggested that a smaller needle-to-pleura angle increases the risk of a pneumothorax (78). Other potential factors for the higher risk of a pneumothorax when lesions less than 2 cm from the pleura are biopsied include multiple punctures and difficulty anchoring a heavy hub cutting needle. A higher risk of pneumothorax following biopsy in patients with obstructive pulmonary disease has been reported in some studies (78,79), but other studies did not find this association (77,80,81). Factors that were not associated with an increased risk of pneumothorax include biopsy of cavitary lesions, biopsy needle size and patient positioning following biopsy (77). Bleeding is the second most common complication of percutaneous lung biopsy, and the two main predisposing factors were lesion size and distance of lesion from the pleural surface. A six-fold increase in bleeding was

 

shown for lesions less than 2 cm in size compared to those greater than 4 cm in size, and lesions greater than 2 cm from the pleura have a ten-fold bleeding risk compared to those abutting the pleural surface (77,82). The presence of a pleural effusion on the side of the biopsy was associated with a decreased risk of bleeding and was found to be an independent risk factor for bleeding following biopsy (77).

## Cryoablation

Cryoablation is a percutaneous minimally invasive technique used for the treatment of lung tumours in non-surgical candidates. Cryoablation causes coagulative necrosis of tumour cells and its vasculature. During cryoablation, a 2-to-3-cm rim of normal tissue surrounding the lesion should be ablated to achieve a margin of safety. The cryoablation probe is introduced into the tumour and cooled to –40 ℃ for about 10 minutes, then thawed for 8 minutes and then cooled once again for a further 10 minutes. Ice formation around the probe disrupts cell membrane function and enzymes, and creates a relative hypertonic extracellular environment causing intracellular dehydration by osmosis. The rapid return of water into the cell during the thawing process causes cell lysis. Direct damage to small (<3 mm) vessel walls and vessel stasis supplying the tumour may also play a role in tumour destruction (83). There is limited long-term outcome data for lung tumours treated with cryoablation. A Japanese series of 20 patients with 35 treated lesions followed for a median of 28 months showed a local recurrence rate of 20% (84). Another study investigated patients with stage I NSCLC who were unsuitable for standard surgical resection, and showed a 3-year survival rate of 77%, 88% and 87% when treated with cryoablation, radiofrequency ablation (RFA) or sublobar resection, respectively (85). Although cryoablation is comparable to other ablative techniques for the management of non-surgical candidates with lung cancer, longer term follow-up data are required to determine its role in the management of lung cancers.

## Radiofrequency ablation

RFA is a technique that involves the placement of an electrode into tissue to cause focal destruction with thermal energy, which is generated by friction secondary to oscillating tissue ions that occur when an alternating electric current in the frequency of 460-500 kHz (radio waves) is applied. Heating tissue to 50 ℃ for at least 5 minutes causes cells to undergo coagulative necrosis. Therapeutic RFA aims to heat tissues to 60-100 ℃, which leads to near instant cell death through protein denaturation (86). Pulmonary lesions are ideal for RFA because air in lung parenchyma surrounding the lesion provides thermal insulation to allow concentration of the applied radiofrequency (RF) energy within the lesion. Non-surgical candidates or patients who refuse surgery are potential candidates for RFA and the decision to treat with RFA should ideally be made in consultation with the interdisciplinary pulmonary tumour board. The most suitable lesions for RFA are less than 3 cm in size, and patients with stage I NSCLC are ideal candidates. Reported long-term survival rates after RFA of stage I NSCLC at 1, 2, 3, 4 and 5 years are 78%, 57%, 36%, 27% and 27%, respectively (87). RFA in combination with conventional radiotherapy has been used to treat inoperable lung tumours because hypoxic cells in the centre of tumour respond poorly to radiotherapy alone. A study showed cumulative survival rates of 50% and 39% at 2 and 5 years, respectively, following combined RFA and conventional radiotherapy for stage I NSCLC (88), and dual therapy achieved better local tumour control and patient survival compared to radiotherapy alone (89). Furthermore, RFA can be used to treat small slow growing pulmonary metastases (90) and to palliate patients with larger tumours that cause chest pain, dyspnoea, cough or haemoptysis (87). RFA of larger tumours often requires multiple overlapping ablations to ensure satisfactory tumour coverage, and recurrence rates tend to be higher in larger tumours than with smaller tumours (87,89).

## Microwave ablation

Microwave ablation (MWA) represents the most recent addition to the growing armamentarium of minimally invasive thermal ablation therapies for the nonsurgical treatment of lung malignancies (91). Microwaves are electromagnetic waves with a frequency range that extends from 300 MHz to 300 GHz. However, microwave generators for clinical use operate at frequencies of 915 MHz or 2.45 GHz (92). Microwaves agitate water molecules, which are small electric dipoles, in the target tissue, and they spin between 2 and 5 billion times per second in an attempt to follow the rapidly alternating electric field (92,93). This leads to heat generation through friction. Conduction and convection allow further tissue heating beyond the directly agitated water molecules (94). Temperatures thus generated, usually in excess of 100 ℃,

 

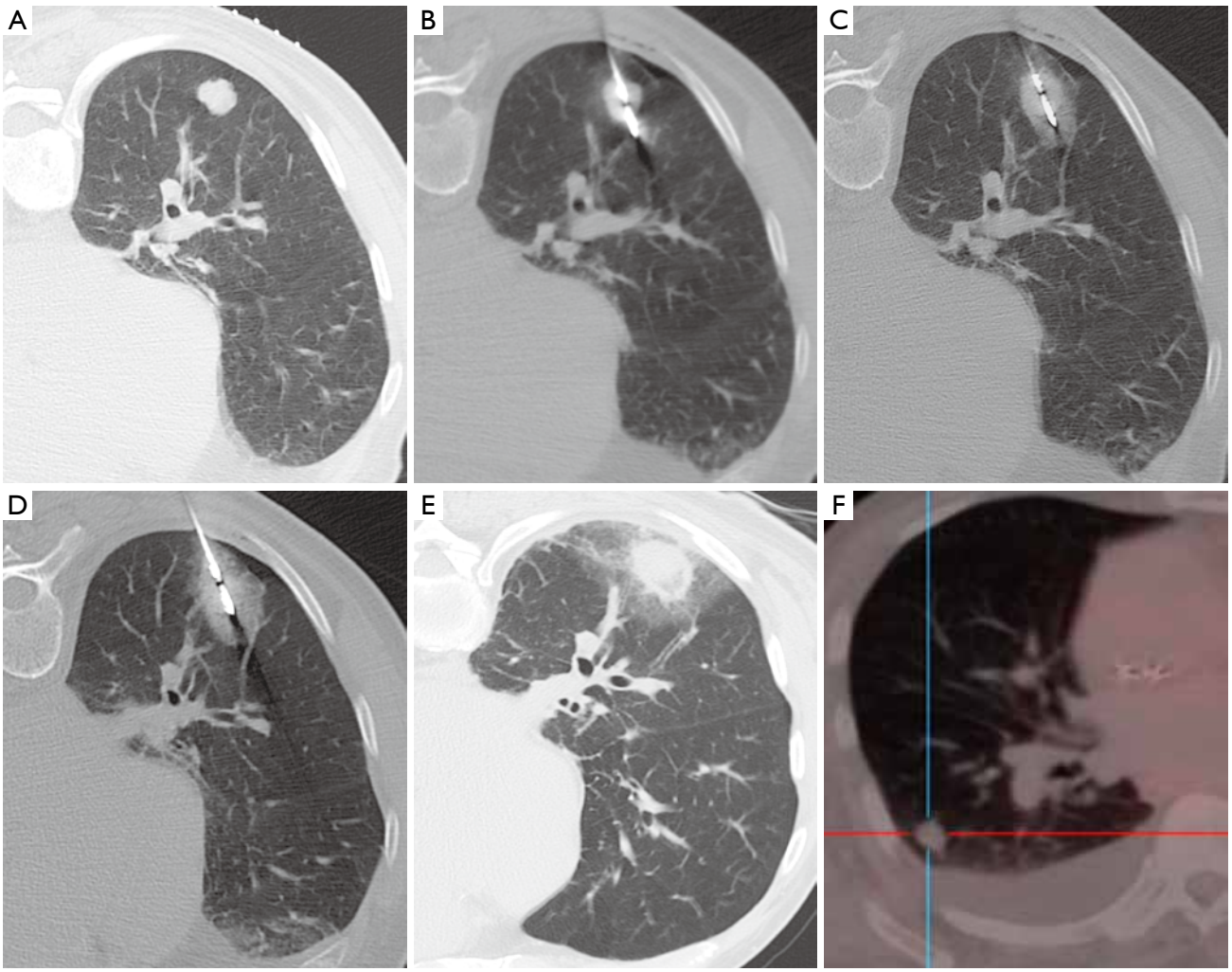


**Figure 2** A 70-year-old man with cardiomyopathy and new solitary melanoma metastasis to the right lower lobe. A. Prone axial CT image shows a lobulated 1.6 cm tumour; B. The feed point of the microwave antenna is positioned within the centre of the tumour; C, D. At 5 minutes following the start of ablation (C), there is ground glass opacity forming mainly on the far edge of the tumour, and at 10 minutes (D), a 3-10 mm circumferential rim of ground glass opacity has formed around the tumour; E. At 3 hours following ablation, there is marked (>1 cm) circumferential ground glass opacity around the tumour; F. Axial FDG-PET/CT image 6 months following MWA shows complete lack of FDG uptake at the site of tumour, indicating eradication of tumour. New cardiac-related pleural effusion is present.

lead to almost instantaneous irreversible cell damage. The centrifugally growing coagulation necrosis around the active tip of the microwave antenna is spherically shaped. It should ideally encompass the target tumour and a circumferentially surrounding safety margin (*Figure 2*). This safety margin, ideally at least 6 mm in thickness, is necessary to destroy tumour cell nests and satellite foci in the immediate periphery of the tumour not perceivable on cross-sectional imaging. A smaller safety margin carries a higher risk for local recurrence (95).

### *Advantages of MWA over RFA*

There are several advantages of microwave over RF energy. RF heating requires an electrical conduction path and is, therefore, less effective in areas of low electrical conductivity and high baseline impedance, such as lung parenchyma. This results in heating of the target tissue only immediately adjacent to the RF electrode (96,97). Microwaves are capable of propagating through many types of tissue and effectively heating them, even those

 

with low electrical conductivity, high impedance or low thermal conductivity (98). Unlike RF and laser, microwaves can penetrate through the charred or desiccated tissues that build up around all hyperthermic ablation applicators which results in limited power delivery for non-microwave energy systems (99). Multiple microwave antennae can be simultaneously powered to maximise the ablation volume when placed in close proximity to each other, or when widely spaced, to simultaneously ablate several tumours, such as multiple pulmonary metastases (95). Larger and more homogeneous ablation volumes can be achieved with MWA because the rapid heating with MWA results in less susceptibility to heat sink effect (92). Further advantages of MWA over RFA include no requirement for grounding pads which avoids potential pad site burns, and implanted cardiac devices are less prone to malfunction (100,101).

Detailed histopathological assessment of microwave ablated lesions has confirmed the concentric layered ablation zones post RFA described by Clasen *et al.* (102). The central inner necrosis is surrounded by an intermediate zone of equally irreversibly destroyed tissue corresponding to the safety margin strived for. The outer zone of ground glass opacity encompasses a haemorrhagic ring, which in turn is surrounded by oedema and a lymphocytic infiltrate (103). In these outermost layers, there was only partial thermal cell destruction seen with RFA (102). Vital histochemical nicotinamide adenine dinucleotide staining of resected lung tumours which have undergone intra-operative MWA immediately prior to resection confirmed cellular death (because of a lack of mitochondrial enzymatic activity) in a much larger ablation zone (104). No viable cells could be detected within five of the six ablation zones; uniform cellular death was shown to extend through sharp well-demarcated transition zones separating viable and nonviable ablated cells (104).

### *Patient selection and method*

Patients selected for MWA are usually deemed medically inoperable. Exclusion criteria for MWA include uncontrolled primary tumour, radiologic evidence of lymph node metastases, extrathoracic spread, infiltration of the chest wall, mediastinal structures, main bronchi or main pulmonary arteries, sepsis and irreversible coagulopathy (94,105). Patients who have undergone prior surgery (including pneumonectomy), chemotherapy or radiotherapy are usually not excluded. Some patients may have resectable tumours, but have declined surgery. The patient is positioned in the CT scanner that allows the shortest and safest access route to the tumour. Crossing of fissures should be avoided whenever possible. The skin is prepped and draped as usual, and local anaesthetic is infiltrated along the needle tract. A short cut into the skin allows for a smooth passage of the antenna. Under visual guidance, preferably CT fluoroscopy, the antenna is advanced in a stepwise manner into the tumour. Calcified pleural plaques and cartilage should be avoided because the fragile microwave antenna is at risk of fracture if forced through rigid tissue (106). Conscious sedation or general anaesthesia can be used with no difference in complications and outcome between the two modalities (107). Single ablation duration depends on tumour size, location and power capacity of the generator, but usually does not exceed 20 minutes. It is advisable to perform a limited CT scan during the ablation cycle to identify any displacement of the antenna from its original position or early complications. Only a few centres routinely administer prophylactic antibiotics for the procedure (108). Immediate post-procedural recovery includes continuous monitoring for pulse and oxygen saturation, and blood pressure measurements taken every 15-20 minutes. Other observations are performed as per the hospital's policy. A baseline chest radiograph is performed 3 to 4 hours following the ablation. In most centres, patients are hospitalised after the procedure and discharged the following day provided no complications have occurred. In principle, the procedure can be performed on an outpatient basis, but it is recommended to observe them overnight because of the potential for delayed complications.

### *Complications*

Complications resulting from ablation procedures should be classified in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) (109). The complication rate from MWA varies and can be expected to be higher in patients who have poor underlying pulmonary reserve. Pneumothorax is the most common immediate complication with a reported incidence of up to 43% (110), but less than one-third of these patients require a chest tube (105,110,111). Post-ablation syndrome, defined as a constellation of productive cough with or without minor haemoptysis, residual soreness in the treated area, and fever occurring several days after ablation, is reported in 2% of cases (105). Small pleural effusions not requiring thoracentesis occur in around a quarter of ablations. Cavitary changes are reported in up to 43% of ablated

 

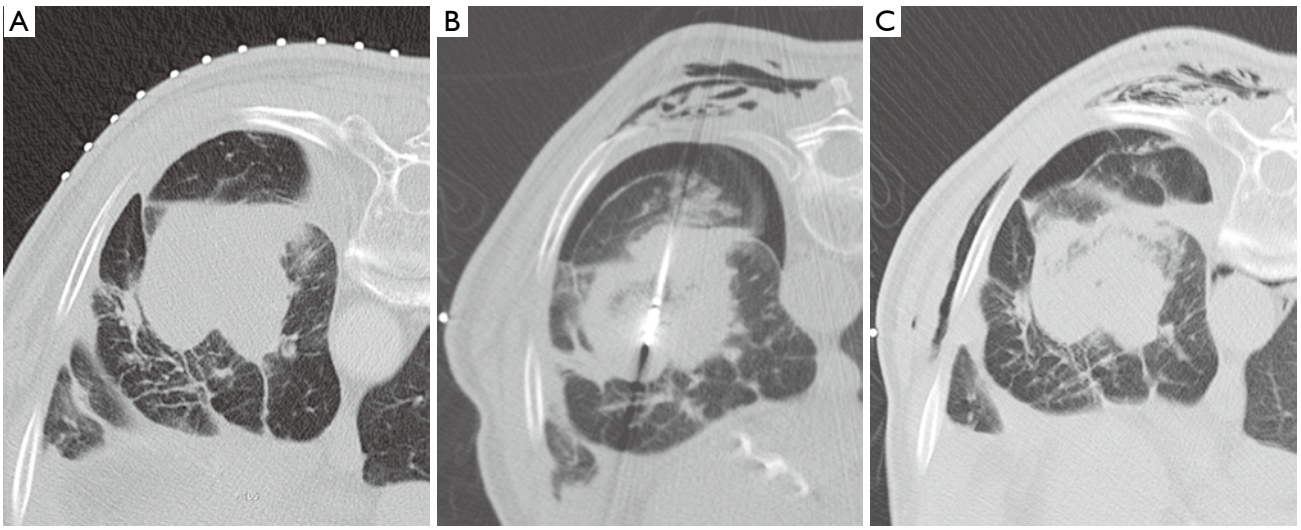


**Figure 3** A 72-year-old man with incomplete response to external beam radiation to left lower lobe NSCLC, who presented for salvage MWA. He had an intractable cough throughout the procedure. A. Prone axial CT image showed a 5.5 cm mass before MWA; B. Prone axial CT during the procedure showed a small pneumothorax and surgical emphysema developing around the antenna entry site; C. Prone axial CT at the end of the procedure shows the pneumothorax has remained similar in size, but had increased surgical emphysema.

tumours, 14% of which display air-fluid levels that usually involute spontaneously (105). Infective complications (abscess, pneumonia) are rare (105,110). Chest wall emphysema occurs in approximately 20% of cases (unpublished author's experience) and is usually concurrent with a pneumothorax (*Figure 3*). Ablated tumours abutting the visceral pleura result in pleural thickening in over one-third of cases (105), and prolonged pleural retractions occur in a small proportion of these cases. Up to 15% of patients require hospitalisation after MWA primarily due to pneumothoraces (105).

There is scarce comparable long-term outcome data for the effectiveness of MWA in lung cancer owing to the relatively recent addition of MWA to the armamentarium of minimally invasive hyperthermal treatment modalities; different MWA protocols that use different ablation systems operating at different frequencies with different shaft cooling mechanisms, different antennae size and different active tip lengths; and heterogeneous patient population treated, including treatment-naïve primary lung cancer, locally recurrent primary lung cancer following prior therapy, synchronous or metachronous lung cancers, and pulmonary metastases. Two recent publications using the same MWA device and with similar protocols showed promising short to mid-term results. In a homogeneous patient population of early stage NSCLC, the local control rate was 88% and 75% at a median follow-up of 6 months and 1 year, respectively (110,111).

### *Post-treatment evaluation*

CT is the imaging modality of choice for follow-up despite additional radiation exposure. A common post-ablation surveillance protocol is to perform a CT study the day following ablation to assess for complications, and this study can be used as a reference for comparison with subsequent studies, which are performed at 3 , 6 and 12 months during the first year, and at 6-monthly intervals thereafter (110). A thin (<5 mm) symmetric circumferential rim of peripheral enhancement is seen up to 6 months following ablation and is considered a sign of benign reactive enhancement. Irregular focal soft-tissue enhancement of >15 HU is, however, considered to be a sign of residual or recurrent disease (105). The initial size of the ablation zone is supposed to be much larger than the treated tumour as it encompasses the surrounding safety margin. Continuous shrinkage thereafter should occur and this usually leaves a small focus of atelectasis (*Figure 4*) or scar. FDG-PET imaging is considered to be more sensitive for detecting early tumour recurrence. The specificity, however, is low in the early post-ablation period. Performing FDG-PET scans sooner than 6 months following ablation should be

 

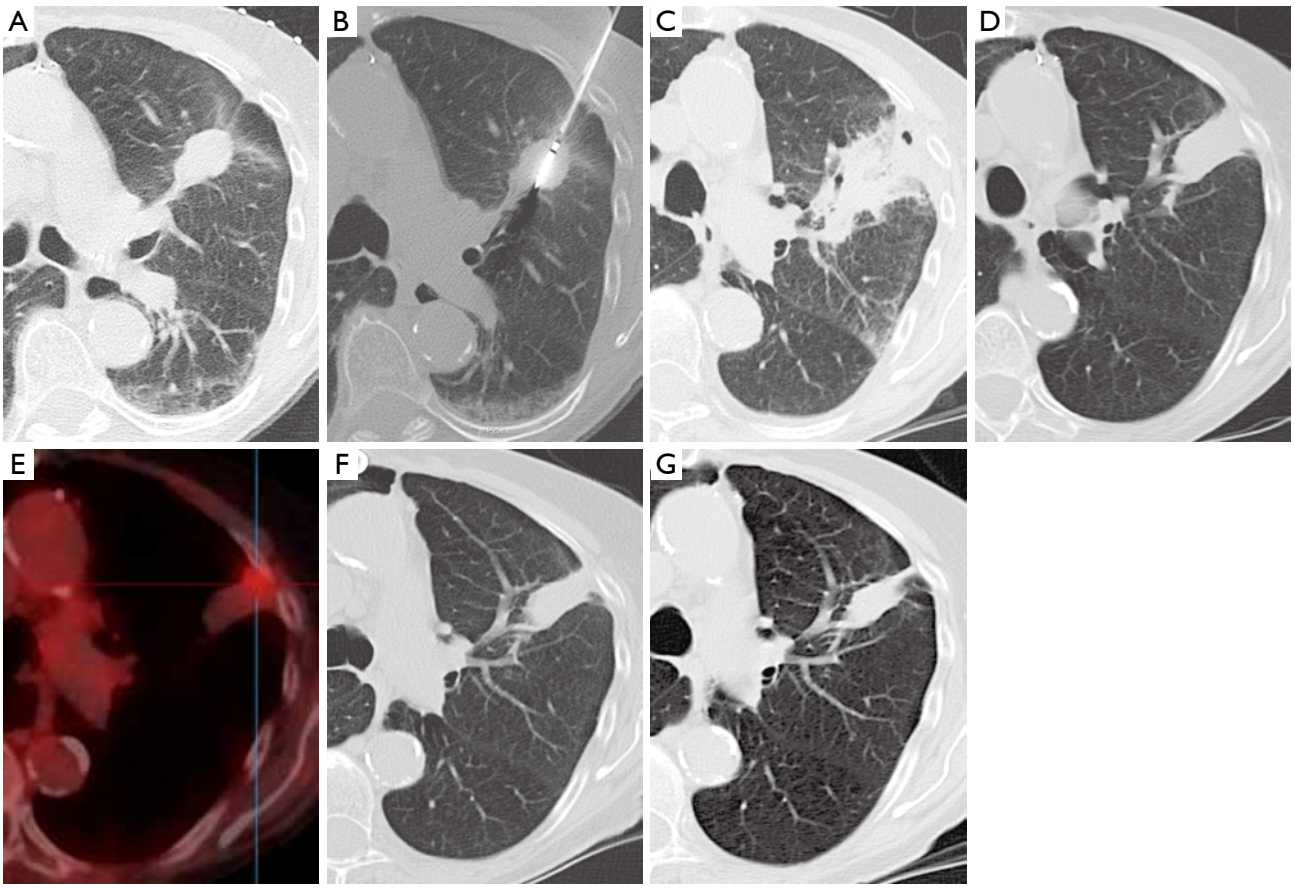


**Figure 4** A 75-year-old ex-smoker with prior RFA of biopsy-proven left upper lobe NSCLC. FDG-PET 3 months following RFA was equivocal for residual tumour and repeat treatment with CT-guided MWA was performed. A. Axial CT image shows a 3 cm left upper lobe mass; B. Axial CT shows microwave antenna is positioned within the centre of the mass; C. Axial CT 24 hours following MWA shows ablation site encompasses target lesion. There is a focal pleural effusion with small cavity, and surrounding atelectasis and ground glass opacity changes; D, E. Axial CT (D) and axial fused FDG-PET/CT (E) 6 months following ablation show resolution of the ground glass opacity and shrinking of the ablation volume, but a residual broad-based pleural contact remain. FDG-PET/CT shows lack of FDG-avidity of the ablated lesion but mild sub-pleural FDG uptake, likely inflammatory; F, G. Axial CT 12 months (F) and 24 months (G) following ablation show further gradual shrinking of the ablation volume and narrowing of the pleural contact.

discouraged to ensure a low false-positive rate (112,113). In addition to the FDG-uptake values, the pattern of FDG uptake is also indicative of ablation success or failure (113). Modified response evaluation criteria in solid tumours (RECIST) criteria, which incorporate both the CT and FDG-PET appearances of the lesion following ablation, are considered the most appropriate tool for follow-up assessment (114).

## Conclusions

The current challenge for imaging is to exploit the advantages of each imaging modality and integrate them into a clinically useful algorithm. At present, CT and PET/CT are recommended for lung cancer staging, and MR imaging is used for evaluation of suspected T3 and T4 disease. A few recent studies suggest that MR is equivalent to FDG-PET/CT for staging NSCLC. New developments in CT, PET/CT and MR have the potential to provide improved anatomical and functional assessment of lung cancers that result in more individualized and targeted therapy. Cryoablation, RFA and MWA are promising powerful percutaneous techniques for curative-intent therapy or localised palliation of lung cancer, but available short-

 

to mid-term data suggest MWA to be superior to RFA. However, more mid- and long-term data are required to assess for survival and cancer-free outcome following such therapies.

## Acknowledgements

None.

## Footnote

*Conflicts of Interest*: The authors have no conflicts of interest to declare.

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# Central airway tumors: interventional bronchoscopy in diagnosis and management

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**Abstract:** The diagnosis of central airway tumors is usually challenging because of the vague presentations. Advances in visualization technology in bronchoscopy aid in early detection of bronchial lesion. Cryotechnology has great impact on endobronchial lesion sampling and provides better diagnostic yield. Airway tumor involvements result in significant alteration in life quality and lead to poor life expectancy. Timely and efficiently use of ablation techniques by heat or cold energy provide symptoms relief for central airway obstruction. Prostheses implantation is effective in maintaining airway patency after ablative procedure or external compression. Combined interventional bronchoscopy modalities and other adjunctive therapies have improvement in quality of life and further benefit in survival. This review aims to provide a diagnostic approach to central airway tumors and an overview of currently available techniques of interventional bronchoscopy in managing symptomatic central airway obstruction.

**Keywords:** Central airway obstruction; bronchoscopy; intervention; ablative technologies; stents

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## Introduction

Patients with central airway tumors usually have nonspecific clinical manifestation which can lead to delayed diagnosis. Computed tomography (CT) scan is the best noninvasive method for airway lesion evaluation (1). Bronchoscopy is still the mainstay to approaching endobronchial lesion. The conventional methods to obtained specimens include forceps biopsy, brushing or washing the lesion under direct vision. However, the diagnostic yield of conventional forceps biopsy is limited because of the small size of tissue sample and crush artifacts (2,3). Newly developed cryotechnology provide a larger sample than that of conventional forceps biopsy and has better diagnostic yield (2).

Dyspnea is the major symptom in patients with central airway obstruction which limits the daily activity of patients. Unfortunately, not only 20% to 30% patients with primary lung cancer experience this suffering symptoms, 2% patients with solid tumors also have endobronchial metastasis which may postpone their anti-cancer therapy because of severe dyspnea (4,5). In recent decades, interventional bronchoscopy has been an effective treatment modality for central airway obstruction (6-8). In patients with limited performance status due to central airway obstruction, the functional status will improve after interventional bronchoscopy and have the chance to receive chemotherapy (9,10). The exercise capacity, lung function and quality of life are improved after therapeutic bronchoscopy (11). Moreover, the survival may also be prolonged after airway stenting in selective situation (12,13).

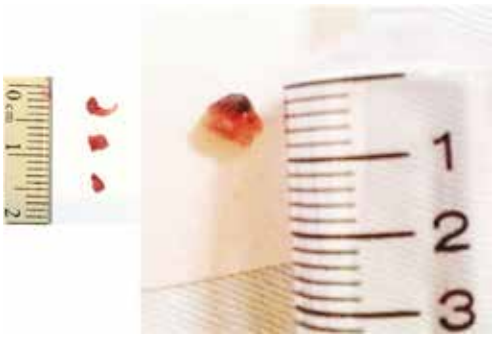

**Figure 1** Specimens comparison between traditional forceps biopsy (left) and cryotechnology (right).


**Figure 2** Types of central airway obstruction.

Here, we provide a clinical review of interventional bronchoscopy in diagnoses and management of central airway tumors.

## Diagnostic modalities

### *Computed tomography*

Only less than 30% patients with tracheal tumors have been diagnosed via chest radiography (14). Traditional CT scan is more sensitive and can provide information on the extent of airway lesions. Newly developed multidetector CT (MDCT) can accurately detect airway tumor locations, natures, quantities (1). The extra luminal anatomy is also clearly depicted. Thus, MDCT is a rapid and non-invasive method to provide comprehensive information about the extent of disease process before surgery or interventional bronchoscopy (1).

### *Visualization of bronchoscopy*

Bronchoscopy is the mainstay to approaching endobronchial lesion under direct vision. In addition to the conventional white light bronchoscopy, autofluorescence (AFB) and narrow band imaging (NBI) are new visualization techniques of bronchoscopy which can aid detection of bronchial mucosa lesions (15). Although the specificity of AFB is low and similar to white light bronchoscopy, there is no doubt in usefulness of detecting early bronchial mucosal lesion and evaluating the margin of mucosal involvement (16,17). NBI is designed to detect angiogenesis and neovascular lesion. The diagnostic accuracy is increased under NBI bronchoscopy (15). Both of them have superior sensitivity compared with white light bronchoscopy [3-5]. Endobronchial ultrasonography (EBUS) is also helpful in evaluating the extent of airway lesion involvement (14,18).

### *Tissue sampling: forceps versus cryotechnology*

Forceps biopsy under direct bronchoscopic vision is the most common method to obtain tissue sample from endobronchial lesion. However, the size of tissue sample is limited by the forceps size. Small samples with crush artifacts are probably insufficient for accurate diagnosis. The diagnostic yield is only 85% of conventional forceps biopsy and patients usually have to repeat bronchoscopy (2,3).

Cryotechnology has been used as a therapy for central airway obstruction and hemoptysis (19). The samples from cryotechnology are larger than conventional forceps biopsy and have better diagnostic yield (95% to 100%) (3,20,21) (*Figure 1*). Besides, the tissue architecture will not be damaged by cryotechnology and thus facilitate histological analysis (22). Tumor bleeding is a major concern after biopsy. Theoretically, vasoconstriction and capillary microthrombosis after cryotechnology may ameliorate bleeding (20,23). Hetzel *et al.* (3) reported a greater incidence of mild bleeding after cryobiopsy. However, the rate of severe bleeding is comparable of forceps biopsy and cryobiopsy. In recently published, prospective study, two cryo biopsies were found to be optimal for diagnosis and greater than three bryobiopsies will increase the risk of bleeding (24). Cryotechnology has been a considerable choice for endobronchial lesion biopsy with better diagnostic yield and minimal complication.

## Management

There are three types of central airway tumor involvement: endoluminal (tumor within airway), extraluminal (airway narrowing from external compression), and mixed (6) (*Figure 2*). A variety of techniques in endoluminal tumor debulking has been developed and has been shown to be effective in relieving symptoms (22). In addition to extraluminal and mixed type central tumor involvement,

 

**Table 1** Types of central airway obstruction and treatment modalities

| | Intraluminal | Extraluminal | Mixed |
|---|---|---|---|
| Mechanical debulking | + | – | + |
| Electrocautery | ++ | – | + |
| Argon plasma coagulation | ++ | – | + |
| Laser | ++ | – | ++ |
| Cryotherapy | +++ | – | +++ |
| Stent | | +++ | ++ |

–, not recommended; +, weakly recommended; ++, recommended, +++, strongly recommended.

airway stenting is also useful in preventing recurrence and restoring the airway patency after intraluminal tumor debulking (25). The choice of techniques depends on the characteristics of stenosis, the condition of patient, available techniques and the operator's expertise (*Table 1*).

### *Rigid bronchoscopy and mechanical debulking*

Rigid bronchoscopy is a traditional procedure, which has been introduced under general anesthesia (26). Contraindications of rigid bronchoscopy include cervical spine instability, facial trauma, laryngeal obstruction (27). The easy airway security and large working space provide more space for interventional procedure processing. However, in patients with severe airway obstruction and respiratory failure will experience great risk of general anesthesia because of high oxygen demand and illness severity (28).

Recently, Vishwanath *et al.* (29) reported their 30-cases experience of solely mechanical debulking under rigid bronchoscopy in managing central airway tumors. The success rate reached 82.6%, however, the complication rate was as high as 32.3% with significant bleeding in 25.8% patients. Although they suggested that mechanical debulking under rigid bronchoscopy was probably quicker than thermal ablative therapy, there was no direct comparison of procedure time between different methods. Combining mechanical debulking with a complementary thermal ablative procedure may be a safer choice in bleeding control (25).

### *Electrocautery*

Electrocautery uses high-frequency electric current to cause heating which leads to coagulation or tissue vaporization (30). It can be delivered via rigid or flexible bronchoscopy. The effects depend on the power setting, surface area, electrical properties of tissue and the contact time (22). In one large retrospective series of electrocautery for airway obstruction, the luminal improvement was achieved in 78% patients with 6.8% complication rate (31). Electrocautery provided equally effective and constant palliation in patients with airway obstruction as that provided by neodymiumdoped:yttrium-aluminum-garnet (Nd:YAG) laser therapy. However, the cost of electrocautery was significantly lower than Nd:YAG laser (32). Thus, electrocautery is a more accessible modality worldwide.

The complications include damage of underlying cartilage which may lead to airway stenosis, bleeding, perforation, pneumothorax, malfunction of pacemaker (22). Besides, airway fire is also a major concern in the presence of high oxygen concentration and flammable substance (such as silicone stent or endotracheal tube). The above complications could be ameliorated after restricting the fractional inspired oxygen less than 40% and limiting the power output do not exceed 30W (30).

### *Argon plasma coagulation (APC)*

APC is a non-contact method of electrocautery and can be introduced via both rigid and flexible bronchoscopy (33). The noncontact feature of APC allows extent and rapid coagulation, but the depth of penetration is more superficial (2–3 mm) and limited by increased tissue resistance after coagulation and desiccation (33,34). The major applications of APC are hemostasis and tissue destruction and particular effective in vascular lesion (35). Besides, APC is an effective therapy for airway obstruction secondary to endobronchial lesion (36). Not only significant endobronchial tumor reduction, clinical dyspnea score and forced expiratory volume in one second (FEV1) are also improved after procedure (37). Because of the superficial effect and superiority in hemostasis, APC is usually used as a part of multi-modality approach for tumor debulking (33).

The complication rate of APC is approximately 2% (30). The most severe fatal complication is intracardiac gas embolism and cerebral embolism (38,39). The above conditions may be minimized by keeping the flow to less than 0.8 L/min and maintaining a safe distance of 2–5 mm (34).

### *Laser*

Laser therapy is a widely used ablative technique for tumor

 

debulking which can be performed using flexible or rigid bronchoscopy with different gases (22). Neodymium: yttrium-aluminum-garnet (Nd-YAG) laser is the most frequently used (34). The most common indication is relieving central airway obstruction. It is particularly effective for intraluminal and mixed type airway obstruction and less suitable for extraluminal compression (40). In additional to constant and immediate effect in tumor shrinkage, the quality of life and overall health are also improved significantly in patients with malignant central airway obstruction due to lung cancer (41). Although laser monotherapy is quite effective in alleviating symptoms from malignant central airway obstruction, survival benefit will be improved when it combined with multimodal adjuvant therapy (including brachytherapy, chemotherapy, radiotherapy, stenting, chemoradiotherapy) (42). However, the high cost of laser therapy is a disadvantage of the usefulness worldwide and can be alternated with electrocautery, APC or cryotherapy (32,40).

The complication rate of laser therapy is around 8%, including hemorrhage, endobronchial fire, pneumothorax, and air embolism (40). The periprocedural death is 1–3% (30). Because of the inability to visualize penetration depth, perforation of major vessel will lead to fatal hemoptysis. This can be avoided by limiting the power less than 40W (34,40). Endobronchial fire can be prevented by restricting the fractional inspired oxygen less than 40%. Besides, patients who were over 60 years of age, with arterial hypertension or chronic obstructive pulmonary disease were associated with higher complication rate (43). Thus, in additional to the modification in setting, the patient selection is also important to minimizing complications.

### *Cryotherapy*

Cryotherapy uses extremely cold (–70 ℃) to tissue and causes tissue necrosis with repeated freezing and thawing cycle (30). It can be introduced with rigid or flexible bronchoscopy. The effect of cryotherapy is usually delayed but prolonged, with capillary microthrombi formation (25). The efficacy depends on the cooling rate, the minimum temperature reached, the cycle of freezing and thaw (22). Unlike thermal ablative therapy (electrocautery, laser, APC), cryotherapy has no risk in airway fire and will not lead to tissue edema after procedure (23). Because of low water content of cartilage, collagen and poorly vascularized tissue, cryotherapy has very small effects on them. As such, the scarring is minimal and the damage of cartilage is few (23). Cryotherapy is mainly indicated for a palliative treatment for intraluminal airway obstruction and not recommended in submucosal lesion or extraluminal compression (34). The overall success rate of significant recanalization exceeded 80% in one systematic review (44). In addition to improvement in dyspnea, cough, and hemoptysis, the lung function, performance status is also improved after cryotherapy (19). When combined with systemic chemotherapy and/or radiation, the survival benefit is significant (9,45). As the effect of cryotherapy is delayed, it is usually not suitable for patients with impending respiratory failure secondary to airway obstruction. Use the principle of cryoadhesion, cryosurgery has been performed with rapid relief of tumor obstruction. However, additional modalities, such as APC, are required to achieve hemostasis (34). Recently, Boujaoude *et al.* reported one case with acute central airway obstruction has been managed successfully with cryosurgery alone using "freeze and pull" technique. Although the experience is few, however, it provides the opportunity for patients with emergent airway obstruction under high oxygen requirement to be liberated from mechanical ventilation (46).

The complication rate is low (0–11%), most of them were minor and easily manageable (44). The risk of perforation and airway fire are non-existent, since the cartilage is cryoresistant. Thus, cryotherapy is safe while the inflammable substance is nearby the obstructive lesion (*Figure 3*).

### *Stent*

The endobronchial stent is the main choice to alleviate extraluminal airway compression and is also available to relieve intraluminal and mixed type central airway obstruction when combining with other endobronchial therapies (25). Airway stent is usually a palliative treatment for malignancy. It provides a bridge for airway patency in patients undergoing systemic chemotherapy or radiation. Although the overall survival was not changed, the median survival time could be increased after airway stenting if it is combined with adjuvant therapy (47).

Theoretically, the ideal stent should be strength enough, not migrate, easy to insert and remove, flexible enough to mimic airway physiology, not impair mucociliary clearance, not induce granulation tissue formation, and cost-effective (26). However, it has not been developed.

Before stent implantation, the size, diameter and length have to be chosen according to CT scans and bronchoscopy.

 

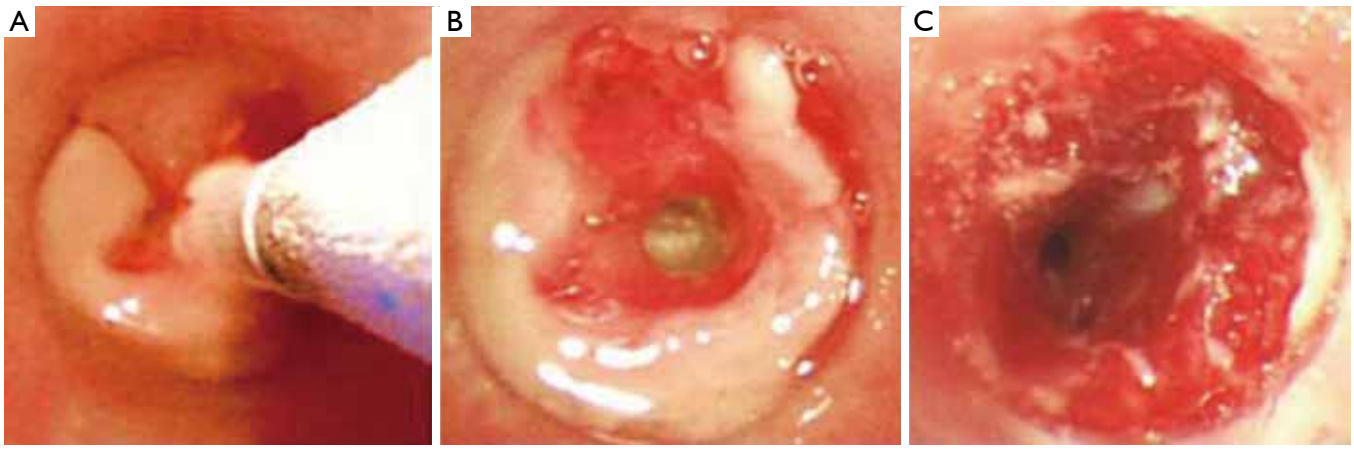


**Figure 3** Cryotherapy successfully recannulized airway obstruction secondary to silicone stent induced granulation.

**Silicone stents**

Silicone stent has to be deployed by rigid bronchoscopy under general anesthesia (30). The most commercially available silicone stents are Dumon stents, which have two main types: straight and bifurcated stents (26). The size, length and diameter are chosen preoperatively and can be adjust by cutting. Because it is easy to insert and remove, with few granulomatous reactions, silicone stent has been recommended as first line treatment and is particularly suitable for benign lesion for the longer lifespan (25).

The major drawbacks of silicone stent include the necessity of general anesthesia, higher migration rate, mucus plugging, thicker wall and lead to narrow internal diameter. Mucolytic nebulization is essential to prevent dense secretion and asphyxiation (25).

**Self-expandable metallic stents (SEMS)**

SEMS is mainly used to treat airway obstruction or tracheoesophageal (TE) fistula due to malignancy (*Figure 4*). Metallic stent is also an alternative choice in benign disease if the patients are poor surgical candidates or the airway is highly tortuous (30,48). SEMS can be introduced via rigid and flexible bronchoscopy. There are partial covered, fully covered and uncovered stent. Covered stent is preferred in malignant lesions and particularly suitable for covering TE fistula (49). Uncovered stent is mainly used in highly distorted stenosis. Unlike silicone stent, SEMS provide thinner wall construction, greater airway diameter, better conformation with irregular airway, easier placement and less migration rate. The size of stent should be chosen accurately before procedure. The length of stent has to provide 0.5–1.0 cm overlap at each end of the stenosis. The diameter of the stent should be 1–2 mm greater than the estimated diameter of the airway (30). Fluoroscopy is usually necessary for SEMS placement. However, it is not available in many intensive care units (ICU) and requires special facilities. Lin *et al.* (28) reported 26 mechanically ventilated patients have been successful inserted metallic stent under flexible bronchoscopy without fluoroscopy guidance. More than half patients have liberated from ventilator successfully.

Metallic stent is effective in reliving symptoms of airway obstruction, facilitating to liberate from ventilator, improving pulmonary function and performance status (50-52). Compared with poor performance status, patients with malignant central airway obstruction under intermediate performance status have survival benefit after airway stenting (12). This suggests that timely airway stenting before morbid complication is quite important.

The complications of SEMS include stent malposition, migration, fracture, mucus impaction, halitosis, bacterial colonization and granulomatous tissue formation. In uncovered and partial covered stent, the re-epithelialization and excessive granulation formation in the edges are the most frequent complications, which cause the difficulty in stent removal (48,53). Benign structure airway obstruction prior to stent implantation is an independent factor for granulation tissue formation (54). SMES fracture is of major concern because of the possibility of complete airway obstruction and perforation (55). Pretreatment tortuous airway in 3-dimensional CT scan predicts metallic stent fracture. SEMS implantation in such situation should be cautiously evaluated (55,56). Besides, the complication rate in benign conditions is twice higher than malignant disease

 

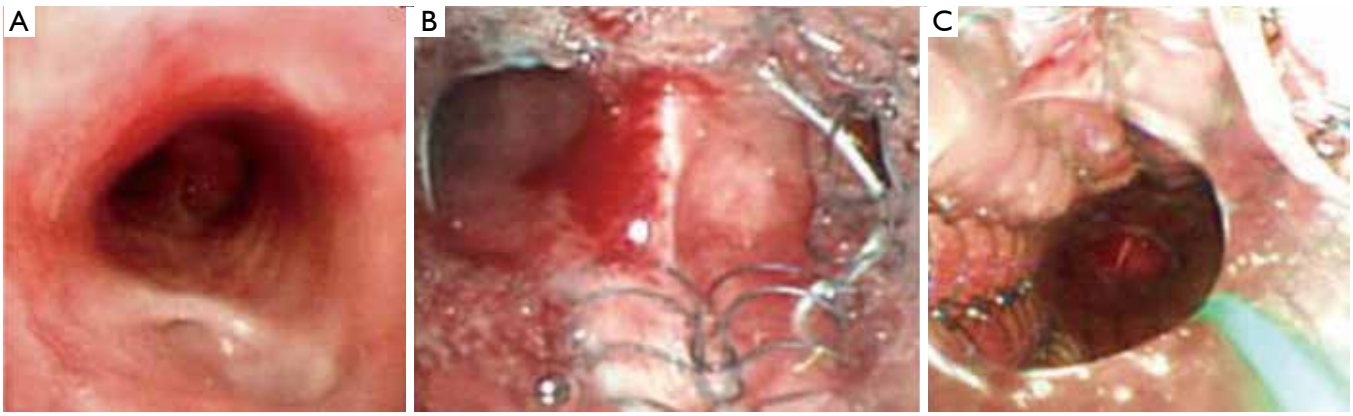


**Figure 4** Self-expandable metallic stents (SEMS) implanted successfully for covering tracheoesophageal (TE) fistula in patient who was under mechanical ventilation without fluoroscopy guidance.

(42.2% *vs.* 21.1%) owing to the longer follow-up period and longer lifespan (51). In one largest series of lung transplant recipients, the 5-year survival was significantly lower in patients receiving metallic stent insertion. Re-stenosis and airway bacterial colonization are the major problems (52). Because of severe complication after long term SEMS implantation, the US Food and Drug Administration (FDA) has warned that metallic stent is not advised to treat benign disease.

### Developing stents

Concerning the granulation tissue formation after airway stenting, drug eluting stent with mitomycin C have been observed to reduce granulomatous reaction and less mucus trapping. In animal studies, cisplatin eluting stent have steadily and sustained released drug up to 4 weeks and helpful to against malignant cells (57).

In benign or reversible cases, the airway stent is usually temporalily needed. There are 70% of patients with post-intubation or post-tracheostomy tracheal stenosis had been successfully treated by silicone stent implantation after 18 months (58). Thus, the removability of stent is quite important. Biodegradable stent has been designed to maintain airway patency for a predetermined duration. It is a temporary support device until the natural tissue regains its strength and can be removed by cellular activity in a biological environment. There are four human studies until now. Only one adult study showed relative good outcome up to 4 years, the outcomes of the other 3 pediatric studies were not satisfactory and were associated with repeat stenting after stent absorption. Besides, the cost of biodegradable stent is much higher than others. The safety and toxicity are also the major concerns (59).

Symptoms from central airway tumors result in poor quality of life and disaster outcome. The survival would not exceed 1–2 months if the patient is untreated. However, in such situation, patients' performance status, pulmonary function and comorbidities are usually limited by the possibility of surgery (25). Interventional bronchoscopy provides a less invasive choice with high technical success rate (90–98%) and is effective for central airway obstruction to improve quality of life and survival (10,11,13). The complication is relative rare (3.9%) with few mortalities (0.5%) (60). Nevertheless, the benefit is difficult to predict in patients under different situations. Guibert *et al.* (61) conducted a retrospective study involving 204 patients with malignant central airway obstruction. They found that higher American Society of Anesthesiologists (ASA) score, non-squamous histology, metastatic tumors and those who were treatment-naive patients had the worst survival. In one largest, multicenter, prospective study, Ost *et al.* (10) demonstrated that patients with ASA >3, renal failure, primary lung cancer, left mainstem involvement and TE fistula were associated with failure. They also found that the complication rate was higher in those with ASA >3, re-do bronchoscopy, receiving procedure under emergent or urgent situation. Thirty-day mortality was associated with poor performance status and ASA >3 (60). However, the patients with higher baseline Borg score had the greater improvement in dyspnea and quality of life. Since patients at the highest risk may have the greatest benefit, therapeutic bronchoscopy should not be withheld from patients solely based on risk assessment (10).

 

## Conclusions

Newly developed visualization technologies of bronchoscopy provide more rapid, accurate, precise diagnosis of endobronchial lesions. Cryobiopsy is a safe technique with greater diagnostic yield and provides a better specimen quality than traditional forceps biopsy.

Interventional bronchoscopy enables the restoration of airway patency and plays an important role in the treatment and palliation for malignant airway obstruction. Mechanical debulking, electrocautery, APC and laser provide immediate symptom relief under urgent situation. Cryotherapy is preferred to use in the selective situation because of the delayed effects. Airway stenting is particular suitable for extraluminal compression and is also effective for intraluminal involvement. Drug eluting and biodegradable stents being developed to reduce the complication after long term implantation. Since more complication and less benefit have been expected in urgent situation, timely interventional bronchoscopy should be prudently considered before morbidity coming. The selection of modalities depends on the patients' condition, disease manifestation, availability of equipment and physicians' expertise.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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Interventional Diagnostic Technique

# Lung cancer diagnosis and staging in the minimally invasive age with increasing demands for tissue analysis

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**Abstract:** The diagnosis and staging of patients with lung cancer in recent decades has increasingly relied on minimally invasive tissue sampling techniques, such as endobronchial ultrasound (EBUS) or endoscopic ultrasound (EUS) needle aspiration, transbronchial biopsy, and transthoracic image-guided core needle biopsy. These modalities have been shown to have low complication rates, and provide adequate cellular material for pathologic diagnosis and necessary ancillary molecular testing. As an important component to a multidisciplinary team approach in the care of patients with lung cancer, these minimally invasive modalities have proven invaluable for the rapid and safe acquisition of tissue used for the diagnosis, staging, and molecular testing of tumors to identify the best evidence-based treatment plan. The continuous evolution of the field of lung cancer staging and treatment has translated into improvements in survival and quality of life for patients. Although differences in clinical practice between academic and community hospital settings still exist, improvements in physician education and training as well as adoption of technological advancements should help narrow this gap going forward.

**Keywords:** Lung cancer; staging; molecular testing; minimally invasive; endobronchial ultrasound with transbronchial needle aspiration (EBUS-TBNA); interventional pulmonology

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## Introduction

Lung cancer is the leading cause of cancer deaths worldwide. The most frequently encountered primary lung cancers include epithelial-derived non-small-cell lung cancer (NSCLC), with adenocarcinoma and squamous cell carcinoma as the main histologic subtypes; and neuroendocrine carcinomas, with small cell lung cancer (SCLC) as the major high-grade neuroendocrine carcinoma. Most NSCLCs are diagnosed at advanced stages, and historically (up to the early 2000s), palliative therapeutic decisions were based solely on the differentiation between NSCLC and SCLC. Hence, the main diagnostic modalities and focus on tissue acquisition were geared towards obtaining small samples for simple histopathological characterization that would be added to non-invasive imaging studies to complete tumor, node, metastasis (TNM) staging. The paradigm of NSCLC histology not otherwise specified (NOS) with advanced TNM staging drove the development of anti-cancer therapies for NSCLCs in the 1980s, 1990s, and early 2000s; with the evidence-based introduction of platinum-doublets as the main palliative modality for stage IV NSCLC (1).

A need to better define NSCLC subtypes occurred in the early 2000s with the introduction of novel cytotoxic chemotherapies (pemetrexed) and biological agents

 

(bevacizumab) that had enhanced efficacy or worsened toxicity, respectively, based on histology (2,3). To this end, a diagnosis of NSCLC NOS was no longer sufficient, and the more widespread use of both histochemical and immunohistochemical ancillary studies helped to more consistently distinguish adenocarcinoma from squamous cell carcinoma in small biopsy/cytology specimens. The 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) lung adenocarcinoma classification was developed by an international core panel of expert medical oncologists, pulmonologists, pathologists, and thoracic surgeons, to address minimum requirements in immunohistochemical testing markers to differentiate between adenocarcinoma and squamous cell in small samples that were previously classified as NSCLC NOS (4). This shift in tumor acquisition goals and requirements, continues to reverberate in clinical lung cancer care and drug development, with, for example, the initial approval by the US Food and Drug Administration (FDA) of the immune-checkpoint, anti-programmed death-ligand 1 (PD-1) inhibitor, nivolumab, for advanced squamous cell lung cancer (5).

The need for adequate tissue for the diagnosis and management of NSCLC has increased substantially over the last decade, as new anti-cancer therapies have begun to explore vulnerabilities in the genomic underpinnings of cancer. Cancer is a heterogeneous group of diseases that leads to invasion and metastasis, induction angiogenesis, replicative immortality, resistance to cell death, reprogramming of energy metabolism, evasion of immune surveillance, circumvention of growth suppressors, and sustained proliferative signaling (6). The latter is especially prevalent in subgroups of NSCLC, since sustained proliferative signaling is usually derived from genomic mutations in key oncogenes that encode for activated tyrosine kinases.

Three main genomic events lead to the direct activation of tyrosine kinases in NSCLC: overexpression or amplification (due to increased copy numbers of a certain oncogene), mutation (due to point mutations or insertions/deletions), and rearrangement with partner genes (by preserving or activating the kinase domain of oncogenes). The most prevalent oncogenes that are amplified, mutated or rearranged in NSCLCs are listed in *Table 1* (7-9).

Tyrosine kinase inhibitors (TKIs), small molecules that can block the function of kinases, have been developed as precision therapies in NSCLC. As of mid-2015, EGFR and ALK mutations are the most prevalent, clinically relevant driver oncogenes in NSCLC care. First generation reversible EGFR TKIs (gefitinib and erlotinib) and second generation irreversible EGFR TKIs (afatinib) have been shown in multiple randomized phase III trials to be superior to standard platinum-doublet chemotherapies in the first line treatment of advanced EGFR mutant lung adenocarcinomas and are FDA approved for use in this setting (10-13). In addition, novel third generation covalent EGFR TKIs that are more specific to the most common first/second generation TKI resistance mutation (EGFR-T790M) are active and have FDA 'breakthrough' review designation.

ALK mutations in lung adenocarcinomas occur through gene rearrangements (the most common partner is EML4) that lead to constitutive activation of the tyrosine kinase domain of ALK. The multitargeted ALK/MET/ROS1 TKI crizotinib led to significant responses in phase I and II trials of ALK rearranged lung adenocarcinoma, and phase III randomized trials in the second line (crizotinib versus docetaxel or pemetrexed) and first line (crizotinib versus platinum-pemetrexed) setting have confirmed that crizotinib is more effective than chemotherapy for these tumors (14-17). The FDA label of crizotinib requires tumor identification of ALK rearrangement status. In addition, the second generation ALK TKI ceritinib is FDA approved for the therapy of crizotinib-resistant ALK rearranged lung adenocarcinoma and the related compound alectinib has a FDA breakthrough designation (18,19). Other TKIs have differing levels of evidence for off-label use in lung adenocarcinomas with other genotypes (*Table 1*).

To standardize the use of tissue for the ever-changing needs of molecular diagnostics in lung cancer, in 2013, IASLC, Association for Molecular Pathology (AMP), and College of American Pathologists (CAP) published minimum molecular testing guidelines for selection of lung cancer patients for EGFR and ALK TKIs that are now widely used for day-to-day medical oncology care (20). The current guidelines prioritize use of rapid single gene assays for these two driver oncogenes. However, it is becoming evident that technological advances have reached a point where comprehensive molecular profiling using a variety of next generation sequencing (NGS) platforms is feasible in routine clinical practice; with a multitude of commercial or academic vendors providing Clinical Laboratory Improvement Amendments (CLIA)-certified NGS assays that use formalin-fixed paraffin-embedded (FFPE) specimens or cytology specimens to isolate DNA and/or RNA for analyses of a targeted panel of genes to select for the most readily targetable alterations (*Table 1*) (21,22).

Therefore, the need for sufficient, high-quality tissue

 

**Table 1** Known driver mutations in NSCLC with associated targeted therapeutics

| Molecular target/driver oncogene | Prevalence (%) | US FDA-approved TKIs in 2015 | US FDA-breakthrough designation TKIs in 2015 | Off label use of TKIs with significant level of evidence (NCCN category 2A) | Off label use of TKIs with lesser levels of evidence |
|---|---|---|---|---|---|
| Adenocarcinoma | | | | | |
| *KRAS* mutations | 25-30 | None | None | None | None |
| *EGFR* mutations | 15-20 | Erlotinib, afatinib | AZD9291, rociletinib | N/A | N/A |
| *ALK* rearrangements | 3-7 | Crizotinib, ceritinib | Alectinib | N/A | N/A |
| *ROS1* rearrangements | 2-4 | None | Crizotinib | Crizotinib | Cabozantinib |
| *MET* exon 14 skipping mutation | 2-4 | None | None | None | Crizotinib |
| *ERBB2* mutations | 1-3 | None | None | None | Afatinib |
| *BRAF* mutations (V600E) | 1-3 | None | Dafrafenib, dafrafenib + trametinib | Dafrafenib, vemurafenib | N/A |
| *RET* rearrangements | 1-2 | None | None | None | Cabozantinib |
| *MET* amplification | 1-2 | None | None | Crizotinib | N/A |
| *MAP2K1* mutations | 1 | None | None | None | None |
| *NTRK1* rearrangements | <1 | None | None | None | None |
| *FGFR2/3/4* rearrangements | <1 | None | None | None | None |
| Squamous cell carcinoma | | | | | |
| *FGFR1* amplifications | 15-20 | None | None | None | None |
| *FGFR2/3/4* mutations/ rearrangements | 5-10 | None | None | None | None |
| *PI3KCA* mutations | 5-10 | None | None | None | None |
| *DDR2* mutations | 1-5 | None | None | None | Dasatinib |

NSCLC, non-small-cell lung cancer; FDA, Food and Drug Administration; TKIs, tyrosine kinase inhibitors; N/A, non-applicable.

material for diagnosis, staging, and treatment selection has grown significantly, concurrently with the expansion of minimally-invasive tissue acquisition methods. We will address current minimally invasive methods for tissue acquisition in the diagnosis and management of patients with lung cancer, their performance characteristics, and consider current gaps in patient care in different practice environments.

## Minimally invasive techniques for tissue acquisition

Prompt and accurate diagnosis and staging of patients with lung cancer should be sought through an efficient process: one that minimizes the number of procedures before initiating treatment. Ideally, the preferred initial procedure would be able to simultaneously provide tissue for diagnosis, tumor classification, molecular testing, as well as provide staging information. However, this may or may not be possible depending on the individual patient and the need for sufficient and appropriate tissue for current and future cytological, immunohistochemical, and molecular studies. The available techniques are: mediastinoscopy, endobronchial ultrasound with transbronchial needle aspiration (EBUS-TBNA), endoscopic ultrasound (EUS) with fine needle aspiration (FNA), traditional bronchoscopic TBNA and computed-tomography guided core needle biopsy (CT-CNB) or CT-FNA. The overall performance measures of these different techniques are summarized in *Table 2*.

 

**Table 2** Non-invasive and minimally-invasive staging modalities for non-small cell lung carcinoma*

| Procedure | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Number of studies | Number of specimens | Cancer prevalence (%) |
|---|---|---|---|---|---|---|---|
| CT | 55 | 81 | 58 | 83 | 43 | 7,368 | 30 |
| Integrated PET-CT | 62 | 90 | 63 | 90 | 19 | 2,014 | 22 |
| Mediastinoscopy^ | 81 | 100 | 100 | 91 | 35 | 10,648 | 34 |
| TBNA | 78 | 100 | 100 | 77 | 27 | 2,408 | 81 |
| EUS-FNA | 89 | 100 | 100 | 86 | 26 | 2,443 | 58 |
| EBUS-TBNA | 89 | 100 | 100 | 91 | 26 | 2,756 | 58 |
| EBUS-TBNA + EUS-FNA | 91 | 100 | 100 | 96 | 7 | 811 | 33 |

*, median data values, compiled from the most recent 3rd edition ACCP Guidelines for the Diagnosis and Management of Lung Cancer [Silvestri *et al.* (23)]. PPV, positive predictive value; NPV, negative predictive value; PET-CT, positron emission tomography-computed tomography; TBNA, transbronchial needle aspiration; EUS-FNA, endoscopic ultrasound guided fine needle aspiration; EBUS-TBNA, endobronchial ultrasound with transbronchial needle aspiration; ^, includes traditional mediastinoscopy and video-assisted mediastinoscopy.

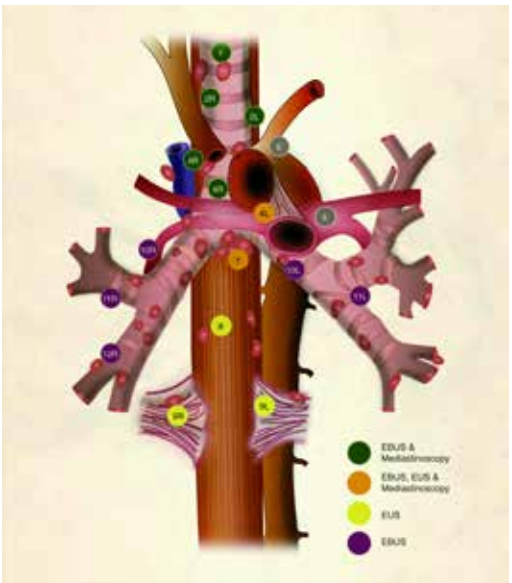


**Figure 1** Lymph node map adapted from the 2009 IASLC lung cancer staging project. The lymph node stations are color coded to indicate the minimally-invasive staging techniques that can readily access each lymph node station. The close proximity to vascular structures highlights the importance of direct visualization or ultrasound guidance to avoid bleeding complications. EBUS, endobronchial ultrasound; EUS, endoscopic ultrasound; IASLC, International Association for the Study of Lung Cancer.

### *Mediastinoscopy*

Mediastinoscopy is a surgical procedure that allows for the exploration of the superior mediastinum from the sternal notch to the subcarinal space and sometimes can reach the main bronchi (*Figure 1*). It is done under general anesthesia, with the neck maximally extended and through a 2-3 cm collar incision at the sternal notch carried out through the platysma. The strap muscles are separated to expose the trachea and after incising the pretracheal fascia, the pretracheal plane is developed. Finger dissection is initially used as caudally as possible while palpating key structures such as the innominate artery and the aortic arch. This space is then used to advance the video-mediastinoscope. This process is continued by using suction/coagulation device sweeps to advance caudally. Before carrying out biopsies, the surgeon identifies the innominate artery, aortic arch, pulmonary artery and the azygos vein. Occasionally, the appearance of a lymph node and a vascular structure are similar, and a fine needle is used to gently penetrate the structure and identify if there is blood flow or not (24).

In a similar fashion to EBUS or EUS, exploration of the lymph nodes starts on the contralateral side of the tumor to rule out N3 disease and then proceeds in a systematic way. The subcarinal lymph nodes are usually sampled last because bronchial artery and perinodal bleeding can be more difficult to control. It is important to mention that, by convention, the specificity and positive predictive values of cervical mediastinoscopy are considered 100%, as entire lymph nodes are excised for histologic evaluation. However, positive results are not confirmed by other tests. The median sensitivity of conventional mediastinoscopy is reported to be 78% with a median negative predictive value of 91% (23). Video-mediastinoscopy has a median

 

sensitivity of 89% with a negative predictive value of 92%. Although rare, complications occur in 3% of cases with serious bleeding in 0.4% occasionally requiring mediastinotomy (25,26). Mortality is under 0.5% (27,28).

There are two technical variations of mediastinoscopy intended for systematic removal of mediastinal lymph nodes: video-assisted mediastinoscopic lymphadenectomy (VAMLA) and transcervical extended mediastinal lymphadenectomy (TEMLA). These two procedures, also called "supermediastinoscopies", are not widely used but their exceptional operating characteristics warrant a comment. Both are done through an incision similar to the one used for mediastinoscopy but with systematic removal of the lymph nodes. In VAMLA, the removal of subcarinal and right inferior paratracheal lymph nodes en block followed by the left inferior paratracheal lymph nodes is done through a 2-blade spreadable mediastinoscope (29).

In TEMLA, a sternal retractor elevates the sternum allowing for complete mediastinal lymphadenectomy from the supraclavicular to the paraesophageal lymph nodes. A thoracoscope is also used to remove the subaortic and para-aortic lymph nodes (30).

Although both are rarely used, the sensitivity of VAMLA was close to 100%, while TEMLA has shown to be superior to mediastinoscopy and EBUS (31,32).

Interestingly, some experts and authors of the prior research studies, conclude that VAMLA and TEMLA have no current role in the routine mediastinal staging of lung cancer. In part due to their invasiveness and high risk of complications when compared to equally accurate but less invasive options including EBUS and EUS (33). Furthermore, VAMLA and TEMLA are not mentioned (23) or recommended only within clinical trials (34) in the most recent guidelines for staging of lung cancer.

### *Endobronchial ultrasound with transbronchial needle aspiration (EBUS-TBNA)*

Endoscopic techniques have emerged as the procedure of choice for diagnosis and staging of lung cancer (23). These techniques have also been associated with lower morbidity and mortality, and have been suggested to be more cost effective than mediastinoscopy (35,36). Complications are very rare, with the rate of pneumothorax between 0.07% and 0.2% (37). The procedure is usually done in the outpatient setting by pulmonologists, interventional pulmonologists, or thoracic surgeons in a procedure suite or in the operating room. Anesthesia largely depends on local practices, but may involve moderate sedation or general anesthesia. A dedicated flexible bronchoscope with an ultrasound (5, 7.5, 10 and 12 MHz) at the distal end is inserted through the mouth, an endotracheal tube, or a laryngeal mask and advanced to the distal trachea where apposition of the ultrasound probe to the airway wall reveals adjacent structures in high detail. After identifying the lymph node station based on anatomic landmarks, a 21 or 22 gauge needle is advanced under direct visualization on ultrasound.

Although there is no consensus on the number of times each lymph node is punctured (passes), in our experience, three passes with 15 needle excursions per pass provides diagnostic material in over 95% of cases (38). After each pass, the needle is withdrawn and a small amount of material can be either placed on a slide for immediate preparation or the entire sample can be placed in a preservative solution for cytologic analysis and cellblock preparation. As shown in *Figure 1*, EBUS can access the following stations: 2R and 2L (upper paratracheal), 4R and 4L (lower paratracheal), 7 (subcarinal), 10R and 10L (hilar), 11R and 11L (interlobar), on occasion 12R and 12L (lobar) as well as paratracheal and parabronchial masses that occur close to the airway. At least one case series that encompasses multiple institutions described access to station 5 (subaortic) through a transpulmonary artery route (39).

### *Endoscopic ultrasound guided fine needle aspiration (EUS-FNA)*

EUS is also a real-time ultrasound procedure guiding trans-esophageal needle aspiration. It allows posterior mediastinal sampling through the esophageal wall. The lymph nodes preferentially accessible to EUS are the inferior pulmonary ligament (level 9), paraesophageal (level 8), subcarinal (level 7), and left paratracheal (level 4L) (*Figure 1*). However, anterolateral paratracheal (levels 2R, 2L, and 4R) are difficult to sample with EUS. EUS also has a high safety profile, similar to EBUS (40,41). The main feature that sets apart EUS from other techniques is the access to locations outside of the mediastinum, such as the left lobe of the liver, a significant part of the right lobe of the liver, and the left adrenal gland (42). Given its relative strengths and weaknesses, it is best to think of EUS as a complement to EBUS for the diagnosis and staging of lung cancer patients. When used in combination, the yield is higher than with either technique used alone. Pooled analyses have shown sensitivity of 91% and specificity of 100% (23,43).

 

### *CT-guided biopsy*

Computed tomography provides details on the anatomic location, shape, margins, attenuation of the primary lesion as well as the extent of invasion of the chest wall, presence of suspicious mediastinal, hilar, segmental lymph nodes, and proximity to surrounding structures (44). However, this radiologic evaluation is not entirely specific and should not be used as the single source of staging. The median sensitivity and specificity of CT for identification of mediastinal lymph node involvement were 55% and 81% respectively (23). Other studies have shown similar low sensitivity when pooled in meta-analysis demonstrating sensitivity of 51-64% for NSCLC (45,46). Whenever CT guidance is used to obtain tissue by core needle biopsy or fine needle aspiration, the pooled sensitivity and specificity are 90% and 97% respectively (47). However, the complications include a 15% risk of pneumothorax and 1% risk of major hemorrhage (48). The risk factors for major complications during trans-thoracic needle aspiration include emphysema, small lesion, greater depth of needle penetration, and multiple needle passes. For these reasons, it is not common to use trans-thoracic needle aspiration to sample mediastinal lymph nodes.

In summary, the different minimally invasive techniques are designed to help clinicians identify lung cancer patients who are likely to benefit from primary resection, neo-adjuvant chemotherapy and/or radiation, or palliative chemotherapy. However, recent studies suggest that the strategic combination of staging techniques (such as EBUS, followed, when negative, by mediastinoscopy) provides better outcomes and may be more cost-effective (49). A study by Farjah and colleagues reported severe underuse of multimodality staging; with the use of multimodality staging increasing over time from 1998 to 2005 resulting in an association between use of multimodality staging and improved survival, irrespective of the stage of disease (50).

If only imaging studies are used for staging, 15-40% of patients will be denied curative intent therapy (51). For these reasons, radiologic images that are concerning for lung cancer or metastatic disease should be confirmed with cytology or histopathology. Inadequate lymph node evaluation is unfortunately common and its consequences are hard to estimate, but likely translates into reduced lung cancer survival if nodal disease is not identified and treated (52-54).

## Lymph node mapping

Regardless of how thoracic lymph nodes are sampled for staging purposes, it is important to use a common vocabulary when describing the location of these lymph node stations as well as to state what specific lymph node stations were sampled. The Japanese (Naruke) and US/European (Mountain and Dresler) lymph node maps were reconciled into a single universal map by the IASLC in 2009 (55). This provides a uniform, specific anatomic definition of the lymph node stations, and facilitates the identification of the exact location during surgery, radiologic interpretation and minimally-invasive biopsy techniques (see Rami-Porta *et al.* in this special issue). It is recommended that we abandon loose anatomic descriptions such as "lower paratracheal" or "parahilar" as these terms are not specific to a lymph node station and can easily be misinterpreted.

## Definitions for mediastinal lymph node evaluation

Using standard definitions for the thoroughness of mediastinal nodal staging is as important as using a uniform mediastinal lymph node map (56). The following categories have been used for surgical staging, but they can easily be extrapolated to minimally invasive techniques such as EBUS TBNA. The extent of lymph node assessment can be broadly categorized into the following groups (57):

(I) Random sampling: the sampling of lymph nodes by convenience or by preoperative or intraoperative findings. The most common situation is the sampling of a single enlarged lymph node. Unfortunately, this practice has been found to be very common in the mediastinoscopy literature (52).

(II) Systematic sampling: the sampling of predetermined lymph node stations, such as 2L, 4L, 7, and 10L for a left-sided lung tumor, and 2R, 4R, 7 and 10R for a right-sided tumor.

(III) Mediastinal lymph node dissection: the complete surgical removal of all identifiable mediastinal lymph node tissue based on anatomic landmarks.

(IV) Extended lymph node dissection: the removal of bilateral paratracheal and cervical lymph nodes by formal dissection.

(V) Lobe-specific systematic node dissection: the removal of ipsilateral mediastinal lymph node tissue based on the location of the tumor.

## Guidelines on tissue acquisition and processing for diagnosis, staging, and genotyping

The American College of Chest Physicians (ACCP) evidence-

 

based clinical practice guidelines, the European Society of Thoracic Surgeons (ESTS) guidelines, and Cancer Care Ontario (CCO) Program in Evidence-Based Care Practice Guidelines are in agreement on their recommendations for indications and techniques for invasive staging (23,34,58). It is important to emphasize that random sampling or sampling of a single enlarged lymph node is considered inadequate surgical staging. Some authors have extrapolated this to minimally invasive techniques and have advocated against random sampling (59). It is recommended that appropriate staging include stations 2R, 2L, 4R, 4L, and 7. However, TBNA of lymph nodes that are smaller than 5 mm is very difficult and likely will result in sub-optimal amount of tissue for diagnosis. Clinically suspicious lymph nodes, such as enlarged (≥1 cm short axis diameter) or FDG-avid nodes, should also be sampled. Guidelines, such as those published by ESTS, the United Kingdom's National Institute for Health and Care Excellence, and CCO, recommend that appropriate lymph node assessment should be systematic and include a minimum of three mediastinal lymph node stations, one of which should be station 7 (subcarinal) (34,58,60).

## Sample acquisition and processing differences: how does needle aspiration (cytology) differ from core biopsy (histology)?

It is important to have an appreciation for how small biopsies obtained by minimally invasive means are processed and evaluated by the pathologist/cytopathologist. In general, these small biopsies or cytology specimens must be sufficient to establish a diagnosis of malignancy, to make a reliable subclassification of disease (e.g., adenocarcinoma *vs.* squamous cell carcinoma) using immunochemical stains, and, increasingly, for molecular testing to identify targetable driver mutations. The amount of information to be gleaned from these small biopsies and cytologic specimens is great, and has increased dramatically over the past decade.

Minimally invasive biopsy specimens are small, with limited cellular material. Transbronchial/endobronchial biopsies and transthoracic core needle biopsies of lung lesions can provide some tissue architecture, helpful in delineating invasive carcinoma from in-situ/lepidic pattern of spread, though sampling limitations can be an issue for these specimens. Cytologic aspirates (EBUS-TBNA or EUS-FNA) oftentimes lack these architectural cues, though frequently larger tissue fragments that are almost biopsy-like can be aspirated and appreciated on direct smears or cell block preparations. Establishing a diagnosis of malignancy on cytologic specimens should rarely be a problem though, as the cytologic features of malignancy are generally easy to appreciate. In contrast to biopsy specimens, which are nearly always formalin-fixed and paraffin-embedded, cytologic specimens can be processed and evaluated in a number of ways, including by direct smears or touch-preparations of tissue biopsies (either air-dried or alcohol fixed), alcohol-fixed liquid based concentration methods (such as using cytospin, ThinPrep, or SurePath), as well as the creation of a tissue cell block. The latter captures the cellular material into a cell pellet that is formalin-fixed and paraffin-embedded, creating for all intents and purposes a tissue-biopsy-like specimen from which multiple serial slides can be cut from the paraffin block and used for immunohistochemical stains and molecular testing. In reality, the lines between small biopsy specimens and cytology specimens (especially with the creation of a good cell block) have become blurred, with both types of specimens capable of providing specific histopathologic diagnoses and serving as substrates for molecular testing.

In order to preserve cellular material for downstream molecular testing, the 2015 iteration of the WHO classification of lung tumors (61) and the 2011 IASLC/ATS/ERS classification of lung carcinomas on small biopsy/cytology specimens (62) recommends that a focused panel of immunostains be employed for the work-up of a suspected primary NSCLC when histology or cytomorphology alone is insufficient to distinguish adenocarcinoma from squamous cell carcinoma. Specifically, one lung adenocarcinoma marker (traditionally the transcription factor TTF-1) and one squamous cell marker (usually p63 or more recently p40—the N-terminal truncation isoform of p63 shown to be more specific for squamous cell carcinoma) (63). If these results are inconclusive, then second line lung adenocarcinoma markers (such as the aspartic proteinase Napsin-A) and squamous cell carcinoma markers (cytokeratin 5/6) can be employed. A mucicarmine histochemical stain can also be helpful to demonstrate glandular differentiation. Clinical and radiologic correlation are always helpful, to focus the immunohistochemical work-up of carcinoma metastatic to the lungs, especially when more lung-specific markers are negative.

## Genotyping: yield of different techniques

The most current guidelines from the CAP, IASLC, and AMP call for testing all advanced stage lung

 

adenocarcinomas (or mixed tumors with an adenocarcinoma component) for EGFR mutations, generally by PCR-based methods, and ALK gene rearrangements (via FISH assay or with screening immunohistochemistry) (20). Lung cancers are also commonly tested for KRAS mutations which are associated with resistance to tyrosine kinase inhibitors. In addition to these three main molecular targets, the list of less common driver mutations (*Table 1*) in lung adenocarcinoma is growing rapidly. With the growing number of actionable targets for lung cancer, relying on the current paradigm of one-off testing using these small biopsy or cytology specimens will inevitably deplete the cellular material despite the cytopathologist's best efforts to maximize cell block cellularity and minimize material loss during the initial diagnostic work-up. Therefore, a shift towards multiplexed panels seems inevitable in the future (21).

Many groups have published very good molecular testing success rates using small biopsy and cytology specimens. In general, the success rates for small biopsy specimens (including transthoracic core needle biopsies or transbronchial biopsies) are comparable to those for cytology cell block specimens. Recent studies comparing these modalities report a molecular testing success rate for small biopsy specimens of 55-100%, and a success rate for FNA or EBUS-TBNA cell block specimens of 46-95%, depending on the study parameters (64-67). In general, there is a higher molecular testing failure rate from small biopsy or cytology specimens as compared to larger surgical resection specimens, inferred from the limiting tumor cellularity present in the former (68).

A recent publication from the Lung Cancer Mutation Consortium, a multi-institutional program investigating selected oncogene drivers in lung adenocarcinoma, revealed that in an 8-gene panel testing approach, 35% of cytology specimens and 26% of small biopsies were insufficient for molecular testing (compared to only 5% of surgical resection specimens). Importantly however, the authors comment that once a specimen was deemed adequate for molecular testing (i.e., has sufficient tumor cellularity), the specimen type (cytology/small biopsy/surgical resection) had no influence on subsequent molecular testing performance and (69) that minor differences between completion rates were not felt to be clinically significant. Therefore, cytology and small biopsy specimens have been proven to be excellent substrates for molecular testing, as long as enough tumor cells are obtained and the preceding pathologic work-up is efficient and minimizes tumor cell loss.

## Advanced bronchoscopy techniques in non-academic settings

EBUS-TBNA has become increasingly commonplace outside of academic medical centers. However, appropriate training for thorough and systematic mediastinal staging is still lagging (59). Electromagnetic navigation bronchoscopy (ENB), and other advanced diagnostic techniques have also become increasingly commonplace in the community setting. Each of these procedures has an associated learning curve, requiring the development of a systematic approach to proper procedural techniques for biopsies and tissue handling. Increasing interest has led to implementation of training in advanced bronchoscopy techniques in pulmonary/critical care fellowships, as well as dedicated interventional pulmonary fellowships.

For physicians who did not have exposure to these techniques during their formal training, the training options include taking a sabbatical year, participating in an intense 1-7 day course, or direct proctoring by experienced colleagues. Current ACCP guidelines for procedural training are based on minimum number of procedures and not necessarily on the cognitive and technical skills required (70). In the United States, the need for the procedures at community and regional hospitals has led to the implementation of bronchoscopy services, including EBUS, or the creation of referral channels to tertiary care centers (71). Ultimately, the success of community programs depends on adequate investment of human and technological capital, ideally within multidisciplinary teams of pulmonologists, thoracic surgeons, radiologists, cytopathologists, radiation oncologists, and medical oncologists, who should collaborate to apply evidence-based guidelines while continuously evaluating their performance using mutually accepted yield and quality metrics.

A number of authors have advocated the utility of rapid onsite examination (ROSE) for the evaluation of EBUS samples. Although immediate feedback for the bronchoscopist as well as appropriate specimen collection and triage can be helpful in certain circumstances, the current guidelines from the World Association for Bronchology and Interventional Pulmonology state that use of ROSE is not recommended for every case if the operator is experienced (72), and certainly should not limit the implementation of a much needed service for lung cancer patients. In this setting, EBUS-TBNA samples for driver oncogene mutation analysis have been successful in close to 95% of the cases, even with use of a commercial laboratory

 

and no sample enrichment (64). Appropriate tissue handling and preparation with methanol based fixatives and paraffin-embedded cell blocks have been used successfully by our group and others (68,73).

## Conclusions

The diagnosis and treatment of lung cancer has undergone multiple dramatic changes in the last decade. We have a better understanding of the molecular biology of lung cancer and driver mutations that can be targeted through the use of specific tyrosine-kinase inhibitors. Significant technological advances allow interventional pulmonologists and surgeons to obtain diagnostic material in a safe and minimally invasive manner. Ongoing refinements in diagnostic and ancillary molecular testing by pathologists and cytopathologists has allowed small biopsy and cytology specimens to be used to accurately diagnose and characterize lung cancer, helping direct appropriate therapeutic decisions. Moving forward, a pressing task for the health care community at large will be to narrow existing practice gaps between high-performing (often academic) and lower performing (often community-based) care delivery settings.

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Interventional Diagnostic Technique

# Ideal conditions to perform EBUS-TBNA

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**Abstract:** EBUS-TBNA is gaining widespread acceptance as a minimally invasive procedure for mediastinal staging and re-staging of lung cancer, diagnosis of lung tumors adjacent to large airways and characterization of both malignant and benign lymphadenopathy. The aim of this article is to describe the appropriate setting and practical aspects of the procedure that may help at the start of a new EBUS-TBNA program to improve patient safety, comfort and procedural yield according to operator experience, procedure aim, and institutional needs.

**Keywords:** EBUS-TBNA; endoscopy room; anaesthetic management; mediastinal biopsy

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## Introduction

American cancer guidelines have embraced EBUS-TBNA in the diagnosis and staging of lung cancer and recommended it as the initial step in mediastinal staging, over mediastinoscopy (1). However, facilities that can already offer the procedure to their patients are still a minority even in developed countries such as the USA and the UK.

As more pulmonologists and thoracic surgeons are adopting EBUS in their standard clinical practice, there is a pressing need to understand the factors that enhance the performance and yield of EBUS-TBNA.

This chapter is intended to provide the basic notions and practical suggestions to start an EBUS program in the most appropriate setting based on local availability of resources, case mix and expertise.

## Personnel requirements, patient preparation and monitoring

The procedure is normally organized on an outpatient basis, with discharge after adequate recovery.

EBUS-TBNA may be performed by a Thoracic Surgeon or by an Interventional Pulmonologist who has received adequate training in this procedure.

As for flexible bronchoscopy, an intravenous catheter and standard American Society of Anaesthesiologists monitors are recommended, and continuous monitoring of the patient's vital signs and parameters (HR, BP, $O_2$ saturation) is mandatory. An oxygen delivery system, either via a mask with reservoir, a venti-mask or nasal-mask is also mandatory.

Emergency equipment with a defibrillator should be available, and the personnel (physician and nurses) must be adequately trained in its use.

The patient lies in a supine position, and the operator stands at the patient's head, assisted by one nurse.

The EBUS instrument and related devices (light source, processor, conventional monitor (all in one column) and the ultrasound monitor may be placed either on the left or on the right of the patient. In the beginning of the EBUS era, visual and ultrasound monitors were independent. Nowadays, integrated systems are available, allowing the bronchial direct vision and the ultrasound images to be displayed on one screen simultaneously thus saving room space and facilitating the operator's manoeuvres.

Two nurses should be preferably present in the room during the procedure EBUS-TBNA: one nurse will administer topical 2% Lidocaine, prepare the scope and the needle, and assist in their use, and prepare slides for the cytologist and formalin containers for the specimens.

The other nurse will take care of drug infusion during

 

mild sedation (normally benzodiazepines), monitor the patient's vital parameters and control $O_2$ delivery. When an Anaesthesiologist is present, the nurse assists him/her in the management of the patient.

If on-site pathology is available and adequate confirmation is required, a delivery man should also be available for slide transport.

At the end of the procedure, an adequate and thorough check of the tracheobronchial tree is mandatory before removing the bronchoscope from the airways, in order to remove clots and/or secretions, and control possible sites of bleeding.

The patient should be continuously monitored for at least one hour after the procedure (HR, BP, $O_2$ saturation). Oxygen delivering should be maintained, and pain medication should be administered (generally for pharingodinia). Dyspnoea must be evaluated accurately to exclude pneumothorax, asthma, or airway bleeding.

If the patient underwent the procedure under mild sedation only he/she could be discharged after approximately one hour.

If deep sedation (DS) was used, the patient should be controlled for at least 2 hours (in a recovery room or in the department).

## Anaesthetic considerations

When EBUS-TBNA was introduced 10 years ago, it was typically performed using general anaesthesia (GA).

Anaesthetic management is important during EBUS-TBNA for a number of reasons:

First, the ultrasonic bronchoscope has a thicker structure than standard fiber-optic bronchoscopes, intense mucosal contact is necessary to obtain ultrasonic images, and the procedure time is generally long enough to cause considerable patient discomfort.

Second, there is an absolute need to prevent reflex coughing and laryngospasm during the procedure, as coughing and movement of the mediastinum will cause difficulties in obtaining an adequate view of the target lymph nodes or lesion, hamper accurate insertion of the needle and increase the risk of injury to mediastinal major vessels.

Topical anaesthesia with lidocaine 2% is mandatory to suppress the cough reflex, especially with mild sedation or in GA when muscle blockade agents are not used.

GA is defined as drug-induced loss of consciousness during which patients are not arousable, even by painful stimulation, they cannot maintain spontaneous ventilation, and they require an artificial airway.

Total intra-venous anaesthesia (TIVA) provides optimal conditions for EBUS TBNA and it is preferred over volatile anaesthetics, because frequent suctioning of the airway by the bronchoscopist results in contamination of the room atmosphere by volatile anaesthetics and in an inconsistent delivery of volatile anaesthetic gas to the patient.

Combinations of propofol, remifentanil, etomidate, ketamine in a standard fashion are commonly used. Curarisation is infrequently needed.

In such cases, the airway can be secured by a laryngeal mask airway (LMA) or endotracheal tube (ETT, minimum size 8).

Considering the large size of the ultrasonic bronchoscope, a #4 or #5 LMA seems to be the most suitable device to secure the airway and provide adequate ventilation around the bronchoscope. Another advantage of the LMA is that it allows access to higher mediastinal lymph node stations that would otherwise be obscured by the ETT. It may not be appropriate in severe obesity or untreated gastroesophageal reflux (2).

In case of endotracheal intubation, the tube has to be withdrawn to explore higher mediastinal nodes; another disadvantage is that the scope is directed in a central position by the tube and it may be more difficult to get close to the tracheal wall with the tip of the scope and obtain adequate ultrasonographic imaging.

In the only prospective randomized controlled trial of EBUS-TBNA performed under general anesthesia (total intravenous anesthesia with laryngeal mask) *vs.* moderate sedation (topic anesthesia with lidocaine plus a combination of midazolam and fentanyl) diagnostic yield, complication rates and patient tolerance were comparable (3). However, 5 patients in the moderate sedation group (6.7%) did not tolerate the procedure even at the maximal pre-established doses of sedatives, and ultimately required GA.

Nowadays, lack of uniform access to GA in the majority of clinical practice settings and cost issues favour the use of mild or moderate sedation in an advanced Endoscopic room, with or without an anaesthesiologist on site.

Mild sedation (MS), defined by the American Society of Anaesthesiologists as a drug-induced depression of consciousness during which patients respond purposefully to verbal commands or light tactile stimuli with no interventions required to maintain a patent airway or ventilation, can be achieved in several ways, but generally by using a mix of short acting benzodiazepines and opiates.

DS is defined as a drug-induced depression of consciousness

 

during which patients cannot be easily aroused but respond to repeated or painful stimulation, with potential impairment of independent ventilation and potential need for an artificial airway.

In a recent retrospective study by Öztaş and colleagues (4), 152 patients underwent EBUS-TBNA under DS (intravenous midazolam + propofol) administered by an anesthesiologist and 122 patients received just midazolam administered by the endoscopist. The diagnostic yield was not statistically different in the two groups, no major complications were observed in either group and minor complications were similar.

The endoscopist performing the procedure on patients in the second group was highly skilled in the procedure. No data are given about patient or operator satisfaction.

Jeyabalan (5) investigated patient satisfaction with EBUS-TBNA under light conscious sedation (topical lidocaine plus lidocaine and intravenous midazolam and fentanyl) without anaesthetic assistance in a cohort of 82 patients. Sensitivity and negative predictive value for staging and diagnosis in suspected malignancy were 90–80% and 94.1–88.9% and 87.5% and 50% in suspected granulomatous disease. All but 9 patients (87%) stated that they would definitely/probably undergo a repeat EBUS-TBNA.

In a retrospective study (6), Yarmus and colleagues compared 163 procedures performed under DS (continuous iv. propofol with LM or ETT) with 146 performed under moderate sedation (boluses of fentanyl and midazolam). The diagnostic yield was higher in the DS group with shorter procedure time and a higher number of nodes sampled, however firm conclusions cannot be drawn as the procedures were carried out in two different institutions by different operators and pathologists, and the follow-up of negative cases was incomplete.

In another study by Ost and colleagues (7), DS and general anesthesia were associated with more lymph nodes sampled per patient, but this was not associated with higher EBUS-TBNA diagnostic yield.

Anesthesia techniques do not seem to affect the frequency of complications with EBUS-TBNA (8), therefore no evidence exists to strongly recommend one anesthetic method over another as regards diagnostic yield and procedural safety.

The choice is ultimately made according to operator experience, educational needs, procedure planning (full mediastinal staging *vs*. one station diagnosis; tissue sampling for benign *vs*. malignant disease) and institutional standards (9).

## Ideal environment: endoscopy room vs. operating room (OR)

The operating room or theatre provides a fully equipped and protected environment, and specialised staff to assist the patient and the operator during the procedure, including an anaesthesiologist, and advanced anaesthesia and life-support instrumentation.

However, these potential advantages must be weighed against local availability of resources (operating theatre time and personnel) and cost issues.

Mainly, the OR setting allows the endoscopic procedure to be immediately followed by a mediastinoscopy if EBUS – TBNA does not provide a firm diagnosis.

This is more likely at the beginning of the learning curve if the target lesion or lymph nodes are relatively small or rest in a more difficult location (4L).

EBUS-TBNA has a relatively low sensitivity of 57–90% (10) for lymphoma, and a diagnostic yield of 54% to 93% for sarcoidosis (11). In such cases, surgical biopsy is more often necessary for diagnostic confirmation.

EBUS-TBNA can provide adequate material for mutation analysis in cancer patients who are potential candidates for biological agents therapy in roughly 90% of the patients *vs*. close to 100 % with mediastinoscopy (12).

There is thus a potential benefit of performing EBUS-TBNA in the OR for such patients, especially those coming from far away, to avoid readmission after several days or weeks in case of a non-diagnostic result.

In the experience of the Swedish Cancer Institute in Seattle, roughly 50% of the EBUS-TBNA procedures have been carried out in the operating theatre (unpublished data, courtesy of Dr. Jed Gorden). In the University Hospitals of Verona, currently EBUS TBNA is routinely carried out in the operating theatre and 14% EBUS-TBNA procedures have been followed by immediate mediastinoscopy due to inadequate specimens.

In conclusion, the endoscopic room could be appropriate in most cases to carry out EBUS-TBNA and allows significant cost savings without jeopardising patient safety and diagnostic yield.

The operating theatre appears to be the ideal setting both for patient and operator comfort and safety, and to ensure the maximum diagnostic yield in the following cases:

(I) The endoscopy room is not adequately equipped for a safe procedure;

(II) An anaesthesiologist is not available in the endoscopy suite and DS is deemed necessary;

 

(III) There is a high probability that EBUS-TBNA would be inadequate or non-diagnostic;
(IV) Procedural time, individual expertise and financial considerations may all influence the final choice of the appropriate setting in such individual cases.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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Interventional Diagnostic Technique

# Is bronchodilator the correct treatment for COPD subjects before EBUS?

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**Abstract:** Endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA) is a reliable and commonly established technique, enabling real-time guidance of transbronchial needle aspiration of mediastinal and hilar structures and parabronchial lung masses. As EBUS-TBNA has become more available and adopted by clinicians, questions have emerged about the optimal performance of the procedure. Although EBUS is considered safe, there are few complications that could occur during the test, correlated with both the procedure itself and the patient's characteristics. Moreover, this technique is often addressed to patients with overlapping airways diseases, which might have higher risk of complications during the procedure. Chronic obstructive pulmonary disease (COPD) patients could experience EBUS-TBNA with a relatively high frequency due to their risk of developing lung cancer. The irreversible bronchial constriction characteristic of the disease raises some questions on premedication before bronchoscopic procedures. It is mandatory to optimize every aspect of the procedure in order to minimize the risk of complications, especially for fragile patients. Whether the use of inhaled bronchodilators before the procedure could improve the outcome of the procedure in COPD patients is reviewed in this article. No clear indication emerged from the literature suggesting the need of more studies in order to clarify this point.

**Keywords:** β2-agonist; anticholinergic drugs; bronchoscopy; endobronchial; pre-medication

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Endobronchial ultrasound-guided transbronchial fine needle aspiration (EBUS-TBNA) is a relatively novel, minimally invasive methodology to sample peribronchial masses with real-time guidance (1,2), widely used all over the world. The most common indications for EBUS are the staging of the mediastinum for suspected non-small cell lung cancer and the diagnosis of unexplained mediastinal lymphadenopathy. Usually EBUS is well tolerated, with very few major contraindications; guidelines suggest that patients who experienced myocardial infarction should wait 6 weeks before the procedure, which is however contraindicated when myocardial ischemia, arrhythmias, severe hypoxemia at rest, coagulation or platelet function disorders are present (1).

EBUS-TBNA is less available and more expensive than rigid bronchoscopy (RB) which remains the best choice for extraction of airway foreign bodies, when a flexible scope is not suited or in case of large biopsies. However, the diagnostic power of RB in terms of lung cancer staging or evaluation of peripheral pulmonary lesions is lower compared to EBUS-TBNA (3) in the general population and speculatively in COPD patients.

EBUS is generally considered safe (1,4), however, whether performed with anaesthesia or only light sedation, pre-procedural medications are routinely administered and may have side effects. Diagnostic sampling may lead to immediate, although rare, complications, such as intrabronchial bleeding, bronchospasm, hypoxemia, hemodynamic variations and pneumothorax (1,5,6).

We know from the literature that significant fall in Forced Expiratory Volume in 1 second ($FEV_1$), and forced vital capacity (FVC) occurs after endoscopic procedure, during both routine bronchoscopy and procedures, which include bronchoalveolar lavage (BAL) and biopsy (6). This impairment of the lung function reflects the gas exchange efficiency, with a reduction of the $PaO_2$ (7). These events were found in the entire population, both healthy and patients suffering from chronic respiratory disease. Severity of asthma, baseline $FEV_1$ or initial $PaO_2$ did not predict the degree of hypoxemia or the fall of $FEV_1$. It is intuitive that these effects are greater in people affected by respiratory airways disease and correlated with the duration of the procedure (7).

Similar data were also found in the pediatric population showing alveolar hypoventilation during flexible bronchoscopy particularly in cases requiring large amounts of sedation and in patients susceptible to complications from respiratory acidosis (8).

Patients with chronic obstructive pulmonary disease (COPD) can experience flexible bronchoscopy for different reasons. Cigarette smoking, recognized as the major cause of COPD, is also a major risk factor for malignancy, therefore patients with COPD have a higher incidence of carcinoma of the lung, and endoscopic evaluations can lead to earlier diagnosis. However, the authors did not report indication to cope with COPD patients who have low $FEV_1$ and no limit is reported.

Historically, the attention on pre-medication for patients undergoing bronchoscopy was focused on asthmatic patients, because of higher grade of bronchial hyperresponsiveness (BHR). Different kinds of bronchodilator agents were tested, such as a combination of β2-short acting and anticholinergic drugs, administered either topically and systemically (8-11). Therefore, the administration of nebulized bronchodilators has been requested before flexible bronchoscopy in asthmatic patients (12). While some indications are given for asthma, there are no clear results supporting the utility of giving bronchodilators before bronchoscopy in COPD patients. No mention about pre-medication with bronchodilators can be found both in the British Thoracic Society guidelines on diagnostic flexible bronchoscopy (12) and in CHEST guideline for EBUS-TBNA (1).

Bronchoscopic procedures are considered rather safe in COPD patients compared to asthmatics with high BHR. There are only few studies that investigate the preoperative use of bronchodilators on COPD population and not conclusive.

A recent study by Georgiou and colleagues showed that, among a cohort of 92 patients with advanced COPD undergoing EBUS for the evaluation of peripheral pulmonary lesion, 10.6% of them experienced acute respiratory failure (13).

Hattotuwa *et al.* performed endobronchial biopsy and BAL in patients with mild, moderate and severe COPD with 44.5% as mean $FEV_1$, without exacerbation of disease and with suspension of inhaled corticosteroids (ICS) for at least 8 week before the bioptic procedure. Symptoms were treated with salbutamol and/or ipratropium bromide; 2.5 mg of salbutamol were administered to all subjects with the exception of patients with mild disease. Prolonged coughing and transient decreases of oxygen saturations (lowest 88%) occurred in the enrolled patients during BAL, treated successfully with supplemental oxygen. Low incidence of adverse events needing hospital treatment (2%) and low incidence of hemoptysis which resolved spontaneously (3%), were reported in the study, concluding that fiberoptic bronchoscopy, endobronchial biopsies, and BAL can be carried out in selected patients with COPD with a low incidence of adverse events (14).

Stolz and colleagues presented the results of a randomized, double-blind, placebo-controlled trial to evaluate the protective effect of salbutamol in COPD patients who experienced bronchoscopy, and they found that the decrease in $FEV_1$ was similar in salbutamol and placebo arms (15). In this study, the combination of an opiate with a benzodiazepine used for sedation did not cause excessive oxygen desaturation, suggesting that this drug combination could be a reliable choice to sedate these subjects. Furthermore, salbutamol added prior the procedure, represented, in a subgroup of patients, an addition to the maximum combination therapy of two bronchodilators, one long-acting β2 agonist plus one anticholinergic drug, and/or ICS.

No evaluations can be drawn on the protective effect of ICS in reducing bronchial hyperreactivity in these patients before bronchoscopy. Another study, by Inoue and colleagues, investigated the effect of two anticholinergic agents, intramuscular atropine and inhaled ipratropium bromide, on bronchoconstriction in 29 patients who

 

were undergoing diagnostic bronchoscopy. In both the placebo and the atropine group, the lidocaine used as local anaesthesia produced a significant fall of $FEV_1$ and peak expiratory flow rate (PEFR), whereas in the subjects treated with ipratropium bromide, no significant $FEV_1$ and PEFR fall was reported after local anaesthesia. Moreover, the bronchoscopic procedure determined significant decreases in $FEV_1$ and PEFR, but with lesser variations than those reported in the placebo and atropine treated patients, suggesting that an inhaled anticholinergic drug, unlike atropine, might protect patients towards excessive bronchoconstriction during bronchoscopy (16).

In this uncertain scenario, the proper management of COPD patient seems to be the only clear cornerstone.

As showed above, the impairment of lung function and respiratory gas exchange is expected during endoscopic procedures, both routine bronchoscopy and EBUS. There is no clear evidence regarding the utility of short-acting bronchodilators in COPD patients' prior bronchoscopy. It becomes even more important to optimize the maintenance therapy of these subjects, in order to prevent, as much as possible, the drop of lung function parameters and, consequently, the risk of hypoxemia. This concept might be fundamental in COPD with high BHR, who might have more side effects during procedures (17). BHR can cause increase in cough and dyspnea and more severe BHR in COPD is associated with a higher degree of airway obstruction as reflected by lower $FEV_1$ and $FEV_1$/FVC values (18).

In the past years, some studies provided evidence that the decline in post-bronchodilator $FEV_1$ can be reduced by long-term ICS treatment (19-21). Another study showed a deterioration of $FEV_1$, after steroid withdrawal in COPD population (22). In this subset of patients, long-term ICS treatment should be recommended in order to reduce BHR before EBUS procedure.

The proper long-acting bronchodilator must be chosen considering symptoms and exacerbation risk of the patient (23). We know from literature that COPD bronchodilator responsiveness is a continuous variable and classifying patients as "responders" and "non-responders" can be misleading because it changes over time (24). Recently, some studies were conducted trying to evaluate if individual's reversibility could predict the future response to a combination of bronchodilators (25,26). Both short-acting and long-acting medications were tested. These studies showed that the overall extent of clinical benefit obtained with an association of two bronchodilators is related to the response to the single compound. Post-hoc pooled analyses of the same data by Donohue and colleagues showed that the benefits of dual long-acting bronchodilators (umeclidinium/vilanterol) versus single drug were more than additive in subjects who did not respond to both umeclidinium and vilanterol, and additive in responders to only one bronchodilator.

In contrast, umeclidinium/vilanterol had a lower than additive effect in dual responders (26). These results could be the basis for future studies on bronchodilation before EBUS in COPD patients.

The goal should be reaching the highest lung performance that a patient could achieve in order to minimize any possible risk of bronchospasm or lung function impairment during the invasive procedure.

In conclusion, the use of bronchodilators in COPD subjects before EBUS is recommended in order to reduce or minimize the bronchoconstriction due to this procedure, but the type of bronchodilator to be used needs to be more investigated.

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## Footnote

*Conflicts of Interest*: The authors have no conflicts of interest to declare.

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# Conventional transbronchial needle aspiration in community practice

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**Abstract:** Conventional transbronchial needle aspiration (C-TBNA) provides an opportunity to diagnose mediastinal lesions and stage bronchogenic carcinoma in a minimally invasive fashion. The procedure is easy to learn and requires zero upfront cost. Any community pulmonologist can acquire and maintain the skills of C-TBNA without undergoing formal interventional pulmonary fellowship training. Besides being used for the diagnosis and staging of lung cancer, C-TBNA can be used in patients suspected to have benign conditions such as sarcoidosis and tuberculosis. It also contributes in improving the diagnostic yield of flexible bronchoscopy while dealing with endobronchial, submucosal, peribronchial, or peripheral lesions. C-TBNA may be the only diagnostic modality that can be performed in patients in whom mediastinoscopy is contraindicated due to a bleeding diathesis. The procedure is safe and has great potential to augment the welfare of patients with pulmonary ailments. The learning curve of the procedure is short and steep. Every community pulmonologist should be able to perform C-TBNA.

**Keywords:** Transbronchial needle aspiration (TBNA); community practice; diagnostic bronchoscopy

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## Introduction

Transbronchial needle aspiration (TBNA) of the mediastinal lymph nodes was first ever performed by Eduardo Schipetti in 1949; the procedure was indeed performed using rigid instruments. In 1981, Wang *et al.* reported its application via flexible bronchoscope commencing a new era in the field of bronchology (1-6). Since then, the utility of TBNA has extended beyond the mediastinal lymphadenopathy and includes endobronchial as well as peripheral lung lesions and sub-mucosal as well as peribronchial processes (7-14).

The procedure of TBNA can be performed using either the anatomical information provided by the roentgenographic studies or an ultrasonic guidance. The former method is referred as conventional TBNA (C-TBNA) while the latter as endobronchial ultrasound guided TBNA (EBUS-TBNA). A linear probe ultrasound is commonly used to perform the TBNA in a real time fashion. Since the introduction of the EBUS-TBNA in 2003 (15), the role of C-TBNA has been under scrutiny. EBUS-TBNA certainly provides higher diagnostic yield, especially while dealing with the smaller lymph nodes located in the difficult locations such left paratracheal area, yet the procedure has its own limitation. Monetary resources and opportunities to acquire skills at this technique are almost non-existent in the developing world (16). In this context, C-TBNA continues to play a major role in improving the diagnostic yield of flexible bronchoscopy (FB). The procedure is easy to learn and requires zero upfront cost. Any community pulmonologist can acquire and maintain the skills of C-TBNA without undergoing formal interventional pulmonary fellowship training. The following chapter deals with the role of C-TBNA in a community practice.

## Acquiring skills of C-TBNA

In my personal opinion and experience, it is very easy to acquire skills of C-TBNA (17). To begin with, however, every pulmonary fellowship training should offer training

in C-TBNA. However, if one has missed this opportunity there are several avenues to explore. One can be introduced to C-TBNA at any of the hands-on courses being offered throughout the year at various national and international meetings. One can gather preliminary knowledge related to the indications, anatomical landmarks, role of roentgenography, the instrument, the technique, avoidance of the false positive results, handling of the specimen, required team work and complications of the procedure. Such courses also offer practicing C-TBNA on inanimate objects or even animal models.

Selection of the training program depends upon its reputation, faculty and hours of hands-on sessions. Courses with limited number of attendees allow more opportunity for the one on one discussion with the faculty. Use of animal objects also provides feeling close to performing a real procedure. Some programs also provide training on human cadavers. Live demonstrations are also very useful although such practices are becoming infrequent. Reading material and literature provided at such courses is extremely useful as the pulmonologist starts embarking on the procedure. Several manufacturing companies provide digital videos on C-TBNA which are very useful in studying minor details related to the procedure. Visiting a center of excellence where large number of such procedures are performed might add to the confidence of performing the first procedure. There are certain bronchoscopy centers around the world which may allow real hands on experience to qualified individuals at a cost. If there is a possibility of a preceptor ship from a senior or more experienced colleague in one's own institution that could be an invaluable resource.

In other words, C-TBNA can be learned "by the books"; post-graduate courses, workshops or hands-on courses (17). Even in the era of endobronchial and the esophageal ultrasounds (EUS), acquiring skills to perform C-TBNA is essential.

## Setting up the C-TBNA program

Before commencing the C-TBNA program, there are several steps that are crucial. It is mandatory to identify a trained bronchoscopy assistant for the program. He/she should be a fully cognizant of the entire bronchoscopy procedure, cleaning, disinfection and storage of the bronchoscope, types of the needles, specimen preparation and processing. It was very well said by someone that when it comes to bronchoscopy, "you are only as good as your assistant".

Before sending any specimen to the laboratory, a formal meeting with the cytopathologist is essential. This dialogue should include establishing type of preservative to be used, smear techniques, special solutions required for bacterial cultures and lymphoma studies. If there is a possibility, rapid on-site cytological examination (ROSE), that should be certainly explored.

Close collaboration with the thoracic surgeon as well as the radiologist is essential for the success of the program. This would help identify patients who would be best benefitted by the C-TBNA and reduce the need for invasive procedures including cervical mediastinoscopy. It is essential to have a computed tomography (CT) of the chest prior to all elective bronchoscopy procedures. Routinely reviewing the CT scan of the chest of every individual undergoing the procedure with the radiologist, for the accurate location of the lymphnode certainly facilitates the procedure. Such discussions help create a mental image of the aspiration site before entering the bronchoscopy suite.

In these eras of multidisciplinary approach, routine tumor board meetings to discuss the outcomes of individual patients shall increase the academic value of the program.

## Rapid on-site evaluation (ROSE) in community practice of TBNA

ROSE of transbronchial aspirates by a cytopathologist present in the bronchoscopy suit reduces the incidence of inadequate specimens and improves C-TBNA yield in observational studies (18,19). There are several plausible reasons why ROSE can improve the yield of TBNA. Firstly, negative or uncertain findings on ROSE can be addressed immediately with repeated aspirations of the same site with a slightly modified technique. This feedback-guided strategy leads to a variable number of aspirates and is indisputably better than sampling an arbitrary number of aspirates of uncertain quality (19). Secondly, the often minute TBNA samples are handled and processed in the best possible way with ROSE, which is an often overlooked but important factor for good TBNA yield (20). Thirdly, the availability of ROSE leads to a more frequent use of C-TBNA and hence practical expertise, which is likely to improve the performance of both bronchoscopists and cytopathologists (21). Furthermore, ROSE encourages the use of TBNA not only for formal staging but also for submucosal, exophytic and peripheral lesions, which are known to have a good yield with C-TBNA (10). ROSE provides the opportunity to stop sampling when the diagnostic objective has been met.

 

**Table 1** Indications for conventional transbronchial needle aspiration

| |
|---|
| Mediastinal and/or hilar lymphadenopathy |
| Staging of lung cancer or suspect of lung cancer: mainly to prove unresectability |
| Sarcoidosis, lymphoma, PTLD |
| Extrinsic compression of the airway by a peribronchial lesion or a lymphadenopathy |
| Submucosal disease |
| Peripheral nodules or masses: negative bronchus sign (Tsuboi type IV) |
| Endobronchial tumors (necrotic or hemorrhagic tumors) |
| Diagnosis/drainage of mediastinal cysts or abscesses |

PTLD, post transplant lymphoproliferative disorder.

Although some trials showed an increase of diagnostic yield ranging from 25% to 46% when ROSE was used along with C-TBNA (18,20), a randomized trial showed no significant difference between the TBNA group and the ROSE group in terms of diagnostic yield (22). It has been shown that the reduced number of samples sent for pathology and microbiology tests as well as the reduced use of consumables that was possible in the ROSE group likely helped abate the costs of bronchoscopy and compensate for the costs of the cytopathology service (23,24).

It is indeed challenging to carry out ROSE in the community practice as expertise of an expert cytopathologist may not be readily available. However such limitation can be overcome by pulmonologist training him/herself in the interpretation of the cytology specimen. In an elegant study by Bonifazi *et al.*, a good concordance was found between the cytopathologist and an adequately trained pulmonologist while dealing with specimens positive with malignant cells (25,26).

## Indications

C-TBNA provides tissue specimen for either cytologic or a histological examination from beyond the confines of the endobronchial tree. The size of the specimen thus obtained depends upon the gauge of the needle used, 19 *vs.* 22 G.

The indications for TBNA are summarized in the table (*Table 1*). The most common application of TBNA is the diagnosis of mediastinal lymphadenopathy especially in patients suspected to have bronchogenic carcinoma. Conditions such as sarcoidosis, tuberculosis, lymphoma, and post-transplant lymphoproliferative disorders (PTLD) (27) presenting in a similar fashion, can also be diagnosed using C-TBNA. In such cases, the procedure is performed in an elective fashion once the abnormality is detected on the CT scan of the chest. On the other hand, C-TBNA can also be used to sample submucosal as well as peribronchial disease often encountered as an incidental finding during bronchoscopy being performed for other indications. C-TBNA has also been found useful in the diagnosis of peripheral lung lesion especially for those with a negative bronchus sign, often referred as Tsuboi type IV lesion (*Figure 1*). Occasionally C-TBNA is also performed to sample exophytic lesion when excessive bleeding is feared with endobronchial biopsy (EBBx). In experts' opinion C-TBNA produces much less bleeding than EBBx while dealing with highly vascular lesions. Incidentally, superior vena cava syndrome is not a contraindication to performing TBNA. Similarly C-TBNA is performed in cases of necrotic endobronchial lesion where EBBx is likely to be false negative. In such cases C-TBNA is used to obtain tissue from the core of the lesion, to avoid false negativity (28-30).

It needs to be mentioned here that C-TBNA is much less sensitive than EBUS-TBNA while performing mediastinal staging for suspected or known bronchogenic carcinoma. Systemic staging of lung cancer (medical mediastinoscopy) is best performed using EBUS-TBNA under general anesthesia, preferably using ROSE by an interventional pulmonologist. C-TBNA could certainly be used to sample large (>15 mm) mediastinal LN preferably to establish unresectable nature of bronchogenic carcinoma.

## Results

### *Diagnosis specific*

#### Staging of non small cell bronchogenic carcinoma

Accurate staging of lung cancer with preoperative detection of mediastinal spread is critical to planning optimal treatment, including resection with curative intent. Lymph node enlargement on CT scan or uptake

 

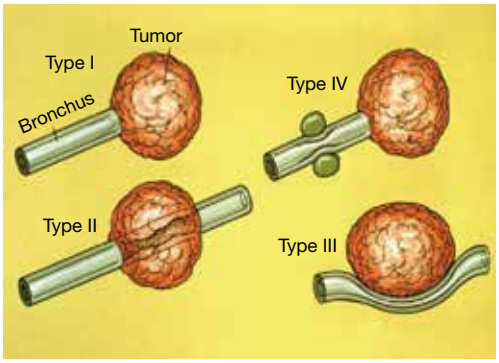


**Figure 1** Tsuboi classification of pulmonary nodule based on anatomical relationship with the adjacent bronchus. C-TBNA increases the diagnostic yield of flexible bronchoscopy while dealing with type III and IV lesions. C-TBNA, conventional transbronchial needle aspiration.

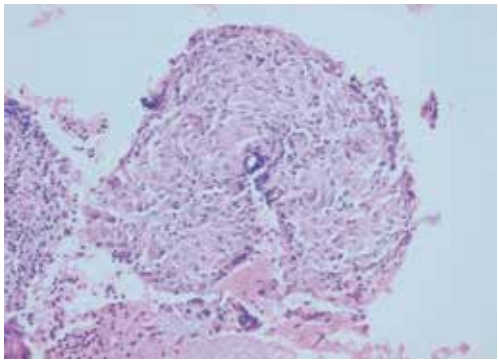

**Figure 2** Diagnosis of sarcoidosis established by 19 G C-TBNA needle in our community practice. Note a large granuloma consisting of epithelioid histiocytes, few multinucleated giant cells, and lymphocytes (HE, 200×). C-TBNA, conventional transbronchial needle aspiration.

of fluorodeoxyglucose on positron emission tomography (PET) does not constitute proof of malignant spread. A 2013 meta-analysis reported sensitivity for CT and PET scan of 55% and 77%, respectively (31). In a community practice, the use of C-TBNA in staging lung cancer is rare as EBUS-TBNA is superior to C-TBNA and has become the preferred first-step procedure (30,32-34).

The yield of C-TBNA in the diagnosis and staging of lung cancer has been reported between 20% and 80% in the literature (14,35,36). A single meta-analysis found sensitivity and specificity of C-TBNA for the diagnosis of non-small cell lung cancer to be 39% and 99%, respectively (33). Carinal involvement, subcarinal lymph node size greater than 1.5 cm and suspected small cell carcinoma are the factors that increase the sensitivity of C-TBNA (21,37). The diagnostic yield of C-TBNA on small cell lung cancer was reported as high as 89% in the literature (38). It needs to be pointed out here that the sensitivity of C-TBNA depends upon the prevalence of the disease in the cohort being studied (39).

## Sarcoidosis

The availability of the 19 G histology needle has expanded the indications for C-TBNA in sarcoidosis; as it is a less invasive, safer, and more economical alternative than mediastinoscopy (*Figure 2*). Several reports have confirmed the diagnostic value of TBNA for the biopsy of mediastinal lymph nodes in patients with suspected sarcoidosis (40-44). A study involving 258 patients with suspected sarcoidosis found the diagnostic yield of bronchoscopy increased from 66% to 78% percent when C-TBNA was added to the transbronchial biopsy (TBBx) (45). A recent randomized multicenter study of 304 patients with suspected stage I/II sarcoidosis (GRANULOMA) reported that compared to transbronchial biopsy, TBNA of mediastinal nodes by endobronchial ultrasound or EUS resulted in a higher diagnostic yield of 80% *vs.* 53% (43). However, the study should be interpreted with caution given that not all patients with stage I sarcoidosis need histologic diagnosis and not all interventional bronchoscopists are proficient in both procedures. Gupta *et al.* have shown that, EBUS-TBNA has the highest diagnostic yield in sarcoidosis, but it should be combined with TBBx for the optimal yield. Incidentally, the diagnostic yield of C-TBNA plus EBBx and TBBx is similar to EBUS-TBNA plus TBBx (44).

## Lymphoma

The clinical utility of C-TBNA in the diagnosis of lymphoma has been limited, since this usually requires larger samples of tissue than are normally obtained by the 22 G needle. However, the availability of the 19 G histology needle, along with the use of flowcytometry to enhance diagnostic yield, may change this assumption (46). The diagnosis of lymphoma, using both cytology and histology needles, has been reported anecdotally, although the overall yield of the procedure in this setting cannot be stated with certainty (27).

## Infections

In the literature, a number of anecdotal reports of infections

diagnosed via C-TBNA have appeared. C-TBNA can establish the diagnosis of histoplasmosis, pneumocystis jirovecii pneumonia, and cryptococcal infection in patients with AIDS (47). In addition, the diagnosis of mediastinal mycobacterial adenitis (due to either mycobacterium tuberculosis or M. avium-intracellulare) has been described in immunocompetent, as well as immunocompromised patients (48-51). Harkin *et al.* demonstrated the usefulness of C-TBNA in HIV patients. Forty-one HIV(+) patients with mediastinal lymphadenopathy underwent 44 TBNA procedures. Of 23 procedures performed on patients shown to have mycobacterial disease, aspirations showed smear positive for AFB in 11 (48%), 14 (61%) specimens grew mycobacteria in cultured material, and caseous necrosis or necrotizing granulomatous lesions were seen in 15 (65%). In 48% and 68% of the patients TBNA was an exclusive diagnostic for mycobacterial disease in two different studies (52,53).

**Miscellaneous**

C-TBNA of submucosal area proximal to an endobronchial tumor to detect local spread may help predict the line of surgical resection in patients with non-small-cell carcinoma (54). C-TBNA has also successfully identified leiomyoma of the esophagus (47), metastatic uterine rhabdomyosarcoma (55), sclerosing hemangioma (56), malignant mesothelioma (57), carcinoid tumors (58) and malignant melanoma (59). Mediastinal cysts have also been diagnosed and therapeutically aspirated using the transbronchial route using TBNA needles (60-62). One report described a patient with a right paratracheal mass on CT scan that was suspicious for malignancy; TBNA revealed serosanguineous fluid suggestive of a sterile abscess, and there was no recurrence on later scans following the aspiration (63). Decompression of a subcarinal cyst using TBNA permitted safe anesthesia and subsequent resection of the cyst in another report (64).

### *Lesion specific*

**Peripheral nodules or masses**

C-TBNA of the peripheral nodules and masses using the 22 G cytology needle has emerged as an extremely useful diagnostic technique. C-TBNA is particularly useful for increasing the diagnostic yield of FB for lesions in which it is not accessible by the common accessories due to the local anatomy and/or its relationship with the adjacent bronchus. Tsuboi type III and IV lesions with negative bronchus sign afford most exclusivity to C-TBNA. A 2013 meta-analysis revealed that the yield of C-TBNA is higher (sensitivity 63%) in peripheral lesions than from either TBBx alone or a combination of TBBx, brushing, and lavage procedures (65). Lesion characteristics predicting the best diagnostic yields are lesions greater than 2 cm in diameter (80% versus 33% to 58%), concurrent mediastinal disease (89% versus 46%), and the lesion being a hematogenous metastasis. The yield from a combination of C-TBNA plus forceps biopsy may be as high as 75%. Although the yield is lower than transthoracic needle aspiration (TTNA), there is a lower risk of pneumothorax (66).

**Peribronchial and submucosal disease**

The diagnostic yield of conventional procedures such as forceps biopsy and brushing tends to be much lower for submucosal and peribronchial diseases than for the exophytic lesions. Such lesions are often covered by normal epithelium, causing suboptimal sampling. Submucosal infiltration by tumor may make tissues firmer, causing the forceps to slide off the lesion and peribronchial lesions are inaccessible to the biopsy forceps by virtue of being located outside the airway. Under such circumstances, C-TBNA to obtain submucosal or peribronchial samples could increase diagnostic yield of FB (9,10,14). In a study involving 31 patients with submucosal and peribronchial disease, it was found that the sensitivity of biopsies obtained by forceps, C-TBNA, a combination of both forceps and TBNA, and a combination of forceps biopsy, bronchial brushing and washing, and C-TBNA was 55%, 71%, 89%, and 97%, respectively (9). Thus, C-TBNA can significantly increase the diagnostic yield of FB while dealing with peribronchial and submucosal diseases.

**Exophytic lesion**

Due to the high yield of forceps biopsy for diagnosing endobronchial lesions (67-100%) suspicious for lung cancer, role of TBNA may be limited (67). However, as discussed earlier, TBNA has been found exclusively diagnostic while dealing with necrotic or hemorrhagic exophytic lesions (21,68). Overall, reported diagnostic yield of C-TBNA for central lesions suspected to be bronchogenic carcinoma is between 70-96% (10,11,58,67,69).

## Complications

Complications of TBNA are uncommon if appropriate precautions are taken and the proper technique is employed.

 

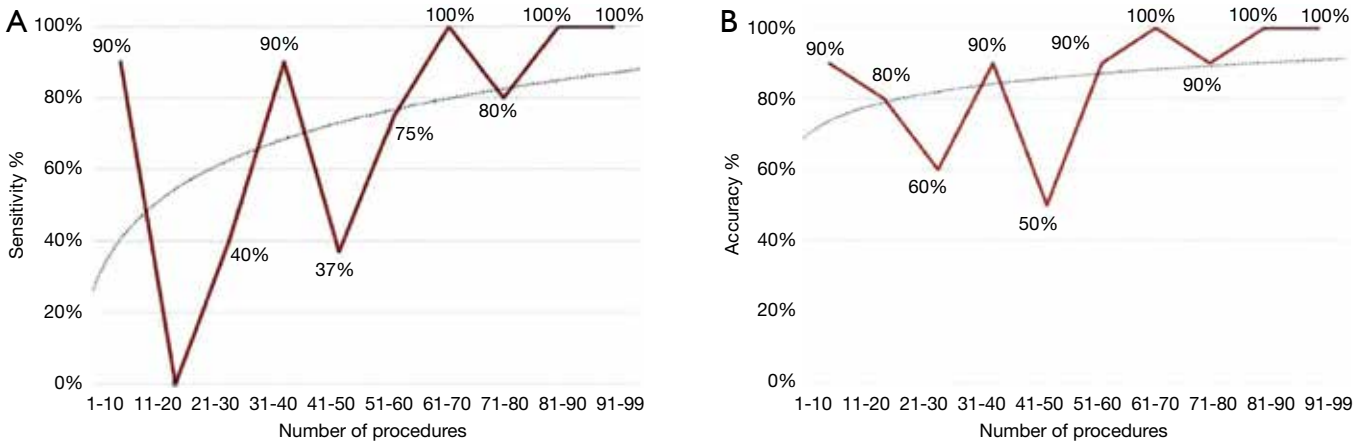


**Figure 3** Learning curve of C-TBNA in a community practice. Note the sensitivity (A) and accuracy (B) plateau around 60 procedures. C-TBNA, conventional transbronchial needle aspiration.

A coagulation profile is not needed prior to TBNA in the absence of a history of a bleeding diathesis (70). Although a variety of complications related to TBNA have been reported, damage to the working channel of the bronchoscope is by far the most important. This complication is more common when a 19 G needle is used, and great care needs to be taken while manipulating the apparatus through the bronchoscope (71). The incidence of fever and bacteremia has been debated, and no firm recommendations can be made regarding antibiotic prophylaxis (72). Transient bacteremia six hours after the procedure with prompt defervescence after antibiotic therapy has been reported. There is a single case report of a purulent pericarditis with polymicrobial mouth flora requiring pericardiocentesis and catheter drainage in addition to antibiotics following a C-TBNA of a mediastinal mass (73). There are no reports of significant bleeding following C-TBNA even in a patient receiving anticoagulation therapy (74). Oozing of a minimal amount of blood from the puncture site may be encountered; the source is usually a dilated blood vessel in the tracheobronchial wall rather than invasion of a major mediastinal vascular structure.

Less frequent complications include pneumothorax, pneumomediastinum, hemomediastinum, and mediastinitis (6,75,76). None of these complications are serious or frequent enough for a community pulmonologist to deter from the valuable procedure of C-TBNA.

## Local experience and the learning curve

At our facility, the possibility of acquiring tools and training required for EBUS-TBNA are close to nil. There are also financial limitations related to the disposable accessories and repair and maintenance of the EBUS scope (77). Beside, our patient volume may not allow adequate number of procedures to maintain proficiency with the EBUS-TBNA. Hence, C-TBNA remains the only option in our environment. Incidentally, there are no interventional pulmonology fellowship programs being offered in our country that provide advanced diagnostic skills. Under the circumstances, we were successful in acquiring the skills of C-TBNA by reading the books and without any formal training. We were also able to achieve proficiency with the procedure in about 60 procedures and have been able to improve the diagnostic yield of bronchoscopy (*Figure 3*) (78).

Our overall diagnostic yield of C-TBNA since the beginning of the program has been between 41% and 50% (17,78,79). This yield in the patients with lung cancer was found to be 66-82% and 75% in patient with sarcoidosis Obviously, our yield was higher with lymphnode size greater than 20 mm than otherwise (17,78,79). Understanding of the mediastinal anatomy, refinement of the technique and the preparation of the specimen were the major determinants of the learning curve and the current success of our program. For a novice bronchoscopist, it would be my recommendation to start performing C-TBNA in patients with large mediastinal LNs, located in the favorable location such as subcarinal or right paratracheal area and where small cell carcinoma is a suspect. I would also recommend that one performs at least 25 TBNAs using a cytology needle (22 G) before embarking on the use of a histology needle (19 G). The latter may require

 

added skill and experience for its insertion through the tracheobronchial wall and to avoid damage to the vascular structures (17,78). It does need to be pointed out that in our part of the world, patients seldom present with resectable lung cancer and even patients with benign conditions exhibit bulky lymphnodes where use of C-TBNA is most appropriate.

## Conclusions

TBNA provides an opportunity to diagnose mediastinal lesions and stage bronchogenic carcinoma in a minimally invasive fashion. In our opinion, acquiring skills of C-TBNA does not require formal interventional pulmonology training and could be learned from the "books". Proficiency could be attained within 60 procedures and acceptable results could be achieved. There is no upfront cost and the procedure can be performed under moderate sedation and local anesthesia in a cost-effective fashion. If a possibility exists, a bronchoscopist can also train him/herself with interpretation of cytology specimen for ROSE. The procedure is safe and has great potential to augment the welfare of patients with pulmonary ailment. Every community pulmonologist should be able to perform C-TBNA.

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## Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

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Interventional Diagnostic Technique

# Navigational transbronchial needle aspiration, percutaneous needle aspiration and its future

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**Abstract:** Peripheral lung nodule evaluation represents a clinical challenge. Given that many nodules will be incidentally found with lung cancer screening following the publication of the National Lung Screening Trial (NLST), the goal is to find an accurate, safe and minimally-invasive diagnostic modality to biopsy the concerning lesions. Unfortunately, conventional bronchoscopic techniques provide a poor diagnostic yield of 18–62%. In recent years advances in technology have led to the introduction of electromagnetic navigational bronchoscopy (ENB) as a tool to guide sampling of peripheral lung nodules. The same principle has also recently been expanded and applied to the transthoracic needle biopsy, referred to as electromagnetic transthoracic needle aspiration (E-TTNA). An improved diagnostic yield has afforded this technology a recommendation by the 2013 3rd Edition ACCP Guidelines for the Diagnosis and Management of Lung Cancer which state that "in patients with peripheral lung lesions difficult to reach with conventional bronchoscopy, ENB is recommended if the equipment and the expertise are available (Grade 1C)". In this review, we will discuss the technology, devices that are available, techniques and protocols, diagnostic yield, safety, cost effectiveness and more.

**Keywords:** Lung nodule; electromagnetic bronchoscopy; transthoracic needle aspiration (TTNA); transbronchial needle aspiration (TBNA)

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## Introduction

The increasing use of chest computerized tomography (CT) scans for respiratory disorders and for lung cancer screening in high-risk patients following the results from the National Lung Screening Trial (NLST) has resulted in the evaluation of pulmonary nodules as a common occurrence for many practitioners (1). The annual number of CT scans currently performed in the United States is approximately 85 million (2). From the NLST we know that 27% of patients had a clinically significant nodule found on low dose CT scan and that screening following their protocol led to a 20% relative risk reduction in lung cancer deaths. However, of the nodules found, more than 90% underwent a diagnostic evaluation proving that 96.4% of those positive screenings were, in actuality, false positives (1). Given the current smoking estimates of the US population and the NLST pulmonary nodule incidence, as many as 1–2 million more suspicious nodules will be discovered annually with lung cancer screening. Lung cancer screening programs are being implemented at many institutions in an attempt to identify, counsel and formulate a plan for evaluation of these

nodules in identified high-risk individuals. Peripheral lung nodule evaluation represents a clinical challenge. Given that the vast majority of these nodules are not malignant, the goal is to find an accurate, safe and minimally-invasive diagnostic modality. Minimally invasive diagnostic procedures include bronchoscopic interventions and non-bronchoscopic techniques such as transthoracic needle aspiration (TTNA) or surgical biopsy. Unfortunately, conventional bronchoscopic techniques provide a diagnostic yield of 18–62% when sampling peripheral pulmonary nodules (3). In recent years, advances in technology have led to the introduction of electromagnetic navigational bronchoscopy (ENB) as a tool to guide sampling of peripheral lung nodules. The same principle has also recently been expanded and applied to the transthoracic needle biopsy, referred to as electromagnetic transthoracic needle aspiration (E-TTNA). The 2013 3rd Edition ACCP Guidelines for the Diagnosis and Management of Lung Cancer state that "in patients with peripheral lung lesions difficult to reach with conventional bronchoscopy, ENB is recommended if the equipment and the expertise are available (Grade 1C)" (4). In this review, we will highlight the current state of navigational transbronchial needle aspiration (TBNA) and percutaneous needle aspiration (PCNA) and speculate on future directions.

## Technology

Electromagnetic (EM) tracking for guidance in medical procedures is based on four basic principles (5):

(I) Creating a magnetic field around the patient;
(II) Utilizing a sensing device to detect location and orientation within the magnetic field;
(III) Reformatting data from a CT scan for 3-D reconstruction that will overlap the location and orientation within the magnetic field;
(IV) Display of a computer interface throughout the procedure to guide the clinician.

In detail, there is a field generator to form a low-strength and varying EM field that will pass through a patient's body. This field then generates current in sensor coils in or on instruments that will be used through the working channel of the bronchoscope in order to determine their x, y and z positions as well as their orientation and rotation around their own axis when the instrument is moved within the EM field. There are several different sensors; the two that are used in medical applications are the 5 and 6 degree-of-freedom sensors. The 5 degree-of-freedom sensor measures the x, y and z positions as well as the pointing direction. The 6 degree-of-freedom adds rotation around its own axis (roll, pitch, and yaw movements) (6). Once the capability to track positioning within the airway is achieved, a map is required to guide the proceduralist to the lesion of interest.

CT scans contain a set of 2-dimensional images formed by pixels that are various shades on a grey-scale, based on their density, and this is measured in Hounsfield Units. Based on these density differences, the various structures of the body are easily defined and delineated from one another. As pixels form images to represent a "slice" of the body with a certain thickness, the pixels contain averaged information with depth. Pixels can therefore be used together to form a 3-dimensional cube called a voxel. These voxels can then be reconstructed to highlight various body structures such as the airways, lymphnodes, lungs, vasculature or tumors that can be used to create several visualizations for display and analysis. Once a 3-dimensional CT scan image is created, it can then be segmented, meaning, certain specific structures can be extracted from the CT images. This technique is used to convert digital imaging and communications in medicine standards (DICOM) images from a CT scan into a structural map of the airways. ENB requires a high-definition of the airways and so thin-section, high-resolution CT scan images are required with a minimum slice thickness of 1.25 mm.

Putting these items together, commercial systems use a sensor probe on their instruments that picks up the EM field generated by the localization system which is comprised of a processor, amplifier and either a location board or a sensor pad and array. When the sensor is placed within the EM field, its position and orientation are displayed on a monitor with the location superimposed upon previously acquired thin-section high-resolution CT images reconstructed into a 3-dimensional airway map. This image-guided localization device has several uses including bronchoscopic guidance for transbronchial biopsies and needle aspirations, fiducial placement and marking of nodules prior to surgery as well as PCNA.

## Equipment

In the United States, there are two EM navigational systems available for clinical use: superDimension (Covidien, Minneapolis, MN, USA, *Figure 1*) and SPiNView (Veran Medical Technologies, St. Louis, MO, USA, *Figure 2*). Both systems are based on the same fundamental concept. A CT scan using a dedicated protocol is obtained for planning

 


**Figure 1** SuperDimension ENB system. ENB, electromagnetic navigational bronchoscopy. [Reprinted with permission from Veran Medical Technologies].


**Figure 2** Veran ENB system. ENB, electromagnetic navigational bronchoscopy. [Reprinted with permission from Veran Medical Technologies].

ENB targets and to overlay the magnetic field to the CT scan and the patient anatomy. The superDimension system (Covidien, Minneapolis, MN, USA) consists of several components. The main processor unit, steerable extended working channel catheter with different tip angulations ranging from 45° to 180°, a locatable guide and the EM board which generates the EM field and lies underneath the patient throughout the procedure. During the pre-procedure planning phase, the target lesion is identified using proprietary software (*Figure 3*, *Figure 4A*).

The SPiNView system (Veran Medical Technologies, St. Louis, MO, USA) uses a tracking pad that serves as a reference point, providing feedback information for the system to maintain registration despite the change in location of the target lesion due to respiratory variation. Ideally, to maximize accuracy, CT scan images are obtained during inspiration and expiration for the computer algorithm to compensate for the dynamic respiratory changes. As with the superDimension system, SpinDrive requires a pre-procedure planning phase that is performed using proprietary software loaded onto a dedicated laptop (*Figure 3*). The main piece of equipment is composed of a central unit with a generator that creates the EM field which projects down, over the patient. Another major difference is in the biopsy instruments. They are always-on tip trackable, eliminating the need for an extended working channel, but limiting the directionality. Because the instruments are tip-tracked, the need for fluoroscopy to ensure appropriate positioning is obviated. The biopsy forceps and brushes are 1.8 mm in outer diameter (OD) and histology and cytology needles are available in 19 and 21 gauge (G) respectively (*Figure 4B*).

TTNA is a non-bronchoscopic diagnostic approach to lung nodules and masses. TTNA of a peripheral lung lesion can be performed under ultrasonography, fluoroscopy or CT guidance.

Recently, the EM navigational technology was incorporated into the traditional TTNA technique creating a novel diagnostic tool and potentially a new paradigm in the evaluation of lung nodules. The SPiNPerc system (Veran Medical Technologies, St. Louis, MO, USA) consists of the same computer unit used with the SPiNView system for ENB, but instead of endobronchial navigation via a trackable bronchoscopic instrument, a 19 G (105 mm length) needle is used for navigation. The needle has two components, a stylet that works as a sensor allowing EM navigation to peripheral pulmonary nodules and the needle itself. Once within the target lesion, the needle works as a

 


**Figure 3** Pre-procedural planning and CT-3D reconstruction overlay. CT, computerized tomography.


**Figure 4** ENB instruments. (A) Extended working channel and Edge catheters; (B) always-on tip-tracked instruments. ENB, electromagnetic navigational bronchoscopy. [Reprinted with permission from Covidien].

 

**Figure 5** Veran SPiNPerc E-TTNA needle. E-TTNA, electromagnetic transthoracic needle aspiration. [Reprinted with permission from Veran Medical Technologies].

working channel through which smaller FNA needles can be passed or core biopsies can be obtained (*Figure 5*) (7). Currently, this approach is only available on the Veran SPiNView System.

## Technique/protocol

### *Planning*

Prior to starting the procedure, the digitized information from each patient's CT scan is imported into the EM navigation system where all views (axial, coronal and sagittal) of the chest are reconstructed using a proprietary software that is unique to each system. Virtual endoscopy images of the airway are reconstructed. Consequently, anatomic landmarks (typically major bronchial tree bifurcations) are identified as coordinates on the corresponding CT as well as on the virtual bronchoscopy image.

### *Registration*

The same identifiable landmarks are then used during real-time bronchoscopy in order to better correlate the CT data and reconstruction to the actual anatomy. With the superDimension system, when these points in the airway are reached, either the sensor can be used to physically touch the airway landmark or a foot-pedal can be depressed to identify the areas that were used in the pre-procedural planning. With the SPiNView, the system automatically registers the patient's anatomy without the need for any manual registration.

ENB with superDimension procedural phase starts by placing the patient on a non-metallic bed equipped with anchors for the navigational board. Once connected with the main station, a rectangular EM field is displayed and three sensors are attached to the patient's chest in a triangular distribution. Registration is confirmed and the operator navigates to the target after which the steerable and locatable guide is removed while the extended working channel is left in place to act as a guide sheath and the biopsies are taken using conventional instruments. The SPiNView system has automatic registration, but requires attaching the sensor pads before obtaining the CT images. Once in the procedural room the patient is positioned in a similar fashion used to acquire the CT scan and the bronchoscopic procedure can commence.

### *Bronchoscopic procedure*

The bronchoscopist navigates to the target lesion steering the bronchoscope with the locatable guide/extended working channel or alternatively using tip-tracked instruments. The system will help to navigate the operator into the correct airway using virtual images and reconstructions of the CT scans. Once in proximity to the target lesion, biopsies, needle aspirates and brushings are obtained.

### *Percutaneous biopsy*

The EM navigational needle is also tip-tracked in real time to the target lesion. Pre-procedural planning is performed as described above. The needle trajectory is guided by multiplanar CT scan images and the virtual 3D reconstruction images. Once in the lesion the needle stylet (sensor) is removed. Fine needle aspiration is performed for rapid on-site evaluation (ROSE) followed by larger biopsies. Multiple core samples are obtained using a 20 G automatic biopsy needle (*Figure 6*). Specimens are typically placed in formaldehyde for pathological analysis. Post procedure evaluation with chest ultrasonography or conventional chest radiography is advised in order to exclude complications such as pneumothorax.

## Diagnostic yield

Multiple factors influence the diagnostic accuracy including location, nodule size, and presence in cross-section of a bronchus leading to the nodule (8). Size has the most studied influence on diagnostic yield and despite some conflicting data, the majority of papers report a sensitivity

 

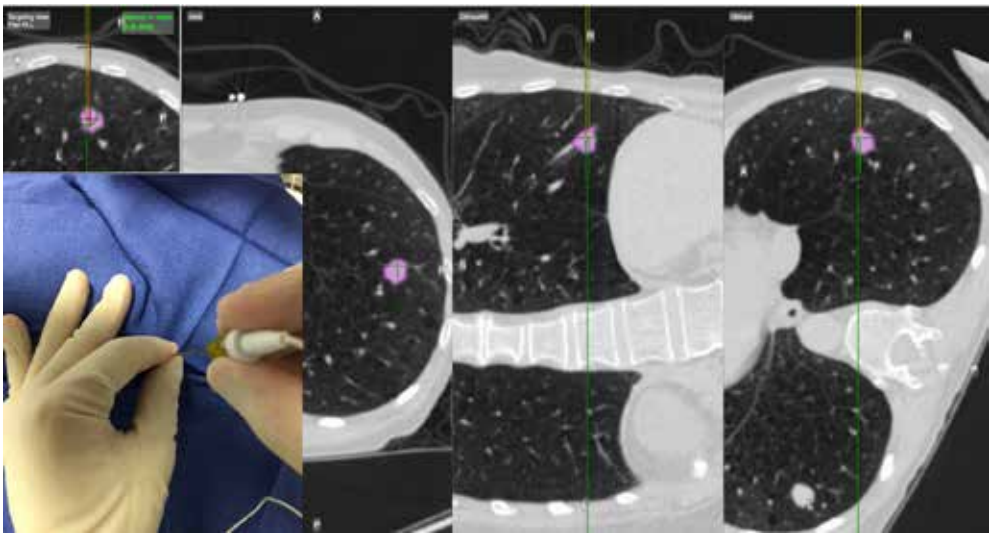

**Figure 6** E-TTNA procedure. E-TTNA, electromagnetic transthoracic needle aspiration.

that is lower for lesions less than 2 cm in size (9-11). Another factor that was recently reported to decrease diagnostic yield is target movement during the different phases of the respiratory cycle. The dynamic nature of the procedure ideally would require a continuous and strict registration to maximize accuracy and prevent sample errors. Chen *et al.* reported an average motion of 17.6 mm for lung lesions when comparing scans during inspiration and expiration. Lesions found to be most susceptible were those in the lower lobes. Interestingly, size and distance from the pleura did not significantly affect respiratory-induced movement of pulmonary nodules (12). Moderate sedation *vs.* general anesthesia selection is an area of much controversy during bronchoscopic procedures. In a recent study no difference was found in diagnostic yield for ENB guided biopsies of peripheral lung nodules though the procedure time was less in the moderate sedation group (13).

ENB is also noted to have a steep learning curve and Lamprecht *et al.* noted an increased diagnostic yield after some procedural experience; with diagnostic yield of 80% and 87.5% for the first 30 and last 30 procedures, respectively (14).

Gex *et al.* performed a systematic review and meta-analysis on diagnostic yield and safety of ENB whereby they reported on six variables associated with higher ENB yields: nodule location in the upper or middle lobes, nodule size, lower registration error, presence of a bronchus sign on CT imaging, combined use of an ultrasonic radial probe and catheter suctioning as a sampling technique (15). Zhang *et al.* in a recent systematic review evaluating ENB showed a pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio and diagnostic odds ratio of 82%, 100%, 19.36%, 0.23%, and 97.62%, respectively. This group re-confirmed the above six variables associated with improved diagnostic yield for ENB (16).

The use of TTNA is mainly based on location of the lesion, availability of less-invasive modalities and proceduralist expertise. Althogh the diagnotic yield varies depending on the technology used, Rivera *et al.* reported that the pooled sensitivity of TTNA for the diagnosis of peripheral bronchogenic carcinoma was 0.90 [95% confidence interval (CI), 0.88–0.91] and when separated by imaging modality, 92% (95% CI, 90–94%) and 88% (95% CI, 85–90%) for studies of CT scan-guided and fluoroscopy-guided TTNA, respectively (17). No clinical trials exist at this time to determine the diagnostic yield for E-TTNA.

## Safety

One of the major advantages of bronchoscopic navigational biopsies is the safety profile. ENB complications include pneumothorax, bleeding and respiratory failure. In general ENB is a low risk diagnostic modality (16). Gex *et al.* reported a pneumothorax of 3.1% of whom 1.6% of patients required further management with a chest tube drainage (15).

Complications related to TTNA include pneumothorax,

 

bleeding, hemoptysis, air embolism and infection. In a study by Wiener *et al.* that included 15,865 patients, pneumothorax risk after TTNA was 15% (95% CI, 14–16%) with 7% (95% CI, 6–7.2%) requiring management with a chest tube (18). Parenchymal hemorrhage and hemoptysis have an incidence of 11% and 7%, respectively. These bleeding complications tend to be self-limited and rarely require active intervention or management (19,20). E-TTNA is no different than other transthoracic biopsies with other imaging modalities and therefore the complication rate is presumed to be similar, with recent studies pending publication.

## Combining modalities

### *ENB and EBUS*

Traditional TBNA and EBUS-TBNA have both been shown to be effective in the diagnosis and staging of lung cancer (21-23). Recent technologies like ENB and radial EBUS have been successfully introduced to the diagnostic armamentarium of peripheral lung nodules. The clinical utility of the combination of different diagnostic techniques have been evaluated by different groups. Utilization of the radial EBUS in combination to ENB provides a real-time verification of the target, theoretically reducing the possibility of sample error. Eberhardt *et al.* reported a diagnostic yield of 88% for the combined procedure versus 69% and 59% for radial EBUS and ENB alone respectively (24). Other hybrid methods include virtual bronchoscopy and radial EBUS. The clinical benefit of this combination has been documented (25). ENB was conceived with the intention to localize and sample lesions that are difficult to access by conventional bronchoscopic techniques. Chee *et al.* demonstrated that ENB improves localization rates after unsuccessful attempts with radial EBUS (93% *vs.* 73%), however diagnostic yield for radial EBUS alone and radial EBUS with ENB were 43% and 50%, respectively (26). Development of instruments that allow ENB with real time EBUS and biopsy capabilities could dramatically contribute to the evaluation of peripheral pulmonary nodules.

### *ENB and EBUS and E-TTNA*

Combination of EBUS-TBNA, ENB and E-TTNA provides a comprehensive, minimally-invasive approach to the diagnosis and staging of peripheral pulmonary lesions. This complement of a bronchoscopic with a non-bronchoscopic biopsy technique consolidates multiple procedures that can be performed in a single setting. A potential algorithm to maximize outcomes would include multiple modalities and ROSE. The procedure would start with convex-probe EBUS mediastinal staging, followed by ENB and biopsy of the peripheral pulmonary lesion which can be confirmed with radial EBUS, followed by E-TTNA of the peripheral nodule if a diagnosis is not confirmed using the bronchoscopic techniques with ROSE. The advantages of this approach may be an increase in overall diagnostic yield as well as a cost-effective approach to the diagnosis of lung nodules in high-risk patients for malignancy. The patient has fewer hospital encounters, more efficient time to diagnosis, less anesthesia and lower cost. Preliminary reports from a recent study by Yarmus *et al.* showed a diagnostic yield higher than 80% for peripheral lesions ranging in size from 12–29 mm. Before widespread use of this suggested protocol, further clinical studies are required.

## Other uses

### *Guidance for lymph node biopsy*

A less common use of EM bronchoscopy is guidance to sample mediastinal and hilar lymph nodes as an alternative to EBUS. The planning and registration is performed as described above, with one of the lymph nodes marked as a target. In this way, the location and distance to the lymph node are determined in real time using EM guidance. The site for transtracheal or transbronchial puncture is then marked by creating an indentation of the airway mucosa with the sensor probe at the desired location. Following marking, standard instruments can be utilized to perform traditional TBNA (27). In a recent study by Diken *et al.*, they reported a diagnostic yield for ENB-TBNA of 72.8% in nodes with a mean size of 17.56±6.25 mm in a cohort of 94 patients with 145 lymph nodes biopsied as compared to 42.2% using conventional TBNA (28). Another study by Gildea *et al.* evaluated diagnostic yield and safety with ENB to sample peripheral lesions (n=54) and lymph nodes (n=31). With respect to lymphadenopathy, their diagnostic yield was 100% for nodes with a mean size of 28.13 (range, 11–72) mm and there were no complications noted with lymph node sampling (29).

### *Dye marking prior to surgery*

Several techniques exist to localize pulmonary nodules for

 

operative excision and they typically require a percutaneous approach to place pleural markers, coils, hook wires or radioactive markers but these procedures, unfortunately, have a high rate of pneumothorax. The premise for use of ENB for localization is that after the lesion is located during navigation and methylene blue is injected near the lesion. The surgeon resects the marked area during the same operative and anesthesia time, and intraoperative frozen sectioning confirms successful resection. This approach greatly aids lung preservation, length of procedural, anesthesia and operating room times, limits cost and makes the work-up and management for a pulmonary nodule efficient for the patient, all while minimizing morbidity (30). Krimsky *et al.* have recently published an approach whereby they "tented" the sub-pleural space adjacent to the nodule with the locatable guide and extended working channel under fluoroscopy and a 25 gauge sclerotherapy needle was used to inject 0.5 mL of either indigo carmine or methylene blue dye at the site. Following marking, the patients were taken to the operating room for a minimally-invasive resection either by video-assisted thoracoscopic surgery (VATS) or robotic-assisted thoracoscopic surgery (RATS) approaches with or without an anatomic resection and lymph node dissection. They found the dye marker outlined the area of interest 81% of the time in 22 patients. One patient had diffuse dye marking of the parietal pleura and two patients the dye was not visualized. The nodules studied had a mean size of 13.4 mm (range, 7–30 mm). No patient had to be converted to an open procedure (31).

A similar technique was published the same year by Bolton *et al.* They evaluated 19 patients who underwent ENB localization and dye marking prior to robotic resection. Their approach differed in that they marked the lesion as well as the nearest pleural surface. Mean size of lesions was 18 mm (range, 8–40 mm and only four patients with lesions >20 mm, all of which were ground glass nodules/masses) (32). Finally, earlier this year, Anayama *et al.* published a technique for the use of thoracoscopy following injection of indocyanine green (ICG) that is delivered bronchoscopically via ENB guidance to a pulmonary nodule without injuring the visceral pleura. They have tested this protocol on three live pigs whereby they created pulmonary nodules with 0.3 mL of 5% agar containing iopamidol. ENB was used to then bronchoscopically inject 0.1 mL of ICG to the area of the nodule. After 6 hours, the lung was examined with a thoracoscope that has near infrared capabilities. The nodules were successfully located and were found to be within 3.3±0.95 mm of the nodule. The benefit of this approach is that ICG is not affected by color changes of the pleura that can occur with anthracosis or underlying pulmonary disease. Contrary to the use of fiducial markers, micro-coils or hook-wires, this approach did not result in pneumothorax. ICG can also notably be confirmed with CT scan prior to surgery (33).

### *Fiducial placement*

Probably the most common therapeutic rather than diagnostic use for ENB is for the placement of fiducials. Fiducial markers are radiographically visible markers that identify the position of a tumor and assists with accommodation for respiratory motion during stereotactic body radiation therapy (SBRT). Fiducials can be inserted via three methods: transthoracic, intravascular and bronchoscopic. Bronchoscopic insertion has a better safety profile over the other two insertion methods with less risk of pneumothorax, pleurisy and pulmonary infarcts (34-36). Ideally, fiducials must have a minimum spatial separation of 20 mm and an angular separation between any groupings of three fiducials of 15 degrees (37). Given this standard, it is advisable to place more than the three required fiducials in case there is migration or expectoration of the fiducial, a known complication of bronchoscopic fiducial placement that occurs 10–26% of the time (36).

Kupelian *et al.* placed metallic markers for radiation therapy in 23 patients for early-stage lung cancer either with CT guidance or using the ENB system transbronchially. They reported a pneumothorax rate of 8/15 (53.3%) *vs.* 0/8 (0%) in each group, respectively. Successful placement and migration rates were equivalent (38). Anantham *et al.* reported on the attempted placement of fiducial markers in nine patients. The overall success rate was 89% and of those with successful placement, 90% of the fiducials remained in appropriate position without migration 7–10 days later when they returned for SBRT planning. A mean number of 4.9 fiducial markers were placed per patient (39). Finally, Harley *et al.* reported on 43 consecutive patients who had 2–5 fiducial markers placed in or around peripheral lung lesions using EBUS. EBUS was combined with ENB when the lesion was difficult to navigate to. In total, 12 patients required navigation with ENB. Thirty of forty-three patients had no evidence of fiducial migration following fiducial placement. Of the 13 patients who had 1 or more fiducials that had migrated, none had any clinical impact on treatment with SBRT. One patient had a small pneumothorax necessitating chest

 

tube placement and 1-day admission and several patients had blood-streaked sputum, but otherwise there were no complications reported (40).

### *Foreign body removal*

Although rare in adults, there is a case report of a foreign body (copper wire) that had been aspirated by a 46-year-old gentleman and had migrated to the right lower lobe causing a chronic cough. Bronchoscopic attempts were unsuccessful as the wire was not visible despite using a pediatric and ultrathin bronchoscope. ENB was then performed and forceps were extended through a guide sheath to successfully remove the wire with resolution of the cough. Utilization of ENB saved this patient from undergoing surgical intervention and can be considered in similar cases (41).

### *Placement of brachytherapy catheter*

There is a technical note published in German describing the successful placement of a brachytherapy catheter after navigation to a peripheral, unresectable, lung cancer in the right upper lobe, confirmed with radial EBUS. This catheter remained in appropriate position for five therapeutic sessions without migration and the patient had an excellent clinical outcome. This technique may become useful in patients who are not surgical candidates, particularly with upper lobe lesions where fiducial markers are less stable (42). Future ENB therapeutic interventions like placement of ablative catheters may be a potential treatment alternative to surgery or SBRT.

## Cost effectiveness

As mentioned earlier, the number of incidentally found pulmonary nodules is increasing with high-risk patients being screened for lung cancer and the use of CT scans for thoracic symptoms and disorders. The probability of malignancy, however, in an abnormal CT scan depends upon the lesion and patient characteristics. The probability of malignancy of a pulmonary nodule can be estimated using existing models (43,44). If the probability of malignancy is high, the patient should go directly to resection. Equally, if the likelihood of malignancy is low, then the patient will undergo radiographic follow-up. The management of a solitary pulmonary nodule of intermediate risk for malignancy (between 5% and 65%) is unclear. In a time where healthcare is required to become more fiscally responsible, cost must be a consideration when selecting a diagnostic or therapeutic modality.

With respect to ENB with or without E-TTNA, although costs are significant, particularly if an additional high-resolution, thin-slice CT scan must be obtained, they are not prohibitive. American insurance companies do currently cover ENB. There are a couple of publications that can help to determine the most cost-effective strategy for diagnosis of a pulmonary nodule. Unfortunately, E-TTNA is a novel modality and has not yet been extensively studied and so is not included in the papers below, though may show an improvement in cost-effectiveness by increasing diagnostic yield in a minimally-invasive and time-efficient way.

The first study is a cost-effectiveness evaluation that was performed looking at initial diagnostic strategies for evaluation of a pulmonary nodule using a decision-analysis model to assess costs and outcomes of PET/CT (watchful waiting) *vs.* CT-guided TTNA *vs.* ENB *vs.* VATS. The base case consists of a 1.5–2 cm, upper lobe, incidentally discovered pulmonary nodule in a patient with a 15 pack-year smoking history and either a spiculated appearance or growth of 15% of this nodule on serial imaging. The above scenario with both a 50% and a 65% pretest probability of cancer were evaluated (45). Diagnostic modalities were compared based on published literature estimates of sensitivity, specificity, complication and outcome probabilities, 5-year survival rates and cost. The study found that when cancer prevalence was 65%, ENB and CT-guided TTNA were the most cost-effective strategies. The decision to use one strategy over the other should be individualized based on size and location (including central *vs.* peripheral and proximity to airways) of the pulmonary nodule. When cancer prevalence was 50%, ENB, CT-guided TTNA and PET/CT had equivalent cost-effectiveness.

Another study by Dale *et al.* was a cost-consequence analysis of ENB *vs.* CT-guided TTNA for a solitary pulmonary nodule (46). The base case is a 65-year-old with >40 pack-year smoking history and a 2-cm solitary pulmonary nodule. The base case would have an approximate 60% chance of malignancy. They found that using CT-guided TTNA or ENB followed by VATS for a non-diagnostic biopsy was less cost-effective than performing serial biopsies. Serial biopsies meant that patients in the ENB arm who had a non-diagnostic ENB biopsy all went onto CT-guided TTNA. Similarly, patients in the CT-guided TTNA arm with a non-diagnostic CT-guided TTNA all went on to ENB biopsy. The serial biopsy approach decreased cost in both arms as the need for

 

VATS decreased, though complications did increase. The cost savings of CT-guided TTNA are largely driven by the high sensitivity thereby leading to less need for VATS to secure a diagnosis. Although ENB is more expensive than CT-guided TTNA overall, there are cost savings with the use of ENB secondary to the minimal complication rate of ENB *vs.* CT-guided TTNA (pnemothorax: 1.6% *vs.* 15%, hemorrhage: 0.1% *vs.* 1% and respiratory failure: 0.1% *vs.* 1%, respectively).

## Limitations

The main ENB limitation continues to be related to the alignment of the EM tracker to pre-procedural CT images. The current findings suggest that the diagnostic yield of ENB may be affected by CT-to-body divergence rather than the size or location of the lesion. CT-to-body divergence is unavoidable as ENB is not a real-time navigational system and this may be one of its current drawbacks. Although ENB is often referred to as the "global positioning systems (GPS) of the lungs" there is a significant difference. GPS devices receive constant positioning feedback regarding their location on a map that is continuously updated; ENB systems do not update the anatomy from the planning CT scan.

These differences could be obviated in the future with the application of CT with ultra-fast temporal resolution and/or respiratory gating.

Other technologies like co-registration and image fusion technology have been used for diagnostic and therapeutic interventions in solid organs and tumors. Application of such modalities in pulmonary procedures would be an alternative to overcome some of the ENB limitations. ENB is a multi-step process that is time consuming and requires a dedicated infrastructure, but there is no doubt of the utility of ENB in the diagnosis and management of pulmonary nodules.

## Future directions

ENB and E-TTNA will continue to strive towards an effective, efficient, minimally invasive and cost-conscious approach to the diagnosis of pulmonary nodules in addition to playing a role in some therapeutic interventions such as fiducial placement, pleural dye marking and foreign body removal. With ENB improving localization of pulmonary nodules, hopefully some localized therapy can be delivered to the nodules (47). Tsushima *et al.* demonstrated the feasibility of fiberoptic bronchoscopy-guided radiofrequency-induced tissue ablation using normal sheep lungs. In this study, coagulation and necrotic tissue formed around the electrode tip created increased tissue impedance and therefore adequate necrosis was not achieved (48).

A later study by Tanabe *et al.* used a cooled electrode probe in humans and achieved an ablative area with destruction of the alveolar space and coagulation necrosis to a maximal area of 12×10 $mm^2$ (49). More study needs to be performed before this should be used as a treatment option.

In order to move in a forward direction, we need to continue to improve upon the diagnostic yield as this modality offers several advantages over other techniques such as CT-guided TTNA and VATS including a better safety profile, particularly for patients who have significant respiratory compromise and cost savings.

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## Footnote

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Interventional Diagnostic Technique

# Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA)—from morphology to molecular testing

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**Abstract:** In recent years, endobronchial ultrasound-guided TBNA (EBUS-TBNA) has emerged as an innovative technique for diagnosis and staging of lung cancer and has been successfully introduced into daily clinical practice with several advantages including minimally invasive approach, safe, cost-effective, real time image guidance, broad sampling capability, and rapid on-site evaluation (ROSE). Both cytological and histological approaches could be useful to have material for diagnosis, immunohistochemical and molecular analyses which may be very important for targeted therapy with successful rate ranging from 89% to 98%. The utility of ROSE during EBUS-TBNA has been matter of debate. Indeed, although some evidence concluded that ROSE does not increase the diagnostic efficacy of EBUS-TBNA, other demonstrated that it improves the diagnostic yield of the procedure up to 30%, allows to avoid repetition of additional diagnostic procedures and reduces risk of complications. Furthermore the sample preparation by cytopathologist is optimized with the aid of direct macroscopic inspection, optimal smearing techniques, and triage of the sample permitting to obtain adequate tissue for diagnosis, ancillary techniques and molecular testing, when needed. Some pathological issues on EBUS-TBNA are reviewed and discussed with particular focus on ROSE and molecular testing

**Keywords:** Endobronchial ultrasound-guided (EBUS); transbronchial needle aspiration (TBNA); lung cancer; immunohistochemistry (IHC); EGFR; ALK

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## Introduction

The traditional approach to the diagnosis of lung and mediastinal diseases has included different noninvasive and invasive techniques performed to obtain diagnostic cytological and/or histological material. Among invasive techniques, aspiration cytology including transbronchial needle aspiration (TBNA) and computed tomography (CT)-guided transcutaneous fine needle aspiration/core biopsy have been used for many decades as an alternative to more invasive surgical procedures. However, in recent years, endobronchial ultrasound-guided TBNA (EBUS-TBNA) has emerged as an innovative technique and has been successfully introduced into daily clinical practice (1). This procedure has joined the use of conventional bronchoscopy and ultrasound imaging, which are two techniques well managed for decades, with needle aspiration beyond the bronchial wall to get material from both lung parenchyma

 

and mediastinal lymph nodes. Indeed, this procedure is of particular interest either to confirm the diagnosis of radiologically detected central lung cancer, or for the staging of known lung cancer by sampling mediastinal lymph nodes. Moreover, EBUS-TBNA can be particularly useful for the diagnosis of localized mediastinal disease or other lung diseases associated with mediastinal lymphadenopathy like sarcoidosis (2).

The results just obtained after the introduction of this novel technique in terms of diagnostic accuracy and safety has convinced clinicians that it may represent an innovative diagnostic tool with several advantages including minimally invasive approach, safe, cost-effective, real time image guidance, broad sampling capability, and rapid on-site evaluation (ROSE) (3,4). EBUS-TBNA has also acquired importance in cases in which surgical procedures are contraindicated or unnecessary, like patients with co-morbidity which increase surgical risks, and it is more suitable for patients with disease not requiring surgery such as lymphomas, germ cell neoplasms or metastatic lung cancers.

Using the EBUS-TBNA approach it is possible to obtain either cytological material (with or without ROSE) or histological cores. Although literature data comparing the diagnostic accuracy between the two material typologies are limited, available information has not demonstrated a significant difference. A perspective study comparing EBUS-TBNA with EBUS biopsy without aspiration has not demonstrated differences in sample quality and diagnostic yield for malignancy (5). Consequently, the choice of the type of material (cytological versus histological) mainly depends on the local expertise and organization.

In this study, we give a review on the practical approach to EBUS-TBNA procedure including cytological, histological, and molecular aspects. The new era of EBUS-TBNA may be resumed as "do more with less" because with a relatively small material we are now able to perform an accurate diagnosis associated with prognostic and predictive morphological and molecular markers.

## Cytology approach to EBUS-TBNA specimens

Considering the cytological approach to EBUS-TBNA specimens, sensitivity in the diagnosis of lung cancer is recorded to be up to 90% after learning curve (4) and diagnostic accuracy for this technique is reported to be higher than that for CT and PET (98% *vs.* 60.8% and 72.5%, respectively). The benefit of ROSE during EBUS-TBNA has been matter of debate in the past few years. Indeed, although some studies concluded that ROSE does not increase the diagnostic efficacy of EBUS-TBNA (6), several other investigations have demonstrated that it allows to improve the diagnostic yield of the procedure up to 30% (7-9) and that the immediate evaluation of sample adequacy allows to avoid additional biopsies, additional bronchoscopic procedures, repetition of other diagnostic procedures or risk of complications connected to bronchoscopy (10). Furthermore, the sample preparation by cytopathologist is optimized with the aid of direct macroscopic inspection, optimal smearing techniques, and triage of the sample allowing to obtain adequate tissue for diagnosis, ancillary techniques and molecular testing (7).

For this reason, the cytopathologist is more and more solicited to offer ROSE evaluation of cytological material obtained during EBUS-guided technique and has assumed an increasingly central role in the management of patients with lung cancer. In situations where financial difficulties do not permit to have enough resources, the cytotechnologists (CyT) may also be asked to give rapid interpretations. The accuracy rate of responses done by CyT (between preliminary and final diagnosis) was shown to be higher for pancreas, liver and bone lesions and lower for kidney and lung lesions (11).

There is a lot of variability in technical methods for tissue acquisition and further treatment of collected specimens. Variability concerns necessity to have ROSE, needle gauge, number of passes and specimens' management. ROSE is essential for appropriateness of tissue management, as abundance of material is now the goal of image-guided procedures for targeted therapies. Moreover, with ROSE, TurnAround Time (the amount of time taken to give a diagnosis, TAT) is reduced. Most studies showed a 90% to 98% concordance between ROSE diagnosis and final diagnoses (8,12). False negative rate due to sampling errors is directly correlated to the lower number of slides examined. EBUS-TBNA is also frequently performed because of the discovery of a PET positive lesion/nodule in patients followed up for previous lung malignancies. In this situation, it has been demonstrated that ROSE significantly reduces false positive rate in PET positive lesions.

Usually, needle gauge used is 22. In our experience, the number of passes is determined by the acquisition of diagnostic material. In case of positive (malignant) diagnosis on one of the ROSE slides, we try to have an idea of the possible diagnosis/differential diagnosis. Thus, we can triage the material appropriately according to the

 

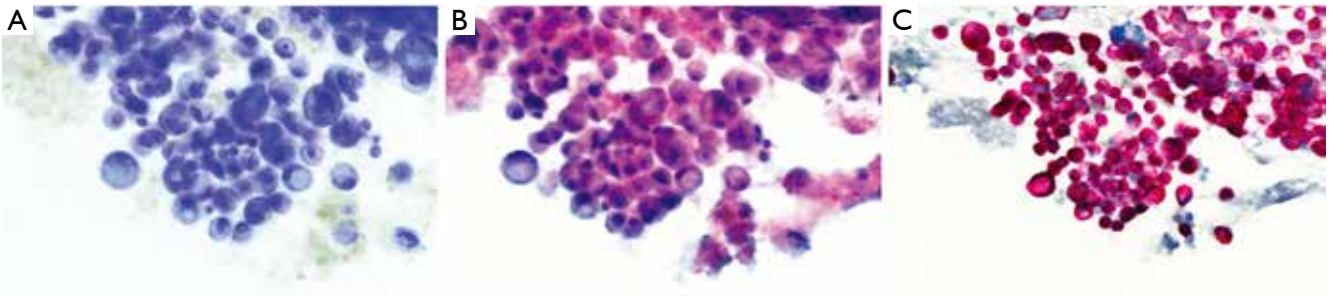


**Figure 1** A 67-year-old female with a history of previous lung adenocarcinoma presented with a PET positive nodule in a para-tracheal lymph node. (A) The ROSE smear showed abundant cellular material with mostly isolated cells. The cells showed enlarged nuclei, prominent nucleoli and cytoplasmic vacuoles. The material was sufficient for diagnosis (working diagnosis: non-small cell metastatic lung carcinoma) (toluidine blue staining, 200×); (B) the same smear stained with Papanicolaou for definitive evaluation confirmed the ROSE diagnosis (Papanicolaou staining, 200×); (C) immunocytochemical expression for CK7 on the same de-stained slide was intense. The final cytological diagnosis was: lymph-node metastatic lung adenocarcinoma (CK7 immunostaining, 200×). In case of need, the same slide could be used for molecular analysis, either scraping the slides or using laser capture microdissection.

preliminary working diagnosis: cell block preparation in case of solid tumor for immunocytochemistry and mutational analysis, flow cytometry in case of suspected hematological malignancies, and sterile sampling for microbiological studies in case of inflammatory process/abscessed cavity. The rest of the passes will be used to enrich one of these possibilities. In case of negative (normal tissue) diagnosis, such as in case of reactive lymph nodes, the needle rinse material after each pass will be used for liquid-based cytological preparation. Three passes are generally sufficient to provide enough material. After each pass, one to three slides can be realized and stained with Toluidine blue (*Figure 1A*). The staining process lasts no more than 10–15 seconds and permits a rapid, almost immediate, response from the cytopathologist or the trained CyT. What should we communicate to the clinicians? Strictly, the most appropriate rapid diagnosis concerns the quantity of material aspired: sufficient (or not) to establish a definitive diagnosis. However, according to the confidence between cytopathologists and clinicians, and also according to the compliance of the clinicians to understand and accept that definitive diagnosis may change the preliminary one, the cytopathologists can also say more: material consistent with a lymph node tissue (thus indicating the appropriateness of the technical aspiration) or consistent with malignant cells (i.e., adenocarcinoma *vs.* squamous cell carcinoma *vs.* small cell carcinoma). This is particularly useful in urgent cases in which a diagnosis of small cell neuroendocrine carcinoma can immediately prompt the clinicians towards a chemotherapeutical decision, instead of a surgical treatment. Once the diagnosis is reached on one smear, all the rest of the material is used to enrich the specimens or for special tests. Once in the cytopathology laboratory, the Toluidine blu smear is then stained with traditional Pap stain for final interpretation (*Figure 1B*) and the rest of the material is treated for liquid-based cytology or cell block preparations. Immunocytochemical stains (*Figure 1C*) and molecular analysis can be done using either stained slides or cell block.

## Histological approach to EBUS-TBNA specimens

EBUS biopsy without aspiration has been referred as "transbronchial needle capillary sampling (TBNCS)" by some authors (5). Since it seems that there is not a significant difference in diagnostic yield between EBUS-TBNA and TBNCS, the choice of the type of material (cytological *vs.* histological) mainly depends on the local expertise and organization. The disadvantage in using histological material mainly relies on the impossibility to have a rapid on-site evaluation. Conversely, the advantage relies on the possibility to have more material for immunohistochemical and molecular analysis which may be very important for certain tumor types including lymphomas and adenocarcinomas (*Figures 2-5*). In addition, lymph node biopsy may be better in getting material than cytological approach when lymph node is fibrotic such as in cases of sarcoidosis (*Figure 6*). From a practical point of view, the material is routinely managed as a histological core biopsy. In our experience, cytological examination of cell block obtained from needle washing material is helpful to get additional diagnostic cells.

 

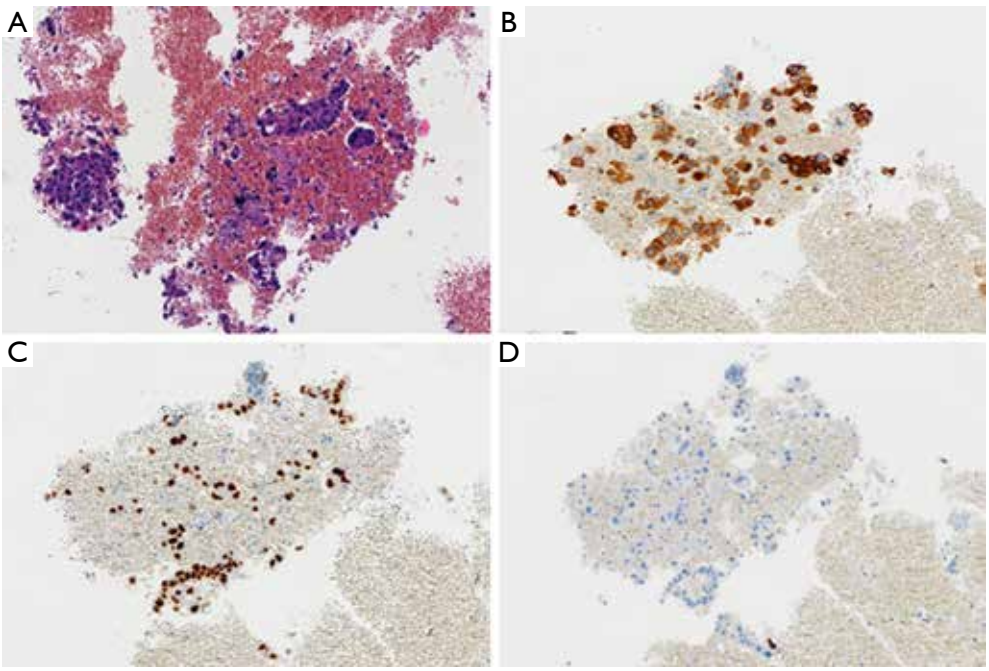


**Figure 2** Histological biopsy of a lymph node with a metastasis from a pulmonary adenocarcinoma. Tumor cells are grouped in cluster (A, ematoxilin & eosin, 100×) and are positive for cytokeratin 7 (B, immunostaining, 100×) and TTF1 (C, immunostaining, 100×), whilst are negative for p40 (D, immunostaining, 100×).

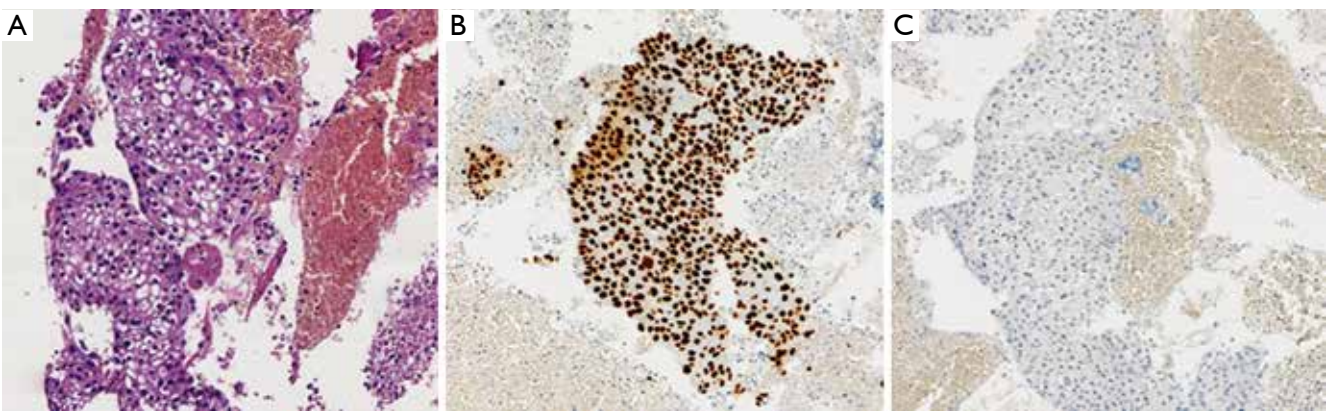


**Figure 3** Histological biopsy of a lymph node with a metastasis from a pulmonary squamous cell carcinoma. Tumor cells show the typical features of a squamous cell carcinoma (A, ematoxilin & eosin, 100×). The diagnosis is confirmed by the immunoreactivity for p40 (B, immunostaining, 100×) and the lack of TTF1 expression (C, immunostaining, 100×).

## Molecular testing

The vast majority of patients with non-small cells lung carcinomas (NSCLC) do not require surgical resection because of the advanced stage at clinical onset. For this reason, the unique specimen available for these patients is frequently represented by small cytological or micro-histological biopsy samples. On the other hand, an accurate and precise diagnosis (i.e., recognition of benign *vs.* malignant, primary *vs.* metastatic lesion and the NSCLC subtyping), together with the determination of predictive biomarkers, are mandatory for treatment selection. In this scenario, the major issue is to maximize all necessary information on cytological or biopsy specimen available.

 

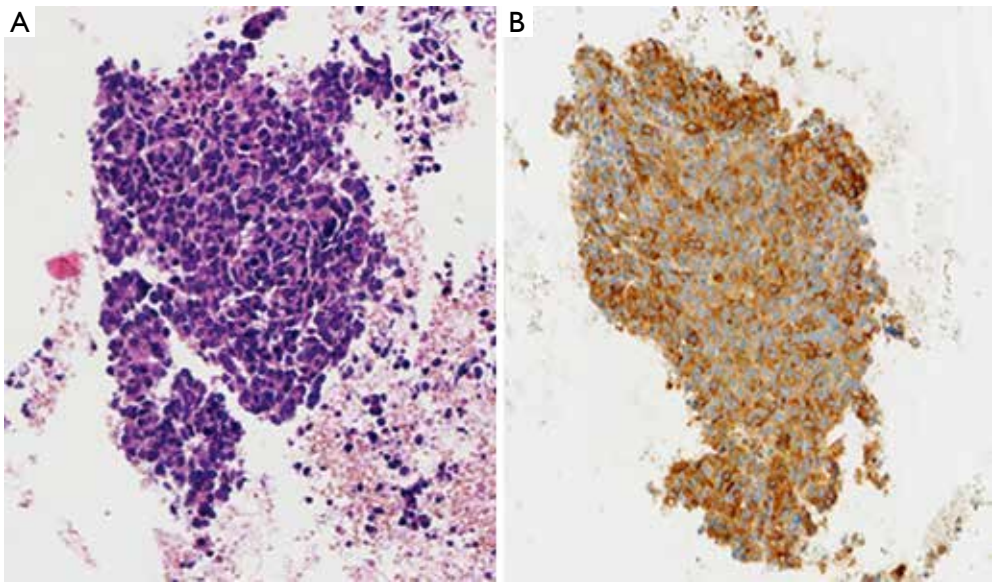


**Figure 4** Example of a metastasis form a poorly differentiated neuroendocrine lung carcinoma. Neoplastic cells are atypical with hyperchromic nuclei (A, ematoxilin & eosin, 100×) and show chromogranin A immunoreactivity (B, immunostaining, 100×).

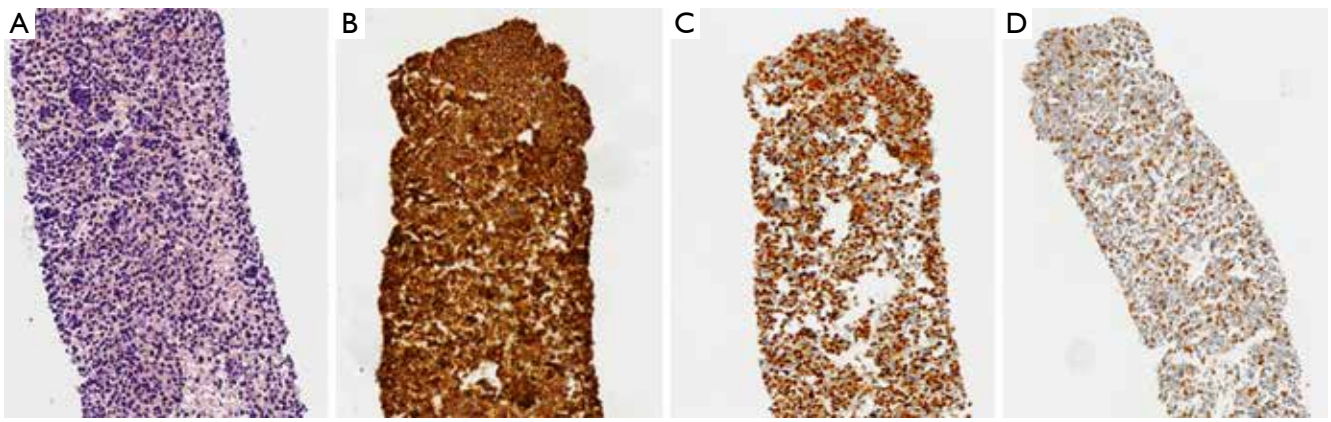


**Figure 5** Trans-bronchial biopsy of a mediastinal enlarged lymph node. Neoplastic cells are monomorphic showing a lymphoid appearance (A, ematoxilin & eosin, 40×). They are positive for CD20 (B, immunostaining, 40×) and cyclin D1 (C, immunostaining, 40×), while being negative for CD3, which shows some residual non-neoplastic T-lymphocytes (D, immunostaining, 40×). The final diagnosis was of mantle cell lymphoma.

Although performing diagnoses on small samples could be easy (in case of morphology-based adeno or squamous cell carcinoma features), in several cases of poorly differentiated or undifferentiated cancers, morphology does not allow a more precise classification and the discouraged term NSCLC-not otherwise specified (NOS) is used. However, major therapeutic advances in lung cancer field require a more precise histological subtyping for therapeutic purposes (13,14). The use of immunohistochemistry (IHC) in these cases is recommended because may add some information about a residual adeno- or squamous differentiation, increasing the refinement of diagnosis and avoiding the use of NSCLC-NOS term (15). Several biomarkers and diagnostic algorithms have been described in the last years and suggested for the most efficient NSCLC subtyping: nowadays, using a small panel of 2 to 4 biomarkers (i.e., TTF1, Napsin A, p40 and CK5/6 or CK7) the proportion of NSCLC-NOS diagnosis could

 

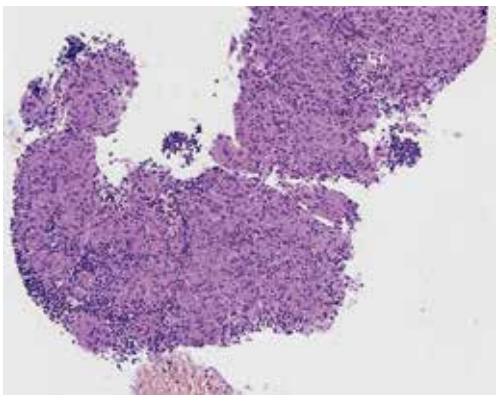

**Figure 6** Trans-bronchial biopsy of an enlarged lymph node. Normal tissue is replaced by epithelioid granulomas suggesting the diagnosis of sarcoidosis (ematoxilin & eosin, 40×).

be widely reduced (15,16). This is an important aim, since morphologically poorly differentiated carcinomas with an adenocarcinoma immunoprofile show the same overall survival of cases with clear morphological features of adenocarcinoma (17,18). Furthermore, the more and more precise molecular profiling of lung cancer has led to the discovering of an increasing number of new driver genes that could become drug target (19). Lung adenocarcinoma is the most studied in this direction because it is characterized by a highly druggable molecular profile. In fact, an increasing number of genes are described as oncogenic drivers and several drugs are developed for each of them (19). As a matter of fact, patients with an oncogenic driver mutation who receive targeted therapy have better survival than patients who do not receive targeted therapy or without an oncogenic driver (20). However, after a honeymoon period of response to therapy, acquired resistances can occur (21). The vast majority of cancers treated with target therapy harbor therapy-induced new genetic changes, in term of both acquisition and loss of gene alterations (22,23). Moreover, histological shift from well differentiated to poorly differentiated small cell cancer has been described as acquired resistance mechanism (23-25). Comprehensive molecular profiling of other more frequent lung cancer types including squamous and large cell carcinoma revealed a marked genomic complexity with less druggable alterations for the first and genetic features typical of other better differentiated carcinomas for the latter (26,27). Finally, with the advent of the target therapy, a new predictive role for IHC has been awarded. Indeed, IHC allows to visualize the presence and tissue distribution of the drug target at the protein level. For example in ALK test, the gene alteration produces a fusion protein which is easily detectable by IHC. To this end, two monoclonal antibodies have been developed and are commercially available: the clone 5A4 (Leica Biosystems Newcastle Ltd, Newcastle Upon Tyne, UK/Novocastra Laboratories Ltd., Newcastle Upon Tyne, UK, and prediluted Abcam, Cambridge, UK), and the clone D5F3 (Cell Signaling Technology Inc., Danvers, MA, USA) with high sensitivity, specificity and reproducibility, as compared to FISH technique. That's why the use of ALK IHC as screening test has been adopted in some countries and only tumors that are positive for ALK IHC, either weakly or strongly, should be referred to FISH for confirmation of a rearrangement (28).

A field in great expansion is the use of immunotherapy in combination with conventional therapy (29). Immune check-point is the receptor-ligand interaction that leads to a modulation of the tumor-induced immune response. The PD-1/PD-L1 interaction is one of the more widely studied because PD-L1 IHC expression on tumor cells has been associated with higher response rate to anti-PD-1/PD-L1 drugs, although some methodological issues have still to be resolved (30), such as the percentage of positive cells to be considered predictive of a satisfactory clinical response and the type of the primary antibody used.

In the last WHO 2015 (15), specific recommendations for pathologists about lung cancer classification in small tissue together with an algorithm for handling samples were published, including three major steps: the accurate diagnosis, the use of IHC for poorly differentiated NSCLC and the requirement of mutational assay. These guidelines imply that the tissue represents the major issue in advanced lung cancer pathology, with some technical aspects to keep in mind for pathologists: first of all the sample evaluation. Pathologist should be present during the sampling procedures to collect clinical information, to handle and prepare tissue sampling for a rapid onsite staining and ROSE which provides a real time evaluation of cytological specimen obtained with cytological sampling (see above). The use of ROSE permits to obtain sufficient tissue for molecular testing with high rate of success (31,32); in fact, although actually there is no evidence to recommend the use of ROSE in all the procedures, guidelines suggest that ROSE should be used when molecular testing is needed (12). A recent randomized trial study by Trisolini and coworkers showed that ROSE is associated with a 10% increase in the success rate of EBUS-TBNA for optimal lung cancer genotyping, with the advantage of reducing the number of re-biopsy because of the minimal tumor burden for

 

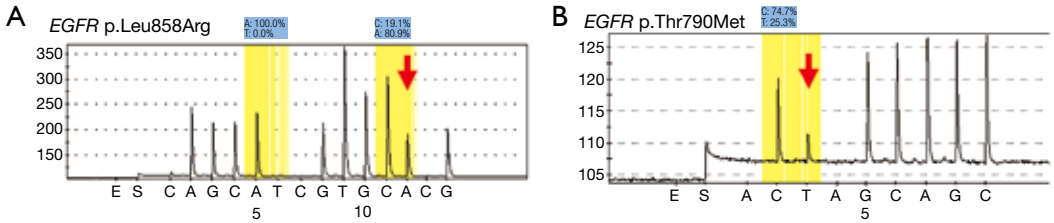


**Figure 7** EGFR pyrosequencing diagrams showing a case with an activating *EGFR* mutations in exon 21 (L858R) and a resistance mutation in exon 20 (T790M). Arrows show the point of the curve where the point mutation occurred.

molecular analysis (33). Finally, when the sample is processed according to routine management, the final sample should be evaluated for the assessment of the amount and quality of the neoplastic cells, necessary for the type and the number of molecular analysis required. At this step, a crucial issue is the choice of the marker to test, the choice of the optimal method to use and the interpretation of results according to guidelines. Nowadays, EGFR mutations and ALK translocation are the most predictive tests required for targeted therapies (34,35), but several other gene mutations (i.e., KRAS, BRAF, etc.) or alterations (i.e., ROS translocation, MET amplification, etc.), predictive of response or resistance to therapy, are also increasing in importance. According to specific gene alterations (mutation, translocation or amplification) a specific method should be used and appropriate tissue amount and quality are required. For example, *EGFR* mutation test requires an adequate amount of neoplastic DNA with respect to normal DNA to maximize the sensitivity of the sequencing method used (i.e., direct sequencing, pyrosequencing, etc. *Figure* 7) and for this reason a sample with an adequate percentage of neoplastic cell with respect to the normal counterpart is necessary. Cytological samples are generally characterized by few neoplastic cells in a background of normal cells: these few cells could be sufficient for a diagnosis of malignancy but not adequate for molecular analyses. To improve the availability and adequacy of cytological material and to avoid the poor neoplastic cellularity of certain cytological samples, an accurate microscopic manual microdissection could be performed in the cell block, smear or core biopsy and multiple sections from cell block could be used to increase the amount of extracted DNA. On the contrary, for ALK translocation assessment, a minimum of 50 neoplastic cells should be present in the same cut section according to the cut-off guideline of ALK translocation assessment based on 50 counted nuclei (*Figure 8*).

Recent guidelines (12) in the material acquisition and preparation to obtain adequate EBUS-TBNA specimens recommend as follows: (I) at least three needle aspirations per site for morphological diagnosis and a total of four passes per site when molecular testing is planned should be performed; (II) preservation of material for production of cell blocks or tissue core for morphological evaluation and for IHC for subtyping NSCLC, when needed, should be planned. There is no quality evidence to suggest the best solution (e.g., formalin, saline or Hank's solution) for cell block preparation and it should be chosen following consultation with local and molecular pathology colleagues; furthermore, no specific slide preparation and staining method (e.g., Wright-Giemsa, Papanicolau, rapid Romanowsky staining) is preferable to others, local expertise and practice should be considered when selecting the slide staining technique; (III) smears, cell block or core tissue can be useful for molecular testing (cell block or core tissue are indispensable to assess ALK translocation, while smear may be successfully used to evaluate the status of EGFR when cell block or tissue core are lacking).

The adequacy rate of EBUS-TBNA for molecular analysis depends on many factors: small sample size, tumor necrosis, sampling of nodal micrometastasis, and contamination of the samples with blood or bronchial cells (32). Several studies demonstrated that molecular analysis can be routinely performed on the majority of samples obtained by EBUS-TBNA with successful rate ranging from 89% to 98% (36,37). Other studies have demonstrated the feasibility of performing complete molecular tests, with or without IHC on EBUS-TBNA sample (38) with respect to other minimally (39) or more invasive procedures (31). However, a question remains: how much tissue is needed? It depends on the history of patient disease because after the diagnosis and IHC and EGFR/ALK analyses, it should be necessary to perform other molecular investigation (i.e., resistance molecular alterations) or the material should be used for patient clinical study enrollment.

Nowadays, we are still limited by the tissue availability because a single step assay is frequently used. In the near

 

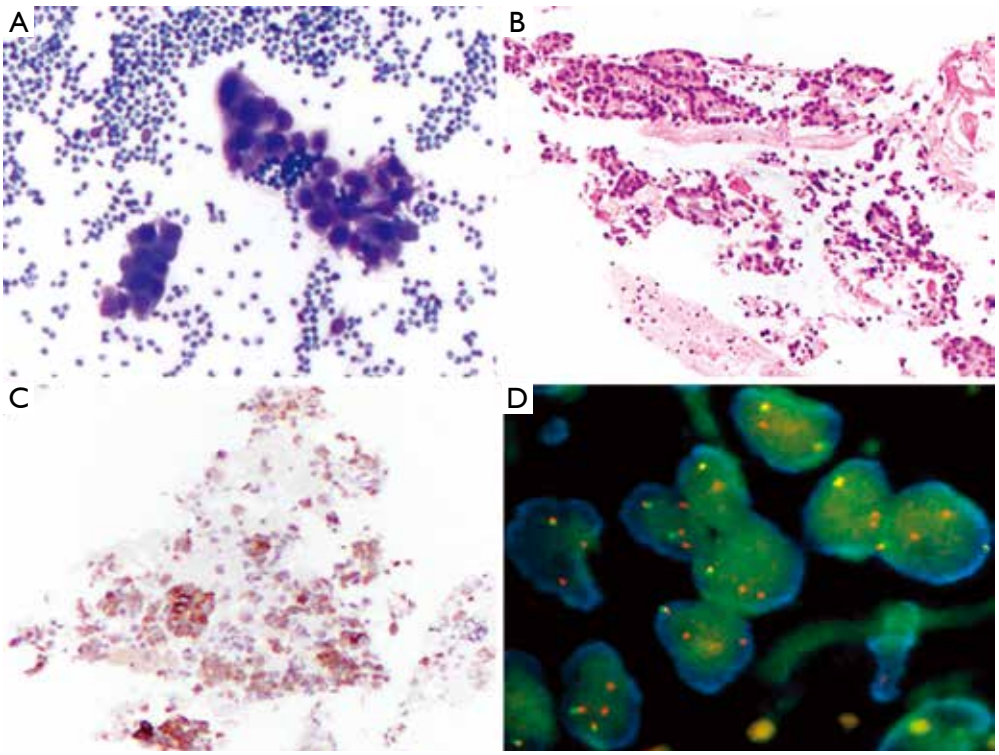


**Figure 8** Lung adenocarcinoma case with ALK determination. Smear specimen showing neoplastic epithelial cells arranged in pseudo-papillary structures (A, Giemsa stain, 200×). Cell block picture showing large amount of adenocarcinoma neoplastic tissue (B, ematoxilin & eosin, 100×). ALK immunohistochemistry (IHC) (clone 5A4) showing the majority of cells with moderate (2+) intensity and some cells with high (3+) intensity score (C, immunostaining 200×). ALK rearrangement was confirmed by FISH analysis (D, fluorochrome, 1,000×).

future, next generation comprehensive analyses will allow multiplex assays with higher speed, higher sensitivity, and high throughput diagnostic results using much minor amount of tissue (40). However, some validation, cost-efficiency and standardization issues should be resolved and they are much near than we think (41).

## Concluding remarks

EBUS-TBNA has emerged as an innovative technique which has been successfully introduced into our daily clinical practice giving several advantages including minimally invasive approach, safe, cost-effective, real time image guidance, and broad sampling capability. It has also acquired importance considering cases in which surgical procedures are contraindicated or unnecessary. Using EBUS-TBNA, we are now able to perform an accurate diagnosis associated to the identification of prognostic and predictive morphological and molecular markers. Considering that about 70% of patients with lung cancer are not candidate to surgery but they may be treated with new target therapies, the introduction of an increasing number of molecular tests will continue to transform our daily practice with the need of even more molecular determination using even low amount of adequate material. The use of EBUS-TBNA could satisfy those requests with safety and cost efficiency.

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## Footnote

*Conflicts of Interest*: The authors have no conflicts of interest to declare.

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Interventional Diagnostic Technique

# Biopsy and re-biopsy in lung cancer: the oncologist requests and the role of endobronchial ultrasounds transbronchial needle aspiration

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**Abstract:** As the leading cause of death worldwide, lung cancer has proven itself incurable in the advanced stages. For early stages, endobronchial ultrasounds transbronchial needle aspiration (EBUS-TBNA) is now considered the standard to assess mediastinal lymph node, to define the multimodality therapeutic approach. In recent years, EBUS-TBNA has extended its use also into metastatic and locally recurrent disease. New molecules, with specific mutations that give resistance to current target therapies, have made re-biopsy at disease progression an important assessment, with therapeutic and clinical implication. Here we present the oncologist's point of view on EBUS-TBNA in the staging process, at recurrence and progression.

**Keywords:** Endobronchial ultrasounds (EBUS); re-biopsy; T790M; lung cancer; review

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## Introduction

### *Lung cancer*

Lung cancer is one of the leading causes of cancer deaths worldwide. The main histological types of cancers are squamous cell carcinoma (SCC), adenocarcinoma (ADC), large cell carcinoma (LCC) and small cell lung cancer (SCLC). In Western countries, the ADC frequency is increasing (>50%), while SCC and small cell are significantly reduced (1).

Accurate staging of the disease is mandatory to determine the prognosis and appropriate treatment. The most significant treatment decision lies on the distinction between those patients who can benefit from surgical resection and those who should receive chemotherapy and radiation therapy or both (2).

## Biopsy

### *Diagnosis*

In case of suspected lung cancer, it is recommended a sequential approach that involves physical examination, radiogram of the chest, chest computed tomography (CT scan) with medium contrast enhancement, bronchoscopy, and cyto-histological definition of the lesion. For central lesions endoscopically visible, histological diagnosis is obtained through cyto-histological samples such as biopsy, brushing, transbronchial needle aspiration (TBNA). Peripheral lesions can be approached percutaneously. The transbronchial approach has lower incidence of complications (especially pneumothorax) and it provides the possibility, during the diagnostic procedure, to sample the lymph nodes by TBNA (3).

The clinical staging is usually performed with non-invasive diagnostic modalities, such as total body CT scan with medium contrast, and/or positron emission tomography (PET). The imaging obtained from these techniques is used to assess the primary lung malignancy, to characterize the mediastinal involvement and to search for distant metastases. Accurate mediastinal staging is a crucial part of the diagnostic workup of every patient with lung cancer, for its prognostic value and for planning optimal treatment. In many cases, the status of these nodes determines whether the disease is surgically resectable. The existence of metastatic contralateral adenopathy (N3) or distant metastasis (M1) contraindicates surgery. Patients with mediastinal ipsilateral lymph node metastasis (N2) may be considered for neoadjuvant therapy followed by surgery based on studies reporting improved survival with this treatment approach (2).

In patients with an abnormal mediastinum (lymph nodes enlargement at CT, with or without a PET increased activity), or with a radiologically normal mediastinum associated with a central lung tumor or with a N1 disease, histological samples of the suspected lymphonodular metastasis are required (4).

Mediastinoscopy and video-assisted thoracoscopy have been the methods of choice to invasively stage the mediastinum before the introduction of endoscopic ultrasounds needle aspiration techniques. Endobronchial ultrasounds transbronchial needle aspiration (EBUS-TBNA) is minimally invasive, safe and well-tolerated method to stage the mediastinum. Furthermore, because its accuracy and cost-effectiveness, endoscopic staging is now the recommended method for invasive mediastinal evaluation (5).

EBUS-TBNA has to be performed in moderate or deep sedation, with a needle of 21 or 22 gauge. The tissue sampling may be run with or without the pathologist's assessment in the endoscopic room (rapid on-site evaluation, ROSE); however, in the absence of ROSE a minimum of three separate steps to sample each lymph-node is suggested (6).

### *Relapsed disease*

Even patients with early disease are at relatively high risk of disease recurrence. Cisplatin-based chemotherapy regimens have decreased the risk of recurrence after surgery and provided modest survival gains. An updated meta-analysis from the non-small cell lung cancer (NSCLC) Collaborative Group demonstrated an average survival benefit of 5.4% at 5 years for patients with resected stage I to III disease (7).

Greater than 50% of disease recurrences occurring after surgery for early stage NSCLC involve local sites (8); detecting mediastinal involvement is crucial for the curative treatment of recurrent NSCLC (9).

EBUS-TBNA can be used for the diagnosis of mediastinal recurrence as a non-invasive approach.

Guidelines recommend the acquisition of additional samples to perform not only the diagnosis of relapse but also additional molecular analysis (6).

### *Role of molecular profile*

In recent years, studies on molecular characteristics of lung cancers showed a role for specific genes that proved to be important therapeutic targets. In NSCLC (especially in 10–15% of the ADC of Caucasian patients and in 40% of Asian patients) activating mutations of EGFR (exons 18, 19, 20 and 21) have been identified. The presence of these mutations is the most important predictive factor for targeted therapies with specific EGFR tyrosine kinase inhibitors (9,10). In fact, only patients with EGFRm+ have good responses to the treatment with first-generation EGFR TKIs, such as erlotinib and gefitinib (11), with improvements in progression free survival, overall response rate and clinical benefit.

Another important molecular alteration that has been documented for ADC is the rearrangement of anaplastic lymphoma kinase (ALK) that activates a specific receptor tyrosine kinase involved in the processes of proliferation and cell survival; it is found in approximately 3–7% of ADC (12,13).

The determination ALK rearrangement is necessary to select patients for treatment with specific tyrosine-kinase inhibitors [crizotinib and ceritinib, approved by European Medicines Agency (EMA) for patients pre-treated with crizotinib] (14,15).

Other molecular alterations that can be tested in ADC, with promising therapeutic implications are the rearrangement of the *ROS1* gene (about 1–2% of ADC) and RET gene. Activating mutations of BRAF (V600E is that non-V600E), amplification of HER2, mutation of PI3KCA and PTEN, amplification and mutations of PDGFR are molecular changes that could have future therapeutic implications in SCC (16).

Currently, only EGFR and ALK represent molecular targets with specific available target therapy and therefore

 

they must be tested in case of metastatic disease. While EGFR and KRAS mutations are usually mutually exclusive, the ALK rearrangement was detected in 1–2% of EGFR mutated tumors (17). The role of KRAS mutation is still uncertain. Therefore, the determination of KRAS remains optional.

EGFR and ALK analysis can be performed on surgical specimens, cytology, and biopsy of the primary tumor and/or metastases.

## Re-biopsy

Re-biopsy is a growing trend in oncology. This is due to many factors, chiefly: (I) finer molecular characterization, through next generation sequencing (18); (II) new drugs capable of overcoming specific resistance mutations (19); (III) less invasive technique to obtain tissue specimen (20). Up until recent years, re-biopsy was a practice confined to cancer that, even in advanced stages, were still managed by surgeons, and/or presented easily accessible sites, such as prostate cancer and breast cancer (21). Things started to change with the advent of target therapy, with many clinical trials having mandatory re-biopsy, and also with the development of less invasive and safer technique to collect tissue specimens. Still, for some years the interest for re-biopsy was confined mostly to research, without it entering clinical practice. It is only in very recent times that re-biopsy is acquiring a growing importance, with practical implication not only for the clinician but also for the patient. As of today, awaiting validation of the liquid biopsy, re-biopsy represents the only instrument to discover specific transformation and targetable mutation in patient experiencing progressive disease.

### *Histology shift*

A known mechanism of resistance to therapy, especially tyrosine kinase inhibitors targeting EGFR, is the transformation of NSCLC, generally ADC, in SCLC (22). One of the first cases of resistance to erlotinib due to the transformation in SCLC was described in 2006 (23). Since then, several others have been reported. Case series give variable percentage for this phenomenon, between 5% and 14%, among patients with EGFR mutated ADC (24,25): although rare, it can still affect at least one patient in twenty. The mutation of the driver gene EGFR, still present after histological shift supports the hypothesis that these are transformations regarding the same tumour and not the growth of a new neoplasm (26). Current understanding still leaves some open questions: is the SCLC already present at diagnosis, in combined-histology tumour, and grows under the selective pressure of therapy for the NSCLC? Or is it a transformation at the molecular level, with candidate gene RB1 as a key player that triggers the histological shift (22)? While further studies enlighten the basis of this transformation, the clinician should keep this event in mind, considering re-biopsy for those patients affected by ADC with rapid progression or unusual behaviour, especially EGFR-mutated ones. The importance of pathological demonstration of a histological shift is due to the mixed response to anti-EGFR observed in these patients (27,28), thus recommending SCLC treatment as the main therapeutic option.

### *Acquired resistance*

A common concept, in microbiology as in oncology, is that a prolonged exposition to certain drugs can select a resistant population, either a bacterium or a neoplastic cell. In the cytotoxic era, the usual strategy to overcome this phenomenon was to combine different chemotherapeutics, with only partial success, limited to haematological malignancies. Acquired resistance was also the limit to the great hopes of target therapy: the majority of patients experience, after a variable interval of time, the ensuing of a resistant clone that causes disease progression. The silver lining to this event is that our deeper understanding of molecular biology has made it possible in some cases to identify the specific mechanisms behind acquired resistance. One of the finest examples is T790M in EGFR mutated lung ADC (29): this mutation is one of the main mechanism of acquired resistance, generally present only in a minority of cells at diagnosis, and much more expressed at disease progression. Beside identifying the mutation, we now have also new tyrosine kinase inhibitors that specifically target T790M, osimertinib (19). In the following years, molecular profiling will become a key part of patient re-evaluations, along radiological assessments and physical examinations, making re-biopsy at progression mandatory.

## Conclusions

Lung cancer represents one of the leading causes of death worldwide, especially in the advanced stages of the disease.

For early stage lung cancer, EBUS-TBNA represents a fundamental evaluation to assess correctly mediastinal

 

involvement. The extent of lymph node invasion is key information, for the oncologist as well as for the surgeon and the radiotherapist, to better define the therapeutic approach.

In recent years, because of better understanding of molecular biology, EBUS-TBNA has gained a role also in the metastatic and locally recurrent disease. New target therapies, aimed at specific resistance mutation, have made re-biopsy a usual assessment at disease progression. This is of paramount importance for the oncologist, to detect histological shift or specific mutation such as T790M for EGFR-mutated ADC. While re-biopsy was, up until recent years, mainly confined to research, as of today it has therapeutic implication and actively change patients' outcome.

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## Footnote

*Conflicts of Interest*: The authors have no conflicts of interest to declare.

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Interventional Diagnostic Technique

# Endobronchial ultrasound-transbronchial needle aspiration for mediastinal staging of non-small cell lung cancer: variability of results and perspectives

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**Abstract:** The remarkable value of endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA) for mediastinal staging of non-small cell lung cancer (NSCLC) is recognized worldwide. Reports from different centers however show considerable variation of EBUS-TBNA performance in terms of diagnostic yield, sensitivity and negative predictive value (NPV). Interpretation of EBUS-TBNA diagnostic efficacy requires clarifying whether the technique is used for purely diagnostic purpose or mediastinal staging, recognizing that different study groups may be inherently heterogeneous and that numerous factors may impact on the procedure outcomes. Review of these factors indicates that the prevalence of N2/N3 disease, the thoroughness of mediastinal sampling and >3 needle passes per target lymph node (LN) [in the absence of rapid on-site evaluation (ROSE)] influence the procedure outcomes, while many details in the sample preparation technique are unlikely to impact on the results and should be left to the proceduralists' preference. Generalized use of a standardized database for prospective collection of relevant EBUS-TBNA data would allow reporting institutional results by sub-groups of N2/N3 disease prevalence and thoroughness of staging, and would help establishing quality standards for the procedure.

**Keywords:** Endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA); lung cancer; mediastinal staging; diagnostic performance

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## Introduction

Over the last 15 years endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA) has emerged as the technique of first choice for biopsy of mediastinal lymph nodes (LN). In patients with suspect/known non-small cell lung cancer (NSCLC), the primary indications of EBUS-TBNA are tissue confirmation of computed tomography (CT)-enlarged or positron emission tomography (PET)-positive mediastinal LN, and systematic mediastinal LN staging, a major determinant of tumor resectability and prognosis. In selected patients with suspected lung cancer, the EBUS-TBNA technique may be used as first-line tissue sampling procedure; if this shows N2/N3 invasion and identifies the lung cancer subtype, simultaneous diagnosis and mediastinal staging of the disease can be obtained, and the duration and cost of the diagnostic process are reduced. Moreover, it may be helpful averting lung tumor biopsy when this is technically difficult, or high-risk (e.g., emphysematous patients), or inappropriate (e.g., patient unfit for surgery).

EBUS-TBNA for diagnosis of malignancy in mediastinal nodes is a highly effective technique, with a low (about 1%) rate of complications, almost exclusively minor (1-5). In the context of NSCLC diagnosis and staging, reports from different centers show considerable variation of EBUS-TBNA diagnostic yield (71–99%) (5-9), and of

**Table 1** Factors possibly affecting the efficacy of EBUS-TBNA for mediastinal staging of NSCLC

| Factors |
|---|
| Prevalence of N2/N3 disease |
| Patient sedation method |
| Sample acquisition and preparation technique |
| Thoroughness of mediastinal staging |
| Learning curve and volume |

EBUS-TBNA, endobronchial ultrasound-transbronchial needle aspiration; NSCLC, non-small cell lung cancer.

key performance indices, namely sensitivity (46–97%) and negative predictive value (NPV) (60–99%) (10). Discrepancies in the reported efficacy of the procedure and lack of generally accepted benchmarks for EBUS-TBNA outcomes complicate the comparison of findings across institutions. The performance indices of EBUS-TNBA mediastinal staging may be influenced by numerous factors (*Table 1*), the most relevant of which are the N2/N3 disease prevalence and the thoroughness of staging (10-12). We will focus on these factors, as they are important for interpreting differences in the procedure efficacy among institutions and for establishing quality standards of EBUS-TBNA practice.

### *Prevalence of N2/N3 disease*

Prevalence of N2/N3 disease in the tested population of NSCLC patients impacts on the diagnostic performance of EBUS-TBNA (12-14). As indicated by the American College of Chest Physicians (ACCP) meta-analysis of EBUS-TBNA mediastinal staging, which included a total of 2,756 procedures (10), the prevalence of N2/N3 disease directly correlates with diagnostic sensitivity and inversely correlates with NPV: with <20% prevalence of mediastinal lymph nodal metastases, EBUS-TBNA showed 78% sensitivity and 96% NPV; with ≥80% prevalence, 96% sensitivity and 83% NPV (12). Because prevalence of mediastinal nodal metastasis is a major bias, it is not surprising that EBUS-TBNA diagnostic performance varies among series with different N2/N3 disease prevalence, and staging results are difficult to translate from one study to another (15). For meaningful assessment of the quality of EBUS-TBNA outcomes, it is necessary to know the prevalence of mediastinal nodal metastasis in the examined population (12).

### *Patient sedation method*

Patient sedation for conducting EBUS-TBNA can be obtained by conscious sedation (usually with fentanyl and midazolam) or by general anesthesia (with propofol and oro-tracheal tube/laryngeal mask). Proponents of general anesthesia maintain that abolishing respiratory variation and cough facilitates sampling when target nodes are small and the patient is scarcely collaborating. Whether the type of sedation makes a difference in the procedure performance has been debated. There are no randomized studies documenting a superior diagnostic performance of EBUS-TBNA with either sedation method. In a retrospective multicentric study of EBUS-TBNA that we recently carried out, sampling adequacy rate was similar with general anesthesia and with conscious sedation (87% and 92%; P=0.09) (16), in agreement with the conclusion of current systematic literature reviews indicating that the choice of sedation method can be left to the operator preference (17,18).

### *Sample acquisition and preparation techniques*

EBUS-TBNA procedures are generally performed with 21-Gauge (G) or 22-G needle. After reviewing the evidence from studies comparing the diagnostic yield of EBUS-TBNA with these two needle sizes, Wahidi *et al.* concluded that either size is an acceptable option (18). Some authors prefer the larger-bore needle (21-G) because it provides more tissue material, which can be used for histology and for molecular studies. In the context of potentially operable NSCLC, for thorough assessment of mediastinal node involvement it is generally agreed that 3 needle passes per target LN should be obtained, if rapid on-site evaluation (ROSE) of samples is not used (17-20). Each pass should include 5 to 15 needle agitations within the target node (18), with or without suction (21). The important indication that three is the optimal number of punctures per target LN was provided by the study of Lee *et al.* who evaluated by EBUS-TBNA 163 LN stations in 102 NSCLC patients (19). In that study, each target LN was punctured four times, however after three passes the sample adequacy was 100%; the sensitivity for differentiating malignant from benign LN stations was 95.3% and did not increase with four passes (19).

The most frequently used techniques for EBUS-TBNA specimen acquisition and processing are cytology slides, cell-block, core-tissue, combination of cytology slides and

 

**Table 2** Mean number of lymph node stations biopsied per patient, diagnostic yield and sensitivity in recent series of EBUS-TBNA procedures for mediastinal staging of lung cancer

| Authors | Year | Patients (n) | LN stations biopsied per patient (n) | Diagnostic yield (%) | Sensitivity (%) |
|---|---|---|---|---|---|
| Yasufuku *et al.* (6) | 2011 | 153 | 2.8 | 71 | 94 |
| Lee *et al.* (5) | 2012 | 73 | 1.9 | 99 | 81 |
| Tian *et al.* (7) | 2013 | 185 | – | 99 | 95 |
| Nakajima *et al.* (8) | 2013 | 438 | 2.2 | 91 | 97 |
| Figueiredo *et al.* (9) | 2015 | 149 | 2.7 | 87 | 96 |
| Median | – | – | 2.5 | 95 | 95 |

EBUS-TBNA, endobronchial ultrasound-transbronchial needle aspiration; LN, lymph nodes.

core-tissue, combination of cytology slides and cell-block. Only few studies comparing these techniques have been published and there is no consensus on the optimal method of specimen preparation (17). In our institute, a study was carried out to identify the best performing technique among those currently available for EBUS-TBNA specimen acquisition and processing; we found that the diagnostic yield with cytology smear and with core-tissue were high and similar (81% *vs.* 87%; P=0.44) (22). In the literature, like in our study, the comparison of cytology smear, core-tissue and cell-block methods showed that no single method is superior to the others (23,24). Notably, we attained the highest diagnostic yield (100%) by combining two methods (cytology slides and core-tissue, or cytology slides and cell-block); however the use of two methods in combination is expensive and time-consuming (22). Considering that familiarity and expertise with a technique impacts on the final results, choice of needle size to use for EBUS-TBNA and of specimen processing method should be left to the operator experience and preference (17).

The influence of ROSE on quantity, quality and yield of EBUS-TBNA samples in patients with known or suspect lung cancer has been the object of a systematic literature review by Van der Heijden *et al.* (17). These authors provided guidelines for specimen acquisition and preparation, indicating that ROSE does not modify EBUS-TBNA diagnostic yield, nor does it affect the number of needle passes, the duration of the procedure, and the complication rate. However, when EBUS-TBNA was the first diagnostic procedure in patients with suspect lung cancer, ROSE was found to reduce the number of additional procedures (25,26).

In conclusion, the sample acquisition and preparation technique are unlikely to impact on EBUS-TBNA diagnostic yield, provided that at least three needle passes per target LN are done (in the absence of ROSE of samples).

### *Thoroughness of mediastinal staging*

Mediastinal nodal staging is a critical step for determining the best treatment of NSCLC. For this purpose, until recently, mediastinoscopy was the generally accepted gold standard, with about 80% sensitivity and about 90% NPV in confirming N2/N3 disease (10). Pretreatment mediastinal staging of NSCLC has been revolutioned by the advent of EBUS-TBNA, a procedure characterized by sensitivity equivalent to that of mediastinoscopy (*Table 2*), but less invasive, less risky, and obviating the need for general anesthesia (10). As a result, in recent years EBUS-TBNA has almost replaced surgical staging by mediastinoscopy in many centers (6,12).

It has been remarked that the reliability of mediastinal staging with EBUS-TBNA, as with other staging techniques, largely depends on the thoroughness of the procedure (10,11,13,19). Thorough mediastinal staging by mediastinoscopy or EBUS-TBNA is best performed with systematic sampling, which requires biopsy of representative LNs in stations 2R, 2L, 4R, 4L, 7 (10). Current guidelines recommend aiming to target at least 3 LN stations (typically 4R, 4L and 7), including those LNs with CT/PET features suggestive of metastasis (6,10,12,20).

Despite these recommendations, in real life the EBUS-TBNA practice is generally characterized by <3 sampled mediastinal nodal stations per patient (27,28), for multiple reasons that include difficult punture of LNs, bleeding, restless patient, longer procedure, ROSE showing metastasis early in the procedure. In early reports of EBUS-TBNA, the median number of mediastinal LN stations

 

sampled per patient was <2 (5), a result that has improved in more recent series (*Table 2*) and that needs further improvement (12). Limited thoroughness of mediastinal staging likely contributes to the variability of EBUS-TBNA staging accuracy in different studies.

Whether mediastinoscopy should be routinely done after negative EBUS-TBNA remains controversial (6,29-31). The prospective randomized trial of EBUS-TBNA *vs.* mediastinoscopy for staging of NSCLC performed by Yasufuku *et al.* showed equivalent effectiveness of the two techniques in determining the true pathologic N stage (6). However, for EBUS-TBNA negative cases at high risk of lung cancer metastases, the current ACCP and British Thoracic Society (BTS) guidelines recommend mediastinoscopy or other surgical approaches to obtain mediastinal nodes' biopsy (10,32).

### *Learning curve and volume*

The skill and experience of the operator, usually an interventional pulmonologist or a thoracic surgeon, influence EBUS-TBNA results. For acquisition of the EBUS-TBNA technique the ACCP, the European Respiratory Society and the American Thoracic Society recommend an initial training of 40–50 supervised procedures. In addition, 20 procedures per year are suggested for maintaining competency (33,34). The speed of learning the EBUS-TBNA procedure varies for different operators, either highly experienced or trainee bronchoscopist (35,36). Furthermore, improvements in performance are reported even after doing 200 procedures, indicating that volume affects the quality of EBUS-TBNA outcomes (36,37). In a recent EBUS-TBNA workshop held in October 2016 in Varese, Italy, a multicentric study was presented that included 485 EBUS-TBNA mediastinal staging procedures in NSCLC patients and compared the outcomes of the five participating units. In all those centers, the prevalence of N2 disease was >70%, but wide variation was found in the rate of inadequate sampling (0–29%) and in the rate of false-negative (FN) EBUS-TBNA results (4–11% of all adequate samples); interestingly, the center with the largest EBUS volume (50 procedures/year) showed the lowest FN rate (4%), and the FN rate inversely correlated (P<0.009) with the volume of procedures in the individual centers (38).

To date, the length of the learning curve for EBUS-TBNA proficiency is unclear and is probably different for each operator; no diagnostic yield cut-off has yet been established to define the standard capability of performing EBUS-TBNA.

## Perspectives

### *Molecular testing*

Improvement of target therapy makes tumor subtyping and genotyping increasingly necessary for management of lung cancer; obtaining from EBUS-TBNA a specimen suitable for molecular analysis is therefore important. The success in performing molecular tests on TBNA samples depends on the absolute number and percentage of malignant cells present in the sampled material, on quality of cell preservation and on type and sensitivity of the test itself (17,39). Recent reports from high-volume centers indicate that 72–97% of EBUS-TBNA samples are appropriate for testing the most frequently used prognostic markers of lung cancer, namely EGFR, ALK and KRAS (17,25,39,40). Both smear and cell block preparation, or core tissue, can be utilized for molecular testing (17,23); however, while EGFR and KRAS status can be determined using all three specimen preparation techniques, the ALK translocation is best assessed using cell block and core tissue (17). Cell block and core tissue are currently judged to be the best material for molecular analysis, suggesting to privilege these two processing methods if possible.

In advanced lung cancer patients whose treatment may vary on the molecular results, a recent randomized trial showed that ROSE increased by 10% (although not significantly) the success rate of EBUS-TBNA for genotyping, and reduced the number of redo procedures and of further investigations (25).

No randomized studies are available on the influence of needle size, use of suction and type of sedation on the adequacy of samples for molecular testing. In patients undergoing EBUS-TBNA for diagnosis and/or staging of suspect/known NSCLC, more than three needle passes may be necessary to obtain sufficient material for molecular testing (18,30); it is therefore recommended that additional samples be obtained for EGFR and ALK testing (41).

### *Quality standards*

The vast majority of published EBUS-TBNA studies consist of retrospective cohort reports without pre-defined standards and represent real life practice. Efforts should be made to shift from targeted sampling of enlarged or PET

 

positive nodes to systematic mediastinal node sampling (12); this will likely improve the thoroughness of staging, the accuracy of EBUS-TBNA and the interpretation of local performance data. EBUS-TBNA guidelines have been made available from expert centers (17,18) but quality standards for assessment of EBUS-TBNA performance have not yet been established, with the exception of the 2014 BTS Quality Standard that states a minimum of 88% sensitivity for mediastinal staging of suspected NSCLC (42). EBUS-TBNA practice needs to be standardized to ensure the best outcomes in all institutions (12). To this effect, the performance of staging could be measured by the sensitivity and NPV metrics, stratifying the population by prevalence of N2/N3 disease, because the latter influences both sensitivity and NPV. The ACCP guidelines on NSCLC staging classify patients into four groups (A, B, C, D), according to the index staging CT scan of the chest (10); this classification correlates with N2/N3 disease prevalence and may be used to define standards for nodal staging and for comparison of EBUS-TBNA outcomes across centers (12). Importantly, for meaningful comparison of EBUS-TBNA results, the data should be gathered prospectively, because those retrospectively collected are frequently uncertain as to the indication to perform EBUS-TBNA (diagnosis *vs.* mediastinal staging), the prevalence of N2/N3 disease, and the exact LN stations successfully sampled. An important step forward will be made when the use of a standardized database for prospective collection of relevant EBUS-TBNA data will be generalized (12).

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## Footnote

*Conflicts of Interest*: The authors have no conflicts of interest to declare.

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Interventional Diagnostic Technique

# The role of endobronchial ultrasound versus mediastinoscopy for non-small cell lung cancer

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**Abstract:** This review provides an update on the current role of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and mediastinoscopy (Med) in assessment of patients with non-small cell lung cancer (NSCLC). Invasive mediastinal lymph node (LN) staging is the major application for both of these techniques. Up until recently, Med was the gold standard for invasive mediastinal LN staging in NSCLC. However, EBUS-TBNA has shown to be equivalent, and in some studies better than Med for invasive staging of lung cancer. EBUS-TBNA offers access to N1 LNs and development of the thin convex probe EBUS (TCP-EBUS) will expand EBUS-TBNA access from the paratracheal region and central airways to more distal parabronchial regions allowing for more extensive N1 LN assessment and sampling more distal lung tumors. EBUS-TBNA is more cost-effective than Med and it is currently recommended as the test of first choice for invasive mediastinal LN staging in lung cancer. Confirmatory Med should be performed selectively in patients with high pretest probability of metastatic disease. Addition of esophageal ultrasound fine needle aspiration (EUS-FNA) may increase diagnostic yield of EBUS-TBNA mediastinal staging. Both Med and EBUS-TBNA can be used in primary lung cancer diagnosis, restaging of the mediastinum following neoadjuvant therapy and in diagnosis of lung cancer recurrence. In the future, a combination of EBUS-TBNA with or without EUS-FNA and Med is most likely going to provide the most optimal invasive assessment of the mediastinum in patients with lung cancer. The decision on test choice and sequence should be made on a case-by-case basis and factoring in local resources and expertise.

**Keywords:** Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA); mediastinoscopy (Med); lung cancer

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## Introduction

Lung cancer is the leading cause of cancer mortality worldwide (1). Despite evolving knowledge of lung cancer, its molecular genetics and improved ways of detection, the overall 5-year survival is still poor at approximately 18% (1). Accurate staging of patients with lung cancer is important as it determines the treatment and affects the outcome. Assessment of patients with non-small cell lung cancer (NSCLC) includes non-invasive staging [i.e., computed tomography (CT) of the chest, PET-CT, MRI of the brain] and invasive staging [mediastinal lymph node (LN) sampling].

In lung cancer patients, the role of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and mediastinoscopy (Med) centers on

 

invasive evaluation, specifically diagnosis and staging. The techniques also have a role in lung cancer restaging following neoadjuvant therapy in patients with N2 disease considered for a definitive surgical management, and detection of lung cancer recurrence.

In this article, we discuss the current role of EBUS-TBNA and Med in assessment of patients with NSCLC.

## EBUS-TBNA and Med—role in lung cancer staging

Mediastinal staging in patients with NSCLC is a crucial step, offering prognostic information and guiding management. Detection of mediastinal nodal metastases can prevent futile surgeries. The non-invasive staging improves detection of intra- and extra-thoracic metastases, however, it cannot provide a definitive tissue diagnosis and is associated with relatively low sensitivity, specificity and high false positive and negative rates (2-8). Thus, CT chest and PET-CT "positive" results should be confirmed pathologically by invasive pre-operative staging (2,9). In addition, invasive mediastinal LN staging is indicated in patients with: (I) tumors >3 cm in size; (II) central tumors (central third of the hemithorax); (III) distinct enlargement or FDG avid N1 LN (2,9,10). Invasive mediastinal staging is also important in non-surgical candidates with clinical Stage IA disease considered for stereotactic body radiotherapy (SBRT) or ablative therapy [i.e., radiofrequency ablation (RFA)] in order to rule out N1 disease which would prelude use of these therapies (2).

Until just over two decades ago, mediastinal LN staging was performed with the use of bronchoscopic technique of a blind conventional TBNA and surgical invasive techniques including: Med, specifically cervical Med and less commonly, left anterior mediastinotomy (a.k.a. Chamberlain procedure). In addition, extended cervical Med, and more recently, video-assisted thoracoscopic surgery (VATS) and "supermediastinoscopies", including transcervical extended mediastinal lymphadenectomy (TEMLA) and video-assisted mediastinal lymphadenectomy (VAMLA) have become available (11,12). EBUS-TBNA has become available for mediastinal LN staging in the last 14 years. All surgical techniques require general anesthesia.

### *Surgical mediastinal LN staging*

Med allows access to the upper paratracheal (stations 2R and 2L), lower paratracheal (stations 4R and 4L), anterior subcarinal (station 7) as well as hilar (stations 10R and 10L) LNs. Med cannot access the pulmonary ligament (station 9), paraesophageal (station 8), posterior subcarinal (station 7), and the aorto-pulmonary window (APW; stations 5 and 6) LNs. The video-assisted Med has now replaced the traditional Med in majority of thoracic surgery centers, increasing procedure safety and diagnostic performance in lung cancer staging (2). Anterior mediastinotomy (a.k.a Chamberlain procedure) allows access to station 5 and 6 LNs via the left second intercostal space (13). Reported sensitivity and negative predictive value (NPV) of anterior mediastinotomy in assessment of AP window LNs is 78% and 91% respectively (2). Extended cervical Med introduced by Kirschner in 1971, and popularized by Ginsburg, allows access to levels 5, 6, 2, 4 and 7 (14-16). Reported sensitivity of extended Med ranges from 71% to 81% while NPV is 91% (13). VAMLA allows access to bilateral paratracheal and subcarinal LNs (17). VAMLA sensitivity in lung cancer staging is: 0.96 (95% CI, 0.81–99.3); specificity, 1 (95% CI, 0.97–1.00); PPV 1 (95% CI, 0.87–1.00); NPV 0.99 (95% CI, 0.95–0.99); and diagnostic accuracy, 0.99 (95% CI, 0.96–0.99). TEMLA is an open technique, allowing access to stations 1, 2R, 2L, 3a, 4R, 4L, 5, 6, 7 and 8 LNs. Large number of nodes can be removed (mean 43; range, 26–85) (11,12). Reported sensitivity and NPV of TEMLA in detection of mediastinal LN metastases is 0.9 and 0.95, respectively. In contrast to other surgical mediastinal sampling methods, TEMLA and VAMLA offer complete lymphadenectomy (17). However, the high rate of complications (6.0–13.2%) make use of both VAMLA and TEMLA unpopular given development of endoscopic techniques with comparable diagnostic yield but much better safety profile and shorter procedure duration (11,12,17,18).

In this review, all Med data presented pertain to video assisted-cervical Med (the most commonly used surgical mediastinal assessment modality), unless specified otherwise.

In mediastinal LN staging of primary lung cancer, Med yield depends on LN location and operator skills (19,20). In a recent systematic review assessing Med performance in 995 patients with clinical N0 to N3 disease, Med sensitivity was 89% and NPV of 92% (2).

Med is an invasive procedure performed in an operating room. It requires general anesthesia. A transverse incision is made above the sternal notch to access the paratracheal fascia. Video mediastinoscope is then inserted into the mediastinum after blunt digital dissection and palpation of the mediastinal vessels with further blunt dissection to access the mediastinal LNs. Generally, Med is a safe

 

procedure, performed in outpatient setting. Reported complication rate is up to 2.5%, including a pneumothorax, infection and injury to the major mediastinal vessels (which can lead to a life threatening bleeding), peripheral nerves (which can result in vocal cord palsy), bronchi and the esophagus. Mortality has been reported at 0.08% in relation to vascular injury (21). The procedure is contraindicated in patients with tracheostomy, severe cervical spine arthritis or instability that prohibits neck extension. Mediastinal adhesions may make a repeat Med challenging (21-23).

### *Endoscopic mediastinal staging with EBUS-TBNA*

Introduction of radial probe endobronchial ultrasound (RP-EBUS) in the early 1990's, has introduced the idea of less invasive mediastinal LN staging in lung cancer (24-27). Besides its role in diagnosis of peribronchial lesions (28,29) RP-EBUS has been used to guide TBNA in patients with mediastinal lymphadenopathy and in lung cancer mediastinal LN staging. Diagnostic yield of RP-EBUS guided TBNA of mediastinal LNs ranged between 72% and 80% [in a population with high prevalence of mediastinal nodal metastasis (86%)] (27,30). However, it wasn't until the early 2000's, and introduction of convex probe EBUS (CP-EBUS) that mediastinal LN staging in lung cancer has undergone a revolutionary change (31,32).

CP-EBUS is a flexible bronchoscope integrated with a convex transducer at the tip which scans parallel to the insertion direction of the bronchoscope. The outer and inner diameters of the insertion tube are 6.9mm and 6.2mm, respectively. Incorporation of EBUS at the tip of a flexible bronchoscope allows for real-time TBNA of the visualized structures (LNs, tumors). The ultrasound probe has B-mode and power color Doppler capabilities, allowing differentiation of LNs from vascular structures. In addition, the newer EU-ME2 processor (Olympus) is equipped with the elastography function. Elastography allows for real time assessment of LN deformability (which may be altered in a pathological LN) taking advantage of the tissue distortion caused by the compressions or vibrations generated by the heartbeat or vascular pulsations) (33). Elastography may offer a useful non-invasive adjunct to endosonographic LN assessment, pointing out the areas which are more likely to be involved with tumor, for a more directed TBNA (34).

Similar to Med, CP-EBUS can access station 2R, 2L, 4R, 4L and 7 LNs. Posteriorly and deep located station 7 LNs may not be readily accessible to Med, resulting in false negative results, but can be easily assessed with EBUS-TBNA (19,35). EBUS-TBNA can reach N1 LNs, including the hilar (station 10), interlobar (station 11) and some of the lobar LNs (station 12) which are not accessible by Med.

Neither EBUS-TBNA nor Med can access prevascular (3A), sub-aortic (station 5), para-aortic (station 6), para-esophageal (station 8) and pulmonary ligament (station 9) nodes.

EBUS-TBNA is a safe procedure, with an average complication rate of 1.23% (95% CI, 0.97-1.48%). Reported complications include: hemorrhage (0.68%), infection (0.19%) (mediastinitis, pneumonia, pericarditis, cyst infection, sepsis) pneumothorax (0.03%). EBUS-TBNA reported mortality is 0.01% (36,37). EBUS-TBNA is an out-patient procedure that can be performed safely in an endoscopy suite, under conscious sedation (38).

The first study report of EBUS-TBNA in mediastinal LN staging in lung cancer showed sensitivity of 94.5%, specificity and PPV of 100%, NPV of 89.5% and diagnostic accuracy of 96.3% (31). The prevalence of mediastinal nodal metastasis was 63%. In 19% of patients, in addition to offering staging information, EBUS-TBNA provided diagnostic information, eliminating the need for further invasive tests. EBUS-TBNA staging, prevented 29 mediastinoscopy, eight thoracotomies, four thoracoscopies and nine percutaneous LN biopsies, streamlining the diagnostic work-up (31). Another study of EBUS-TBNA staging in a population with high prevalence of mediastinal nodal metastasis (98.2%) and mediastinal lymphadenopathy confirmed high diagnostic performance of EBUS-TBNA with sensitivity, specificity, diagnostic yield and accuracy of 94%, 100%, 93% and 94%, respectively. However, NPV was only 11% suggesting that in a population of patients with high pretest probability of mediastinal nodal metastasis, confirmatory Med or other staging procedure should be performed to exclude false negatives (39).

Lung cancer management strategies have now been expanded to include non-surgical strategies like SBRT and RFA. In addition, tissue-sparing surgery (wedge, sublobar resection) have become more popular and may be the only treatment option for non-surgical candidates. Post-SBRT local failure can be as high as 15%. This may be due to undetected nodal metastasis in patients undergoing treatment under presumption that the clinical stage correlates with the pathological stage (2,40-48). In addition, lung cancer screening programs have proliferated since the recent lung cancer screening recommendations of the U.S. Preventative Services Task Force (49). These developments may expand the pool of patients with early disease who

 

**Table 1** Performance characteristics of EBUS-TBNA and Med in mediastinal lymph node staging in patients with lung cancer

| Study | Year | n | Prevalence of N2/N3 disease (%) | Sensitivity (%) | | Negative predictive value (%) | |
|---|---|---|---|---|---|---|---|
| | | | | EBUS | Med | EBUS | Med |
| Ernst *et al*. (20) | 2008 | 66 | 89 | 87 | 68 | 78 | 59 |
| Yasufuku *et al*. (35) | 2011 | 153 | 32 | 81 | 79 | 91 | 90 |
| Um *et al*. (19) | 2015 | 127 | 59 | 88 | 81 | 85 | 79 |

qualify for minimally invasive diagnosis and treatment. Furthermore, given improved survival in patients with single versus multiple N1 LNs involvement, preoperative chemotherapy (not currently standard of care because of the lack of studies proving benefit) may become an option for patients with multiple N1 nodal disease. All of these recent developments stress the growing need for invasive nodal staging that extends beyond the mediastinum and into the hilar, interlobar, and perhaps even the lobar LNs (50). Performance of Med and EBUS-TBNA has been assessed in patients with clinical N0 disease.

A recent systematic review, showed that yield of video-assisted Med, unlike that of the traditional Med, is not affected by the prevalence of mediastinal nodal metastasis (sensitivity of 89% in cN0–3) (2). EBUS-TBNA has varying performance in patients with clinical N0 disease. Some studies report sensitivity and NPV ranging between 89–92.3% and 96.3–98.9%, respectively (44,45), while others show sensitivity and NPV ranging between 35–60% and 88.4–93.4% (41,43). There may be a variety of reasons for this discrepancy aside from clinical expertise of the operator: (I) presence of multiple LNs at a station, but only selective LN sampling; (II) LNs inaccessible to EBUS-TBNA sampling (i.e., vascular structures in the needle path); (III) micrometastases in LNs not sampled (i.e., in many studies the lower limit of LN size considered for TBNA was 5 mm, with LNs smaller than that not sampled); (IV) micrometastases in small LNs which may be more challenging to sample. Some authors reported higher percentage of non-diagnostic results from LNs smaller than 5 mm in size, suggesting that this may represent the lower limit of EBUS-TBNA accessibility beyond which, adequate tissue sampling may be challenging and negative results should be interpreted with caution (35). EBUS-TBNA can accurately distinguish between the pathological N0 and N1 disease with sensitivity, specificity, diagnostic accuracy and NPV of 73%, 100%, 96.6% and 96.2%, respectively (51). Overall, EBUS-TBNA can correctly identify mediastinal nodal metastasis in ~1 out of 3 patients with clinical N0 disease. Given the EBUS-TBNA safety profile and the advantage of access to N1 LNs, staging with EBUS-TBNA may become an important step in work-up of patients with early lung cancer.

To date, systematic reviews and four meta-analysis evaluated performance of EBUS-TBNA in lung cancer staging (2,52-55). Populations with different prevalence of mediastinal nodal metastasis were included (prevalence range 33.7% to 99.3%). Data from nearly 3,000 patients were analysed, 36 studies, spanning 12 years (from 2002 to 2012). Overall, EBUS-TBNA demonstrated excellent sensitivity and specificity of 0.88–0.93 (95% CI, 0.79–0.94) and 1.00 (95% CI, 0.92–1.00), respectively; NPV of 91% (range, 83–96%) (2,52-54).

### *EBUS-TBNA vs. Med: a comparison of diagnostic performance in mediastinal LN staging*

EBUS-TBNA performance in mediastinal LN staging in lung cancer has also been compared to that of Med, in prospective studies (19,20,35) (*Table 1*) and recently in a meta-analysis (56). Populations with moderate and high prevalence of mediastinal nodal metastasis were assessed (prevalence ranged from 32% to 89%). Yasufuku *et al*. performed a first heard-to-head comparison of EBUS-TBNA and Med staging in a cohort of 153 patients with potentially resectable lung cancer. Sensitivity, NPV, and diagnostic accuracy of EBUS-TBNA and Med were 81%, 91%, 93% and 79%, 90% and 93%, respectively. Specificity and the PPV for both staging procedures were 100%. This study demonstrated that in expert hands and controlled setting, EBUS-TBNA is equivalent to Med in mediastinal LN staging (35). Ernst *et al*. study showed similar results (20). Ninety three percent *vs*. 82% of patients with lung cancer evaluated by EBUS-TBNA and Med, respectively, had their pathological stage correctly identified (P=0.083). Overall, sensitivity and NPV of EBUS-TBNA and Med were 89% *vs*. 68% and 78% *vs*. 59%, respectively. However, per LN analysis showed that EBUS-TBNA had

 

higher diagnostic accuracy (91%) than Med (78%, P=0.007). There was a discrepancy in diagnostic yield at station 7 (79% for Med *vs.* 98% for EBUS-TBNA, P=0.007). Recently, Um *et al.* demonstrated that EBUS-TBNA can have a superior to Med performance in lung cancer staging in a cohort of patients with biopsy proven lung cancer (19). EBUS-TBNA and Med sensitivity and diagnostic accuracy were 88% *vs.* 81.3% and 92.9% *vs.* 89%, respectively (P=0.005). No difference was demonstrated between the procedures in specificity (100% for both), PPV (100% EBUS-TBNA *vs.* 89% Med) and NPV (EBUS-TBNA 85.2% *vs.* 78.8% Med). Similar to the Ernst *et al.* study, there was a discrepancy between the modalities in disease detection at station 7 LN, with a non-significant trend towards inferior yield with Med than EBUS-TBNA, 75% *vs.* 82% (P=0.0614). However, Med yield at station 4L was significantly lower than that of EBUS-TBNA (52.4% *vs.* 81%, P=0.0270).

Recently, a large meta-analysis was conducted comparing indirectly diagnostic yield of mediastinal staging with EBUS-TBNA to that of Med (56). Ten EBUS-TBNA and seven Med studies were included. Outcomes of nearly 1,000 patients staged were analysed and compared. Overall, sensitivity for detection of mediastinal metastasis was equivalent between EBUS-TBNA and Med at 0.84 (95% CI, 0.79–0.88) and 0.86 (95% CI, 0.82–0.90), respectively (P=0.6321). Med was associated with fewer false negatives, which in both staging modalities were attributed to metastasis in inaccessible LNs (station 5 and 6) and inadequate sampling at accessible LNs. Med, was associated with more complications (17 *vs.* 4). EBUS-TBNA related complications were minor and resolved without intervention.

These studies confirm that both techniques have similar performance in mediastinal LN staging in lung cancer, with EBUS-TBNA being less invasive, better tolerated and with fewer and only minor complications. These findings led to a recent recommendation by the American College of Chest Physicians (ACCP) and the European Society of Thoracic Surgeons (ESTS) that the endoscopic mediastinal staging with EBUS-TBNA or esophageal ultrasound fine needle aspiration (EUS-FNA) be the tests of first choice in invasive mediastinal LN staging, and that they be followed by Med in case of negative results if the index of suspicion for metastatic disease is high (2,9).

### *Combined ultrasonography*

Given that neither Med nor EBUS-TBNA can access stations 5, 6, 8 and 9 nodes, some authors have advocated for a combined approach, and adding EUS-FNA to EBUS-TBNA [combined ultrasonography (CUS)] for mediastinal LN staging in lung cancer (57,58). EUS-FNA is complimentary to EBUS-TBNA and Med in terms of mediastinal LN access. It allows access to station 2R, 2L, 4L, 4R, 5, 7, 8 and 9 LNs. EUS-FNA can also access L adrenal, left lobe of the liver and celiac axis, some of which are common sites of metastasis from lung cancer. However, due to intervening airways, right sided upper paratracheal (2R, 2L) and lower paratracheal (4R) LNs may be more challenging to access. Detailed performance analysis of EUS-FNA in mediastinal LN staging in lung cancer is beyond the scope of this review, nonetheless, EUS-FNA sensitivity, specificity, PPV and NPV in mediastinal LN staging is equivalent to that of EBUS-TBNA at 89%, 100%, 100% and 86% respectively (2).

CUS has been shown to improve access to the mediastinum (59) and the extended LN sampling that occurs with both modalities combined may improve diagnostic yield as compared to EBUS-TBNA alone, thanks to detection of additional metastatic foci (59-61). The concept of CUS was first presented by Vilmann *et al.* (60). Thirty-one patients with suspected or proven lung cancer underwent CUS. A total of 119 lesions were sampled by EUS-FNA (n=59) and EBUS–TBNA (n=60). Cancer diagnosis was made in 26 EUS-FNA and 28 EBUS-TBNA sampled lesions, respectively. Eleven additional cancer diagnoses and three samples with suspicious cells were obtained by EBUS-TBNA that had not been obtained by the EUS-FNA. Conversely, 12 additional cancer diagnoses, one suspicious and one specific benign diagnosis (sarcoidosis) were found by EUS-FNA that had not been picked up by EBUS-TBNA. Mediastinal involvement was confirmed in 20 of the 28 patients in whom a final diagnosis was obtained. The accuracy of CUS, for diagnosis of mediastinal metastasis was 100% (95% CI, 83–100%).

Whether two dedicated scopes are used (a dedicated EBUS-TBNA scope and a dedicated EUS-FNA scope) or EBUS scope following the EBUS-TBNA is used to perform transesophageal needle aspiration (TENA), CUS sensitivity, NPV and diagnostic accuracy have been shown to remain high and perhaps higher than that of EBUS-TBNA alone (59,61,62). One study reported sensitivity and NPV of CUS of 96% *vs.* EBUS-TBNA alone of 92%, in lung cancer staging. However, no p value was provided for this difference. Another study showed, again, high EBUS-TBNA and CUS sensitivity, NPV and diagnostic accuracy of 84.4%, 93.3%, and 95.1% *vs.* 91.1%, 96.1%

 

and 97.2%; P=0.332, P=0.37 9, and P=0.360, respectively but with no statistically significant difference between the two approaches (59). The diagnostic yield was not affected regardless of whether one or two scopes were used for the CUS (59,61,63). However, one scope CUS significantly reduced procedure time as compared to the two scope approach (25±4.4 *vs.* 14.9±2.3 min, P=0.001) (63).

Based on these results, some authors argue for the use of CUS in mediastinal LN staging in patients with lung cancer and promote the use of EBUS-TENA over EBUS-TBNA for time-saving purposes (61,62,64,65). However, there are some important aspects of these studies that need to be taken into consideration before CUS can be recommended routinely. Herth *et al.* reported only three cases where positive results were obtained exclusively by EBUS-TENA from station 2L, 10L, and 7, all of which are accessible by EBUS-TBNA (61). In another study, three exclusively positive cases determined by EBUS-TENA (2.1% of patients) were from station 4L and 5 (frequently involved together with station 4L which is accessible to EBUS-TBNA). Stations 8 and 9 LNs did not contribute to increased diagnostic yield by EBUS-TENA in that study (59). Overall, prevalence of mediastinal LN metastasis in stations inaccessible to EBUS-TBNA is low, ranging between 0.19–1.2% for station 8, and 0.83–2.2% in stations 5 and 6 (35,58,62). The low prevalence of mediastinal metastasis in exclusively EUS-accessible LNs, limitations of EUS including underdiagnoses of N3 disease in left-sided tumors, and N2 disease in right-sided tumors (due to decreased diagnostic yield resulting from higher rate of false negatives in the R-sided LNs due to reduced LN visualization through the air-filled trachea) and given the equivalent to Med yield of EBUS-TBNA in hands of a skilled operator, may be the reasons behind the lack of statistically significant difference in diagnostic yield when adding EUS-FNA to EBUS-TBNA staging, while a statistically significant increase in diagnostic yield has been achieved by adding EBUS-TBNA to EUS-FNA (66).

The use of EBUS through the esophagus to increase the yield further or CUS using two scopes may not be justifiable from the health economics perspective and instead a selective use of CUS should be implemented if there is a high index of suspicion of metastasis in EBUS-TBNA inaccessible LNs. In 2005, Rintoul *et al.* selectively added EUS-FNA to EBUS-TBNA staging in 7 out of 20 patients subjected to endoscopic staging. Five of those patients had additional pathologic diagnosis detected by the EUS-FNA that wouldn't have been obtained with EBUS-TBNA alone. CUS sensitivity, specificity and accuracy were 85% (95% CI, 54.6–98.1%), 100% (95% CI, 47.8–100%) and 89% (95% CI, 65.3–98.6%), respectively (67).

A recent prospective study of mediastinal staging in patients with lung cancer, compared the yield of combined EBUS-EUS and Med with the results of surgical lymphadenectomy. CUS and Med approach diagnosed additional N2/N3 and M1 disease in 14% of study patients that had not been detected by the Med approach, preventing inappropriate surgical resections. CUS sensitivity, NPV and diagnostic accuracy was 91%, 100%, 96% and 97%, respectively. Interestingly, NPV and diagnostic accuracy of EBUS alone, CUS and Med compared with mediastinal lymphadenectomy at thoracotomy were quite similar (–90%, 95%CI, –0.84 to 0.95) (68).

### *Use of confirmatory Med after negative EBUS-TBNA*

A positive result with mediastinal LN staging with EBUS-TBNA has a significant impact on patient management and may result in improved survival (2,24,69-71). However, if EBUS-TBNA staging is negative, the question remains whether there is a role for a confirmatory Med in this setting, and if so, which patients should it be offered to.

Performance of EBUS-TBNA depends on the operator's skill and prevalence of mediastinal metastasis in the studied population. In skilled hands, performance of EBUS-TBNA has been shown to be equivalent or better than that of Med (19,35). In a population with intermediate prevalence of mediastinal metastasis (35%), Yasufuku *et al.* showed sensitivity and NPV of EBUS-TBNA of 81% and 91%, respectively (35). Combined EBUS-TBNA and Med improved sensitivity to 91% and NPV to 96%. This represents an overall 5% increase in NPV and number needed to treat of nine. In other words, in a population with intermediate prevalence of nodal metastasis, both procedures would have to be performed in nine patients to detect one patient with metastatic disease. In a patient population with clinical N0 disease, surgical staging may not contribute significantly to improving diagnostic yield. Szlubowski *et al.* demonstrated CUS sensitivity, specificity, diagnostic accuracy, PPV and NPV of 68% (95% CI, 48–84%), 98% (95% CI, 92–100%), 91% (95% CI, 86–96%), 91% (95% CI, 70–99%) and 91% (95% CI, 83–96%). TEMLA was performed in 99 patients whose CUS was negative detecting 9 additional cases of mediastinal metastatic disease (8%) (72).

Therefore, in a patient population with clinical N0 disease and low prevalence of mediastinal nodal metastasis,

 

confirmatory Med following negative EBUS-TBNA staging, may not be justifiable. Annema *et al.* compared the yield of CUS and Med combined to that of Med in a population of patients with high prevalence of mediastinal nodal metastasis (49%) (58). Sensitivity for detecting N2 and N3 disease was 79% (95% CI, 66–88%) in Med arm, 85% (95% CI, 74–92%) in CUS arm (P=0.47) and 94% (62/66; 95% CI, 85–98%) for the CUS strategy followed by Med (P=0.02). Evaluating sonography (CUS) and surgical components (Med) separately, showed sensitivity and NPV of 85% and 85% for CUS and 79% and 86% for Med. This demonstrated that Med and CUS staging may be equivalent but that CUS approach followed by Med in CUS negative cases in a patient population with high prevalence of mediastinal nodal metastasis has higher than Med alone sensitivity and results in fewer unnecessary surgeries (7% in CUS and Med arm *vs.* 18% in the Med alone arm, P=0.02). Adding Med to CUS increased sensitivity and NPV of staging by 9% (94%) and 11% (93%), respectively indicating that with rising prevalence of mediastinal nodal metastasis, confirmatory Med may be of value and that the decision about confirmatory testing should be made on a case by case basis. Post hoc analysis of survival data from this trial has recently been reported, showing no survival advantage in the CUS and Med arm as compared with the Med alone arm. This may be explained by insufficient powering of the study to detect survival difference (73).

## Cost-effectiveness of EBUS-TBNA and Med in mediastinal LN staging in primary lung cancer

Multiple studies explored costs, cost-benefit and cost-effectiveness of EBUS-TBNA and Med in lung cancer staging (74-79). In 2006, Meyers *et al.* evaluated cost effectiveness of mediastinal LN staging with Med in patients with clinical Stage I disease, by PET and CT. Prevalence of N2 disease was 5.6% (74). The results showed that routine Med in this patient population is not cost-effective. If neoadjuvant therapy in N2 disease is assumed to convey a survival benefit over adjuvant chemotherapy, suggested by some studies (69-71), then invasive staging may be cost-effective in this patient population (80). Routine Med is, however, cost-effective once the prevalence of mediastinal nodal metastasis exceeds 10% (74). Five years following Meyers *et al.* study, Steinfort *et al.* performed a decision analysis comparing costs of mediastinal LN staging in lung cancer, in which they incorporated EBUS-TBNA into the model. Other strategies included: Med, EBUS-TBNA followed by Med (if endoscopic staging was negative) and conventional TBNA (75). In a population with high prevalence of mediastinal nodal metastasis EBUS-TBNA followed by Med was the least costly strategy, suggesting a clear role for confirmatory Med in some patients, while advocating for EBUS-TBNA as the test of first choice in invasive staging. All studies demonstrate that EBUS-TBNA sensitivity and prevalence of mediastinal nodal metastasis are important factors in deciding on the most cost-effective staging modality. Recent study showed that if the EBUS-TBNA sensitivity of at least 25% cannot be achieved, Med should be the preferred staging strategy. Cost comparison between Med and EBUS-TBNA showed that the needle based technique is less expensive than Med if the staging procedure is performed in the endoscopy suite while it is more expensive than Med if performed in the operating room, however, it generates less waste than Med (75,81).

## EBUS-TBNA and Med—role in lung cancer diagnosis

EBUS-TBNA has also been shown to be a useful modality in the diagnosis of primary lung cancer (82-85). Peribronchial lesions adjacent to large central or segmental airways of the lower lobes can be accessed with EBUS-TBNA with sensitivity and diagnostic accuracy ranging between 82% and 97.2% (82-85). NPV is quite low at 23% (95%CI, 5–53%), indicating that negative results in patients with high pretest probability of lung cancer, should be evaluated with other modalities (83). Only minor complications have been reported including self-limited atrial fibrillation (83). Importantly, no pneumothoraces or bleeding were reported.

Endobronchial biopsy and percutaneous lung biopsy are two commonly utilized modalities for diagnosis of lung lesions suspicious for cancer. Beside exposure to radiation, percutaneous, CT-guided lung biopsy, carries a risk of pneumothorax and or hemoptysis of 30–40% (86,87). Percutaneous lung biopsy in centrally located lesions is more expensive and with lower yield than transbronchial biopsy (87,88). Flexible bronchoscopy may be a useful diagnostic modality if the lesion has an endobronchial component, but without it, diagnostic yield has been reported at 0% (83).

Current CP-EBUS can only assess paratracheal and peribronchial areas located around the main and segmental airways of lower lobes. Majority of lung cancers occur in the right upper lobe and tumors of left upper lobe and

 

lingula are not uncommon. Recently, Wada *et al.* reported on performance of a prototype thin convex probe-EBUS (TCP-EBUS) in a porcine lung (89). The TCP-EBUS has a smaller external diameter of 5.9 mm and grater bending angle of 170° up than the current CP-EBUS (6.9 mm external diameter and 120° up angulation). Thanks to these characteristics, the TCP-EBUS on average has a 14.7 mm greater endoscopic visibility range and a 16.0 mm greater maximum reach than the current CP-EBUS. The TCP-EBUS visualized 1 to 3 distal bifurcations further than the current CP-EBUS, accessing the segmental airways of the left upper lobe and the tracheobronchus (intubation of which, requires significant scope angulation, not possible with the current CP-EBUS). Adequate nodal tissue was sampled from lobar and segmental LNs (89). Improved airway access and ability to sample upper and lower lobe peribronchial tissue and segmental LNs are expected in human lung, given larger than a pig's airway diameter. Performance of the prototype TCP-EBUS offers a promising improvement to diagnosis of peribronchial tumors. In addition, it would improve the assessment of intrathoracic LNs, moving the lung cancer staging beyond the mediastinum and into the segmental and lobar regions and into the upper lobes. This could prove useful in planning treatment for ablative therapy and sublobar resection candidates. In addition, the ability to safely access, sample and accurately diagnose lung cancer in patients with centrally located lesions by EBUS-TBNA opens up a possibility of accomplishing both, obtaining tissue diagnosis from the primary tumor and mediastinal staging in a single procedure, reducing overall costs of the diagnostic work up and accelerating patient's access to appropriate definitive therapy.

In the era of personalized medicine, determining molecular signature of lung cancer has become the standard of care. EBUS-TBNA samples provide sufficient quantity and quality material for molecular testing. Reported adequacy of EBUS-TBNA samples for molecular diagnosis ranges from 77% to 98% (90,91). EBUS samples have one of the lowest insufficiency rates (4%) for EGFR and KRAS mutational analysis (compared with CT-FNA, 7.5%; ultrasound guided/superficial FNA, 10%) and can provide sufficient tissue quantity for multigene testing (i.e., p53 mutation, BRAF and PIK3CA) (90,92).

Med can also be used in assessment of primary lung lesions assessing for presence and the extent of mediastinal tumor invasion (T component). In mediastinal staging studies, Med has been shown to correctly identify mediastinal tumor invasion, preventing futile thoracotomies (58).

## Med and EBUS-TBNA in lung cancer re-staging and recurrence

Neoadjuvant chemoradiation followed by surgery in lung cancer patients with N2 disease may offer survival advantage over definitive chemoradiation, if the mediastinum can be down-staged to N0/N1 preoperatively (93-95). Both Med and EBUS-TBNA have been used for mediastinal restaging (41,96-102). However, performance of both Med and EBUS-TBNA in restaging is worse than in original staging. This is due to LN and mediastinal scarring that results from neoadjuvant therapy and prior Med. In the past, the prevailing thought was that prior manipulation of the mediastinum may make a repeat Med impossible. However, multiple studies have reported feasibility of repeated Med for restaging with 98–100% planned procedures completed (97,100), low morbidity (1.9%) (100) but unfortunately also a death reported in one study due to perioperative bleeding (97). One of the largest series was reported by De Waele *et al.* (97), 104 patients were restaged with Med after neoadjuvant therapy. Med sensitivity, specificity, and diagnostic accuracy were 71%, 100% and 84%, respectively (97). Med prevented 20 futile thoracotomies by detection of persistent N2/3 disease. Patients without nodal metastasis proceeded to surgical resection with median survival of 28 months (95% CI, 15–41 months). Survival in patients with positive and false-negative Med was 14 months (95% CI, 8–20 months) and 24 months (95% CI, 3–45 months), respectively. This suggests that Med is also able to provide a prognostic information. Other studies reported similar performance characteristics for Med with sensitivity of 61–83%, diagnostic accuracy of 84–91% and NPV of 85% (96-98,100). One, study however, showed very low sensitivity and diagnostic accuracy of Med, 29% and 60%, respectively, which was presumed to be due to inadequate sampling of station 7 LN in majority of patients (99).

Sensitivity and NPV of EBUS-TBNA for mediastinal restaging has shown to be lower than in initial mediastinal staging, ranging between 50% and 77%. This is thought to be attributable to LN necrosis and fibrosis (101-104). However, the procedure is safe with no complications reported.

EBUS-TBNA has been evaluated in patients with new mediastinal lymphadenopathy following treatment

 

of lung cancer (105). PET-CT is not highly reliable in assessment of patients suspected to have cancer recurrence. False positives are common and can be related to post inflammatory mediastinal changes due to surgery or related to chronic bronchitis due to smoking (105,106). Pathological confirmation of positive imaging is, therefore, important. In one study, EBUS-TBNA mediastinal LN sampling was performed in patients with progressive mediastinal lymphadenopathy following initial treatment of NSCLC (105). Cancer recurrence and a new primary cancer were diagnosed in 64% and 25% of patients, respectively. Patients diagnosed with early new lung cancer, following EBUS-TBNA staging proving no mediastinal involvement, underwent surgery with curative intent. Patients with recurrence and new small cell lung cancer obtained appropriate therapy. A recent study reported a 100% sensitivity, specificity, PPV and NPV of EBUS-TBNA for assessment of mediastinal LN in patients following treatment of lung cancer (107). These results show that EBUS-TBNA can be used to obtain a definitive diagnosis of newly developed mediastinal and hilar abnormalities after primary therapy in patients with lung cancer. Diagnostic accuracy of EBUS-TBNA in such setting is 95.1%. Added benefit is that the procedure can be repeated safely without additional risk to the patient, even if the mediastinum had previously been assessed by Med.

Due to adhesions that occur following LN dissection during lung cancer resection, confirming cancer recurrence with Med meets the same challenges as using Med for restaging after neoadjuvant therapy (108,109).

At present there is insufficient evidence to clearly define the role of surgical and endoscopic modalities in patients with advanced lung cancer and considered for trimodality therapy and in setting of suspected recurrent lung cancer. Given better performance of Med when performed for the first time, and equivalent performance of Med and EBUS-TBNA in primary mediastinal staging, it appears that saving Med for re-staging after neoadjuvant therapy and staging initially with EBUS-TBNA might be the most cost-effective staging approach in lung cancer patients considered for a curative resection. However, if EBUS-TBNA is performed for restaging, a confirmatory Med should be performed in the event of negative EBUS-TBNA (9). Given excellent performance characteristic of EBUS-TBNA in diagnosis of lung cancer recurrence and the potential challenges of Med, EBUS-TBNA should be used for initial evaluation of new mediastinal lymphadenopathy in patients with prior lung cancer.

## Conclusions and future directions

Lung cancer diagnosis and management have undergone significant changes over the past decade with introduction of the minimally invasive endoscopic techniques. EBUS-TBNA offers an accurate and cost-effective means of mediastinal evaluation at all stages of lung cancer, from the original mediastinal staging to detection of disease recurrence. Quality data on performance of EBUS-TBNA in mediastinal LN staging in lung cancer led to a recent recommendation from the ACCP and ESTS to use the needle based techniques for the initial mediastinal staging (2,9). Currently, endoscopic staging is recommended for patients with distinct mediastinal or N1 LN enlargement on CT chest, or FDG avidity on PET, in central tumors and all patients with T2 tumors (2). When combined with EUS-FNA, EBUS-TBNA offers nearly complete assessment of the mediastinum and may have higher diagnostic accuracy than the previous gold standard, Med in patients with metastatic disease in EBUS-TBNA-inaccessible LNs. When performed by a skilled bronchoscopist EBUS-TBNA can not only provide mediastinal LN staging but also, in some patients, offer diagnosis of the primary tumor including information on its molecular profile (110,111).

Practice of medicine has evolved in many specialities with focus on minimally invasive diagnosis and treatment as well as personalized treatments of disease. At present, lung cancer is being treated not only with surgery but also with therapies like RFA and SBRT. Sublobar resections may become standard of care for T1a tumors (112) and are the only surgical option for patients with significantly impaired lung function (40). In this setting, development of a TCP-EBUS scope opens up a possibility of not only reaching further into the airways and sampling the more distant and upper lobe N1 LNs, but also, personalized therapy where a tumor-specific treatment could be delivered to a metastatic LN or a primary lung tumor, using a real time ultrasound imaging (113,114).

Even though many centers globally have acquired endoscopic ultrasound technology, it is unlikely that Med will be eliminated from the armamentarium of invasive tests used in lung cancer patients. Instead, a combination of endoscopic and surgical assessments will become the standard of care, depending on the unique clinical scenario.

 

This will allow highest diagnostic yield at all stages of the disease and as a result, most optimal patient management. For example, Med is recommended as a confirmatory test in patients with negative needle-based staging in patients with high pretest probability of mediastinal metastasis and it should be the test of first choice for mediastinal restaging, following neoadjuvant therapy (especially if EBUS-TBNA was used to stage mediastinum initially). In addition, despite the recent change in the guidelines and a shift to the minimally invasive endosonography for staging, acquisition of this technology in many thoracic surgery and pulmonology centers is hindered by the lack of EBUS-TBNA expertise and limited resources. Therefore, Med is still the test of first choice in many thoracic surgery programs worldwide for mediastinal staging, restaging and diagnosis of disease recurrence. For these reasons, it important that thoracic surgeons get adequate training in both Med and the needle based techniques like EBUS-TBNA or EUS-FNA and that the focus of lung cancer diagnosis and treatment be on a multidisciplinary approach with a close collaboration of the radiologists, thoracic surgeons, pulmonologists, pathologists and oncologists to ensure the optimal patient management at all stages of the disease.

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## Footnote

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Interventional Diagnostic Technique

# Transthoracic needle aspiration: the past, present and future

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**Abstract:** Transthoracic needle aspiration (TTNA) has been used to diagnose disease in the lung for many decades. Thanks to advances in technology and cytopathology, the diagnostic power, accuracy, safety, and efficacy of TTNA are constantly improving. The transition from fluoroscopy to computed tomography (CT) has yielded better visualization, and ability to enhance sophistication of tools used to biopsy. In addition, needles are being refined for obtaining better biopsy samples and increased capabilities. Because of the minimally invasive nature of TTNA, it is becoming a strong alternative to surgical intervention. In the future, these developments will continue and TTNA will become more efficient, and potentially open a door to personalized medicine. However, there are complications due to this procedure, which include pneumothorax, hemorrhage, air embolism, and others which are very rare. Probability of complication increases when patients are older, have significant past medical history, have larger lesions, and are uncooperative during procedure. Indications, contraindications, and other considerations should be contemplated before a patient is elected for TTNA.

**Keywords:** Lung biopsy; needle aspiration; interventional; computed tomography (CT)

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## Introduction

From as early as 1883 (1), clinicians have used transthoracic needle aspiration (TTNA) to safely and effectively diagnose pulmonary malignancies. Over the years, biopsies through this procedure have become more accurate and efficient due to advances in imaging technologies and cytopathologic techniques. The transition from fluoroscopy to computed tomography (CT) allowed for better visualization and detection of smaller lesions. In addition, developments in cytopathology have facilitated histologic analysis with smaller amounts of required material. Previous studies have shown diagnostic accuracy of benign and malignant disease of TTNA to range from 77-97% (2-4). Increased use of CT-guided TTNA (CT-TTNA) has reduced the need for more invasive surgeries such as thoracotomies and bronchoscopies. As a result, there has been increases in cost savings and decreases in hospital length of stay (2). However, there are few complications that arise from TTNA, pneumothorax being the most common. When making the decision to do TTNA for a biopsy, physicians need to consider from the givens of TTNA and the patient whether the benefits of the biopsy greatly outweigh the risk and consequence of a complication. In this review article, we will discuss what is known about indications, contraindications, imaging modalities, needle types, considerations, complications and management with respect to TTNA, and then comment on the trajectory of TTNA in the future of thoracic medicine.

## Indications

TTNA is mostly used to evaluate an indeterminate pulmonary mass or nodule. This can include almost any

abnormality seen in imaging. Lesions of lung parenchyma, mediastinal, hilar, pleural, and chest wall have been proven to be diagnosable with TTNA (1). In these cases, some institutions would instead use bronchoscopy or thoracoscopic surgery. However, bronchoscopy is limited to central lesions with endobronchial or hilar components (3,5) and thoracoscopic surgery requires general anesthesia and is dependent on the skill of the surgeon (3). In addition, TTNA can be used to sample focal infectious lesions and stage lung cancers or extrathoracic malignancies (3). For these cases, a histological classification would be very useful, enhancing the value of TTNA. Besides neoplastic (benign or malignant) disease, TTNA can be used to diagnose inflammatory disease (1).

## Contraindications

The number one contraindication to TTNA is bleeding diathesis, for which platelet count, prothrombin time, partial thromboplastin time and INR should be obtained prior to procedure. Relative contraindications range from pulmonary hypertension to emphysematous disease and chronic obstructive pulmonary disease (COPD). Large bullae in biopsy path can cause post-procedure pneumothorax. Possibly the most serious contraindication to TTNA is an uncooperative patient. The patient's ability to lie still, hold their breath, and maintain prone position (1,3) are essential to a successful TTNA. For this reason intractable cough and mechanical ventilation are also contraindications.

## Imaging modalities

### *Fluoroscopy*

Fluoroscopic guidance represented the first modality for TTNA (3). Advantages of fluoroscopy include real time visualization, familiarity, and availability. Fluoroscopy-guided TTNA (F-TTNA) has been an alternative to CT-TTNA due to shorter durations, lower incidence of pneumothorax, lower cost and lower radiation dosage (3,6). Disadvantages arise from limitations of fluoroscopy, including poor visualization of small lesions and bullae and safe sampling of central lesions. One study done by Cheung *et al.* (6) investigated combining F-TTNA with CT-TTNA, where a biopsy is done under fluoroscopy and cone-beam CT using a C-arm cone beam CT system. This new biopsy technique took the advantages of fluoroscopy and CT and allowed for diagnosis of small (<30 mm) and deep (≥50 mm) with high diagnostic accuracy and short procedure time (6).

### *Ultrasound*

Ultrasound-guided TTNA biopsy has many advantages, in that it provides real-time visualization, can target nonvascular and nonnecrotic portions of masses (7), and has no radiation. Compared to CT-TTNA, ultrasound is inexpensive and portable. The latter aspect is useful for patients who cannot be transported to the radiology department (3). However, the necessity of adequate acoustics limits the potential of using ultrasound. Masses in the anterior mediastinum and peripheral lung adjacent to the costal pleural surface are difficult to image in ultrasound, but are detectable by CT (3,8).

### *Magnetic-resonance imaging (MRI)*

Magnetic-resonance imaging (MRI)-guided procedures have been shown to yield excellent clinical results in osseous biopsies (9), however, very little has been reported on MRI usage in TTNA (10,11). This might be because CT is generally accepted as the main imaging modality for TTNA. Liu *et al.* (10) showed that MRI-guided TTNA (MRI-TTNA) is comparable to CT in mean procedural time and diagnostic accuracy. Sakarya *et al.* (11), who first reported using an MR fluoroscopy-guided approach to TTNA, showed that MR guidance has good feasibility. Advantages of using MR fluoroscopy include near-real-time imagine and absence of radiation (11). However, with CT imaging, fissures, focal areas of emphysema, and bullae are better detected and during TTNA these areas can be avoided during biopsy (11). This is something that MR imaging cannot account for. In addition, issues with breath-hold duration and patient compliance can create motion artifacts, which means lower MR-image quality.

### *Computed tomography (CT)*

As previously mentioned, CT is the most common modality for TTNA procedures. Advantages of CT guidance are attributed to excellent visualization capabilities. This also includes the visualization of the biopsy needle tip, which facilitates placement and allows for high diagnostic yield (3). However, there are disadvantages, including lack of real-time visualization, greater cost of procedure, more patient

 

discomfort, and higher incidence of pneumothorax (3). Within this modality, there have been many developments. First, conventional CT was used to guide biopsy needle placement. Soon, helical CT emerged and now is very widely used (12). CT fluoroscopy was most recently introduced, and has been proven to be effective because it unites together the visualization of CT and efficiency from fluoroscopic guidance. Unfortunately, this technique is susceptible to irradiation to the physician's hand during the procedure. Yoshimatsu *et al.* (12) conducted a TTNA study using an "I-I device" which functions as a cradle for the needle and a handle to distance a physician's hand from radiation exposure. Results of this study showed decreased radiation dose to physician's hand and faster fluoroscopy and procedure times with equal if not better outcomes than those without the I-I device (12). Surgical forceps or special needle holders are currently used to reduce radiation dose during TTNA procedures (12).

CT-TTNA has been improved upon through the incorporation of other technologies and modalities. About 10 years ago, cone-beam CT had been introduced to interventional radiology as cutting-edge, allowing for real-time fluoroscopy, angiography, CT imaging, and 3D reconstruction capabilities (13). Previous studies have shown high and reproducible diagnostic accuracy with cone-beam CT-TTNA (13,14). Cone-beam CT has even been shown to provide high accuracy, specificity, sensitivity, and positive/negative predictive values with "XperGuide" navigation guidance (15). One group had even combined fludeoxyglucose positive emission tomography (FDG-PET) with CT, and showed improved diagnostic yield in patients with large (≥2.5 cm) intrathoracic lesions (16). Another group had assessed performance of using an optical CT-based navigation system to assist with TTNA. With a technical success of 100%, Grasso *et al.* (17) showed that using this navigation tool with a low dose CT protocol can decrease patient radiation exposure.

### *Navigation systems*

Navigation systems for assisting with TTNA have been shown to be effective in CT and electromagnetic modalities. Electromagnetic navigation bronchoscopy (ENB) has recently started to emerge, and has been quite effective (18,19). ENB uses an image guided localization system that directs steerable bronchoscopic tools to points of interest within a bronchial tree, and has been shown to produce high sensitivity in fine-needle aspiration (19). Electromagnetic Navigational TTNA (E-TTNA) is currently being proposed to maximize diagnostic yield and minimize the need for invasive procedures in conjunction with endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA) (18). Another type of navigation system seen in literature uses virtual assisted lung mapping (VAL-MAP) to provide "geometric" information of the lung surface (20). Bronchoscopic multispot dye-marking was used to produce markings that can be visualized through CT in order to produce 3D virtual images for reference. VAL-MAP was shown in an early experience study to work, but more studies need to be done to assess its safety and efficacy (20).

## Needles

There are many types of needs used in TTNA for biopsies, with various gauges, lengths, tips, and mechanisms. A clinician may select a needle based on preference or patient/lesion characteristics. Mainly, there are aspiration needles, cutting needles, and automated core-biopsy needles. Aspiration needles are thin-walled and flexible (2) and can provide high-quality cellular material for microscopic/cytological diagnosis (3). The Chiba (Cook, Inc. Bloomington, IN, USA) is the most commonly used, and has a 30 degree bevel and sizes ranging from 18-25 gauge (2). This type of needle can be used to diagnose epithelial carcinomas. Cutting needles are used when a histologic specimen is required for analysis. Essentially, cutting needles are modified aspiration needles, with an added cutting tip on the side. Possible cutting tips include a receptacle slot just proximal to the tip, a spring-loaded end cutting tip, or a drill bit styled tip within a guiding cannula (3). Lastly, automated core-biopsy needles (*Figure 1*) retrieve tissue from the patient for histopathologic workup. These needles are useful especially if a pathologist is not on-site, because the needle will obtain similar core samples that are free of crush injury sometimes imparted by smaller conventional needles (2).

## Considerations

The primary consideration a physician must make before pursuing TTNA for a patient is whether the benefits of a biopsy outweigh the risk for complication and toleration of the procedure. Pneumothorax remains the most common complication during and after a TTNA procedure (2,3,21). Many previous studies investigating this connection have proven factors that contribute to this increased rate of

 

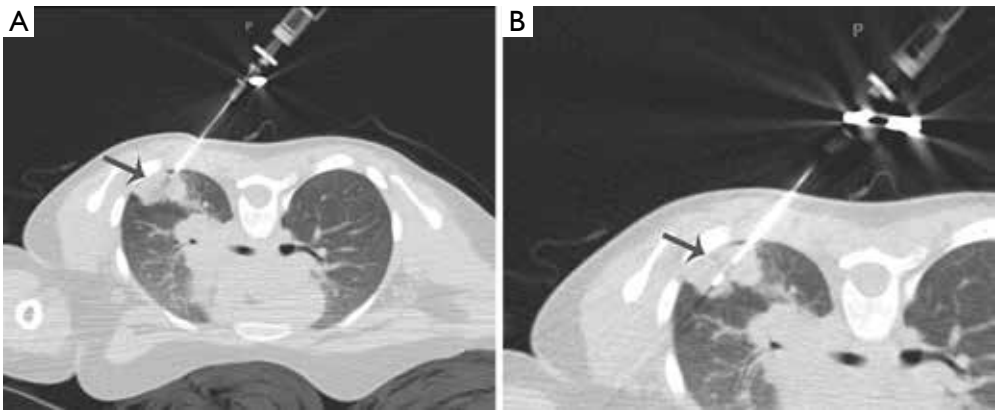


**Figure 1** CT image with lung windows showing needle placement during TTNA for patient 1 in prone position. The same lung lesion pictured in *Figure 1* is shown here. A 20 gauge 11 centimeter core biopsy device was inserted through an 18 gauge 6 centimeter double wall needle with trocar. (A) The needle is inserted through the left posterior chest wall; (B) a zoomed-in image of area where TTNA core-biopsy is taking place. Four core biopsy samples were taken with this method. CT, computed tomography; TTNA, transthoracic needle aspiration.

complication. Geraghty *et al.* (22) showed needle size and patient age to be statistically significant risk factors. In the same study, they measured a 50% reduction in pneumothorax rate associated with using smaller 19-gauge needles instead of 18-gage needles (22). Patients with larger lesions are susceptible to higher pneumothorax rate (23,24) and lower diagnostic accuracy during TTNA (4). Longer needle path lengths in procedure are also significant in increasing pneumothorax rate and decreasing diagnostic accuracy (4). Interestingly, the risk of pneumothorax in TTNA is not dependent on physician experience (23) or needle aspiration technique (2). In one study, pneumothorax incidence was nearly equal in TTNA performed by a junior resident, senior resident or staff physician (23).

Overall, patients who are female, older age (≥70 years), have COPD (25), and/or have presence of emphysema (23) are at higher risk for complications during TTNA. As more and more patients are being diagnosed with thoracic malignancy and undergo TTNA for biopsy, the incidence of complication will definitely increase, especially because smaller growing lesions (<20 mm) can now be detected. Patient lifestyle, age, comorbidities, and experiences at an institution must be taken into consideration before electing for TTNA.

## Complications and management

### *Pneumothorax*

As previously mentioned, pneumothorax is the most common complication as a result of TTNA. The incidence of pneumothorax has been reported to be from 0-61%, with an average of around 20% (2,3,21-23). Increased patient age, obstructive lung disease, COPD, multiple pleural passes, increased duration of procedure, and traversal of a fissure increases the risk of pneumothorax. If a pneumothorax develops during procedure, it can be manually aspirated before the introducer needle is removed (*Figure 2*) (21). It is also recommended that the patient be placed biopsy-side down and given oxygen via nasal cannula. For pneumothoraces that develop after procedure, many steps need to be taken. Small pneumothoraces can be managed with monitoring of vital signs, administration of oxygen, and obtaining a chest film. If films at 2 and 4 hours are unremarkable, discharge can be considered. Pneumothoraces unchanged on film after 4 hours are unlikely to grow (2,26). Larger cases might require image-guided intervention such as insertion of a small chest tube, which happens for around 1-14.2% of patients (3,21). These small chest tubes allow for treatment of potentially significant complication without the need for surgical intervention and can be inserted on an outpatient basis. In addition, the diagnostic efficacy increases for biopsies of lesions with an already treated pneumothorax (1).

Most recently, lung biopsy tract seal plugs have been used to combat pneumothorax (*Figure 3*). Two major types are the Bio-Seal Lung Plug System (Angiotech Pharmaceuticals, Vancouver, British Columbia) and the BioSentry Tract Sealant System (Surgical Specialties, Massachusetts, USA). One study done by Zaetta *et al.* (27) showed significantly

 

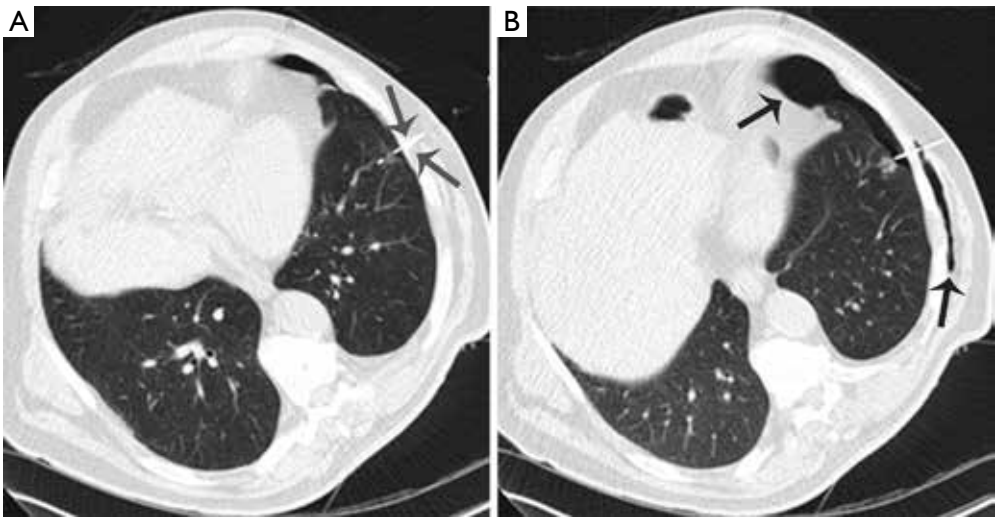


**Figure 2** CT image with lung windows showing needle placement during TTNA for patient 2 with minor complication. (A) The needle is inserted through the left anterior chest wall; (B) black arrows show pneumothorax and surgical emphysema in chest wall. A chest tube was placed for chest resolution in 2 days with water seal drainage. CT, computed tomography; TTNA, transthoracic needle aspiration.

reduced rates of pneumothorax in patients undergoing CT-TTNA. Autologous blood clot seals (ABCS) have also been shown to reduce frequency of pneumothoraces (28).

### *Hemorrhage and hemoptysis*

The second most common complication with TTNA is hemorrhage, with an average incidence of about 11% (2,3,21). Hemorrhages and hemoptysis are considered self-limited and usually do not require intervention. However, the patient should be placed biopsy-side down to prevent aspiration of blood into the opposite lung (2,3,21). Fortunately, many measures can be taken to avoid a hemorrhage or hemothorax. Patients taking anticoagulants or have bleeding diatheses should be contraindicated for TTNA. During the procedure, it is recommended to aim the trajectory of the needle away from the aorta and heart to avoid accidental injury. Massive hemorrhages are very rare, but may require anesthesia consultation to intubate with a double-lumen endotracheal tube (21).

### *Air embolism*

Air embolism in TTNA is extremely rare but can be very fatal if not fixed, leading to cerebral or myocardial infarction, stroke, or death. As little as 0.5 mL of air would be required to induce coronary ischemia or arrhythmias (3). In large cohorts of TTNA patients, there were very few cases of air embolism (occurrence between 0.02-1.8%) (2,21). There are two mechanisms by which air embolisms can occur: (I) placement of the needle tip in a pulmonary vein and removal of the inner stylet and (II) placement of the needle through both a bronchus and adjacent pulmonary vein, followed by creation of a fistula. If an air embolism is recognized, the patient should be placed in the Trendelenburg position to prevent air from being circulated cerebrally (21). Air embolisms can be prevented by occluding the introducer needle with an inner stylet, saline, or a finger. This complication is another reason why patients with intractable coughs should not be recommended for TTNA.

### *Tumor seeding*

Tumor seeding is an extremely rare complication of TTNA, and is reported to have incidence between 0.012-0.061% (3,21,29). Mean time from biopsy to development of metastasis is around 2.6 months (3). At this time, there are no definitive risk factors that can be identified to help prevent tumor seeding (21,29). However, if metastasis occurs but is isolated to the chest wall, wide en bloc resection can be done. Tumor seeding has occurred with diagnoses of pleural mesothelioma and thymoma.

## Future perspectives

After so many years of implementation and research,

 

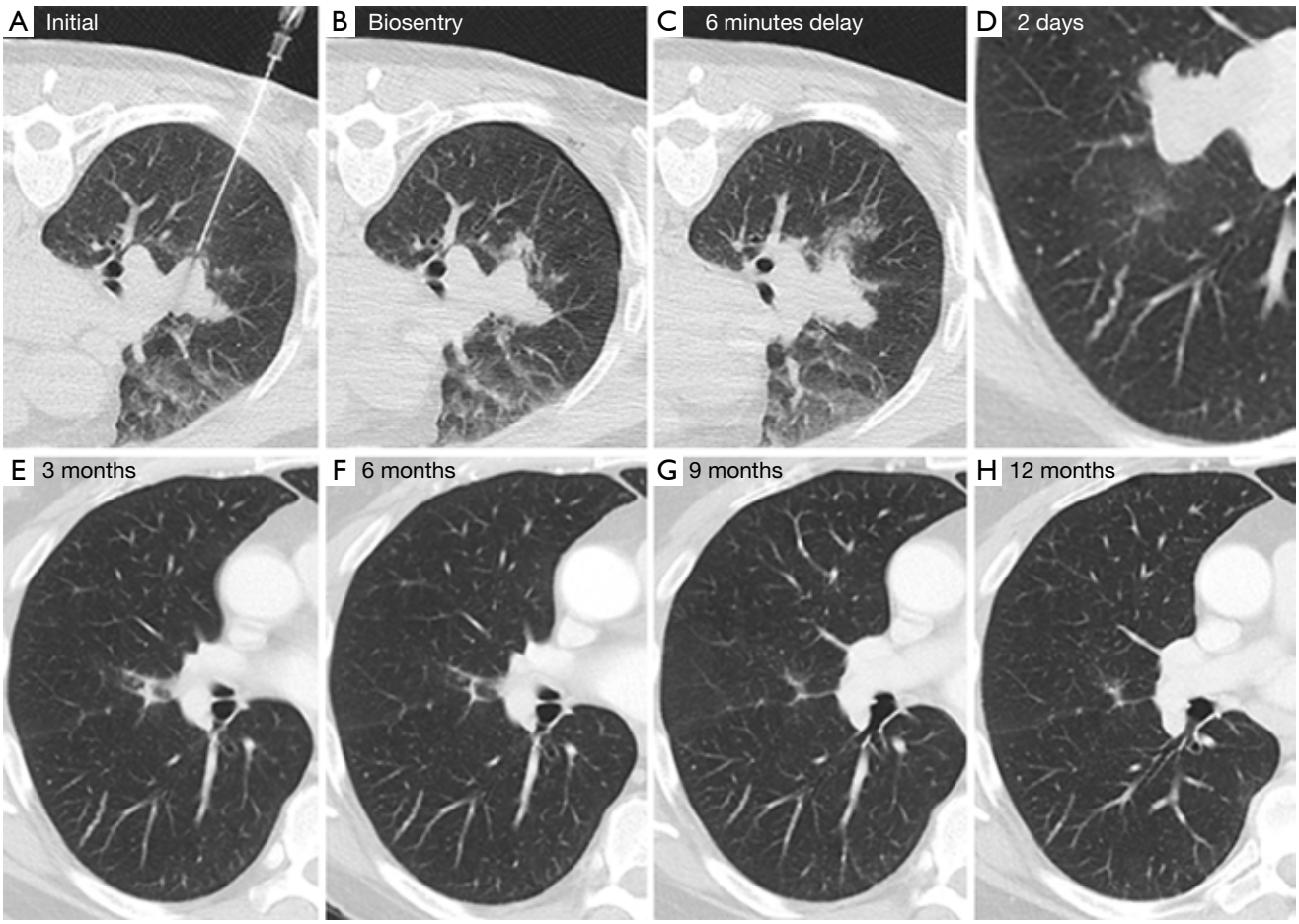


**Figure 3** CT image with lung windows showing TTNA for patient 3, where a sealant (Angiotech BioSentry, Angiotech SuperCore, Bulgaria) was used to prevent pneumothorax using a 19/20 gauge probe. Patient 3 had metastatic melanoma and was on immunotherapy trial. CT, computed tomography; TTNA, transthoracic needle aspiration.

TTNA has been proven to be safe, effective, and very accurate in biopsy diagnosis. Advances in imaging and cytopathology have increased diagnostic power of TTNA, meaning that more lesions (including those previously too small to detect) can be analyzed with less required histologic material. However, because of this the number of diagnoses has and will increase over time. This will inevitably increase complications, which means that there will be more weight on the decision to elect a patient for TTNA. In this case, more studies into risk factors need to be done, especially for complications not as well researched as pneumothoraces. A very key aspect of TTNA is the length of procedure, which has been shown to be a significant risk factor for complication. Future studies on needle type and design may open the door to technologies that will make the procedures more efficient and decrease patient length of stay. Results from a TTNA biopsy will also pave way to a form of personalized medicine. Tissue and cells retrieved during TTNA can be placed through genetic blood testing in order to specifically identify biomarkers and provide tailor-made treatment for each specific patient. These considerations and the prospective trajectory for the field can only increase the safety, efficacy, and acceptance of TTNA as the mainstay procedure to diagnose thoracic malignancy and disease.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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Interventional Diagnostic Technique

# Transthoracic needle biopsy of the lung

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**Background:** Image guided transthoracic needle aspiration (TTNA) is a valuable tool used for the diagnosis of countless thoracic diseases. Computed tomography (CT) is the most common imaging modality used for guidance followed by ultrasound (US) for lesions abutting the pleural surface. Novel approaches using virtual CT guidance have recently been introduced. The objective of this review is to examine the current literature for TTNA biopsy of the lung focusing on diagnostic accuracy and safety.

**Methods:** MEDLINE was searched from inception to October 2015 for all case series examining image guided TTNA. Articles focusing on fluoroscopic guidance as well as influence of rapid on-site evaluation (ROSE) on yield were excluded. The diagnostic accuracy, defined as the number of true positives divided by the number of biopsies done, as well as the complication rate [pneumothorax (PTX), bleeding] was examined for CT guided TTNA, US guided TTNA as well as CT guided electromagnetic navigational-TTNA (E-TTNA). Of the 490 articles recovered 75 were included in our analysis.

**Results:** The overall pooled diagnostic accuracy for CT guided TTNA using 48 articles that met the inclusion and exclusion criteria was 92.1% (9,567/10,383). A similar yield was obtained examining ten articles using US guided TTNA of 88.7% (446/503). E-TTNA, being a new modality, only had one pilot study citing a diagnostic accuracy of 83% (19/23). Pooled PTX and hemorrhage rates were 20.5% and 2.8% respectively for CT guided TTNA. The PTX rate was lower in US guided TTNA at a pooled rate of 4.4%. E-TTNA showed a similar rate of PTX at 20% with no incidence of bleeding in a single pilot study available.

**Conclusions:** Image guided TTNA is a safe and accurate modality for the biopsy of lung pathology. This study found similar yield and safety profiles with the three imaging modalities examined.

**Keywords:** Image guided lung biopsy; transthoracic needle aspiration (TTNA); computed tomography guided TTNA (CT guided TTNA); ultrasound guided TTNA (US guided TTNA); CT guided electromagnetic navigational TTNA

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## Introduction

Image guided transthoracic needle aspiration (TTNA) of lung lesions has been a valuable diagnostic tool since it was first described in 1965 (1). Integral to the evolution of the technique has been the type of image guidance used to direct the biopsy tool to the area of abnormality. As imaging technology has advanced, so has the type of guidance used: plain radiograph and fluoroscopy giving way to computed tomography (CT), ultrasound (US) guided procedures (2,3) and CT guided electromagnetic navigational-TTNA (E-TTNA).

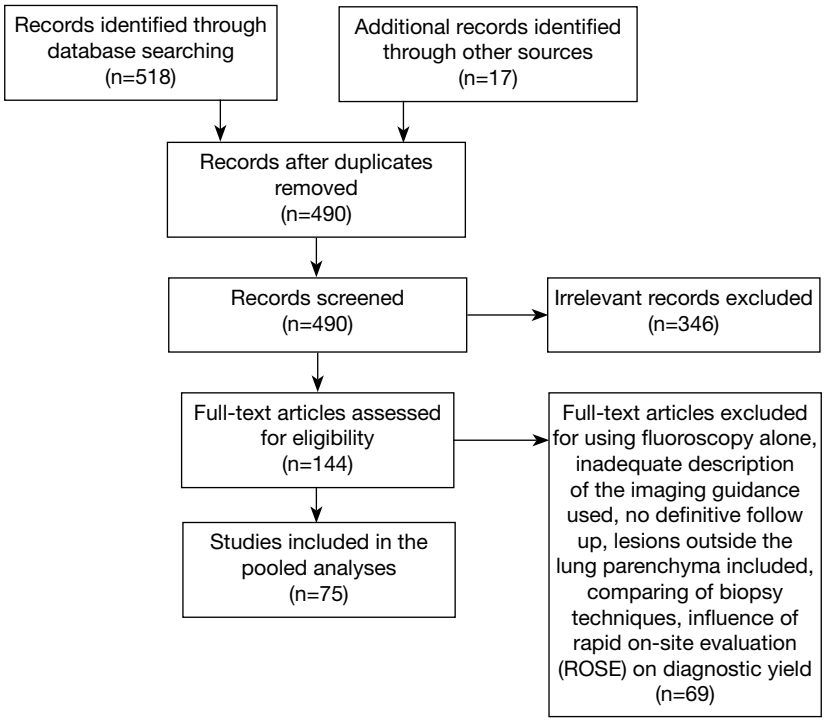


**Figure 1** Flow diagram.

A large body of literature has subsequently explored the technique using CT and US. This literature has focused on the diagnostic accuracy of TTNA, modifications to the biopsy tools used, and the complications. The vast majority of the literature is large case series based with periodic pooled analyses, meta-analyses, and structured reviews of the test characteristics reported (4-7). These analyses have focused on the excellent diagnostic performance of TTNA for the diagnosis of peripheral lung cancer and have included an older and heterogeneous group of procedures guided by plain radiograph, fluoroscopy guided, CT guided, and US.

In this review, we summarize the recent available literature on CT guided and US guided TTNA for lung lesions. Furthermore, we report our case series using a novel electromagnetic navigational technology for TTNA (E-TTNA) and explore future directions in the field (8-10).

## Methods

MEDLINE was searched from inception to October 2015 for all case series designed to describe the test characteristics and complications of TTNA of lung nodules using combinations of the medical subject headings (MeSH terms) "computed tomography", "ultrasound", "transthoracic", "needle aspiration", "needle biopsy", and "peripheral lung nodules". Bibliographies and related articles of included studies were hand searched for additional reports. Research analyzing TTNA guided by fluoroscopy alone, an inadequate description of the imaging guidance used, inadequate confirmation of diagnosis, and analyses that included lesions from outside the lung parenchyma were excluded from our pooled analysis. Articles designed to compare biopsy techniques or examine the influence of rapid on-site evaluation (ROSE) on diagnostic yield were excluded. Non-English language articles were also excluded (*Figure 1*).

For the purposes of the pooled analysis, the overall diagnostic accuracy was defined as the number of true positives (true malignancy found on TTNA) and true negatives (confirmed benign lesions found on TTNA) divided by the number of biopsies done, provided that a definitive diagnosis was achieved based on clinical follow up and/or further invasive testing. Patients who underwent repeat biopsies had each biopsy counted separately. The pooled sensitivity and specificity of TTNA for malignancy was also calculated. If the subset of the test characteristics regarding malignancy were not available, overall diagnostic

 

sensitivity and specificity were reported as indicated in the tables. When reports had adequate diagnostic follow up for only a subset of their study population, the diagnostic accuracy, sensitivity for malignancy, and specificity for malignancy used in the pooled analyses were derived only from the subset with follow up. Primary data was extracted manually from each full text article. When articles calculated the test characteristics of TTNA only after excluding failed procedures (aborted or nondiagnostic) this was noted in the table. Similarly, the safety data was manually extracted and pooled from each full text manuscript.

## Results

### *CT guided TTNA*

#### Diagnostic accuracy

The vast majority of the literature focuses on the diagnostic yield of CT guided TTNA. Forty-eight articles using CT guidance met the inclusion and exclusion criteria based on the search strategy described above. The overall pooled diagnostic accuracy was 92.1% (9,567/10,383) and the sensitivity for detecting malignancy was 92.1% (7,343/7,975). The specificity for the diagnosis of malignancy approaches 100% with rare false positives (*Table 1*). Within each individual study, one factor consistently proposed as influencing the diagnostic accuracy of TTNA was lung lesion size. However, individual studies were mixed in validating lesion size as a predictor of diagnostic failure and were consistently under powered to detect a difference (14,17,20,22,28,30,31,33,36-39,41-44,52,58). When articles restricted to lung nodules ≤2 cm were analyzed with articles that reported diagnostic accuracy stratified by lesion size ≤2 cm, the pooled diagnostic accuracy was still excellent at 92.8% (2,521/2,718) and the pooled sensitivity for detecting malignancy was similarly high at 92.3% (1,497/1,622) (*Table 2*). When nodules were further stratified into ≤1 cm lesions the test characteristics did not decline significantly with a pooled diagnostic accuracy of 92.6% (638/689), and a pooled sensitivity for detecting malignancy at 88.7% (410/462).

Another consistent factor proposed as affecting diagnostic yield was the presence of a ground glass opacity (GGO) component to the lesion being biopsied. However, when articles reporting test characteristics of TTNA of GGO were segregated (*Table 3*), the pooled diagnostic accuracy was still very high at 92.5%, and the pooled sensitivity for detecting malignancy was similar at 91.4% (30-32,35,38,39,50).

Several other factors were inconsistently associated with a lower diagnostic yield in univariate and multivariate analyses including lower lobe biopsy site (28,42,52), acquisition of two or fewer specimens (28), malignant lesions (28,52), benign lesions (25), pneumothorax (PTX) during procedure (52), and use of aspiration needle only (39). Regardless of this mixed data (15,23), a high pretest probability of malignancy is a consistent predictor of high diagnostic accuracy as benign lesions were the most difficult to definitively diagnose on TTNA. Articles that studied patients with a lower pretest probability of malignancy reported the lowest diagnostic yield (46,47).

#### Safety

A sizable amount of case-series data was also available on the safety of CT guided TTNA with seventeen articles identified as specifically describing the complications. Additionally, thirty-six articles designed to describe the test characteristics of CT guided TTNA also provided information on complications encountered (*Table 4*). Generally, the information regarding the most common complications is dominated by the largest, multi-centered case series with over 15,000 subjects (59).

Overall, PTX is the most common safety issue. PTX occurred with a pooled incidence of 20.5% (6,821/33,306) (*Table 4*). The overall pooled incidence of chest tube placement for PTX was 7.3% (2,178/29,930) but varied widely (range, 0-31.1%), likely owing to different and evolving management strategies.

Several risk factors for PTX have been proposed in univariate and multivariate analyses including coaxial stabilizing needle size (13,72), age (13,34,57,72,75), smaller lesion size (23,55,60,64,66,69), depth of lesion (22,23,34,41,53,55,60,62-66,69,72-75), wider trajectory angle (41,63), a higher forced vital capacity (22,63), supine position during biopsy (61), longer puncture time (68), needle passing through a pulmonary fissure (69,75), traversing aerated lung (69,71), emphysema within biopsy path (42,43,72,75), presence of emphysema (73,74), number of pleural surfaces crossed (42,72,75), number of punctures (22,34), anterior biopsy approach (72), posterior biopsy approach (72), lateral biopsy approach (34), and a less experienced operator (66). Once a PTX has occurred, several risk factors for chest tube placement have been consistently identified such as age (52,72), supine position during biopsy (52), benign lung lesion on final diagnosis (52), a history of chronic obstructive pulmonary disease (57,59,60,62,72), emphysema within biopsy path (75),

 

**Table 1** Test characteristics for CT guided transthoracic needle biopsy for pulmonary lesions

| Study | Year | No. | Type of biopsy | Sensitivity (%) | Specificity (%) | Diagnostic accuracy (%) | Lesion sizes (cm) | Other |
|---|---|---|---|---|---|---|---|---|
| Larscheid (11) | 1998 | 109* | 22 or 23-G TTNA | 91 | 100 | 89 | <1 to >6 | |
| Lopez Hänninen (12) | 2001 | 79 | TTCNB 20-G | 96 | 100 | 95 | 0.5-6 | |
| Geraghty (13) | 2003 | 676* | TTNA 18 or 19-G | 91 | 99 | 94 | <1 to >2 | |
| Yankelevitz (14) | 1997 | 114 | TTNA 20 or 22-G | 94 | 100 | 75 | ≤3 | |
| Charig (15) | 2000 | 185 | TTCNB 14, 18, or 20-G | 93 | 100 | 94 | 1.3-11.2 | |
| Hirose (16) | 2000 | 50 | TTCNB 18-G | 89 | 100 | 90 | 0.8-6 | |
| Arslan (17) | 2002 | 294 | TTNA 22-G | 88 | 100 | 82 | 1 to >6 | |
| Lucidarme (18) | 1998 | 89* | TTCNB 18-G | 93 | 100 | 90 | 0.9-8 | |
| García Río (19) | 1994 | 84 | TTNA | 76 | 100 | 82 | 1.8-4 | |
| Wallace (20) | 2002 | 57* | TTNA 20 to 22-G | 82 | 100 | 88 | ≤1 | |
| Laurent (21) | 2000 | 66* | TTCNB 20-G | 91 | 100 | 91 | <2 | |
| | | 132* | TTCNB 20-G | 96 | 100 | 96 | >2 | |
| Ohno (22) | 2003 | 162 | TTNA 22-G | 87 | 100 | 77 | ≤2 | |
| Heyer (23) | 2008 | 172 | TTCNB 16-G | 93 | 100 | 95 | 0.8-7.6 | |
| Montaudon (24) | 2004 | 605 | TTCNB 20-G | 92 | 99 | 94 | Range | |
| Yeow (25) | 2003 | 631 | TTCNB 16 to 20-G | 93 | 98 | 94 | Range | |
| Priola (26) | 2007 | 612 | TTNA 21, 20-G, or TTCNB 18-G | 90 | 99 | 83 | <1 to 11 | |
| Bladt (27) | 2006 | 66* | TTCNB | 81 | 100 | 84 | <1 to >3 | |
| Hiraki (28) | 2009 | 1000 | TTCNB 20-G | 94 | 99 | 95 | <1 to >3 | |
| Inoue (29) | 2012 | 66* | TTCNB 20-G | 95 | 100 | 95 | 0.5-3.5 | Pure GGO |
| Hur (30) | 2009 | 28 | TTNA 20 to 22-G | 71 | 100 | 82 | 0.8-2.8 | GGO |
| Yamauchi (31) | 2011 | 67 | TTCNB | 97 | 100 | 97‡ (2) | 0.6-4.7 | GGO |
| Yamagami (32) | 2013 | 85 | TTCNB | 88 | 100 | 91 | 0.4-3 | GGO |
| Yamagami (33) | 2004 | 22 | mixed | 93 | 100 | 95 | 0.7-2 | Difficult lesions |
| Yang (34) | 2015 | 311 | TTCNB 18-G | 95 | 97 | 93 | ≤3 | |
| De Filippo (35) | 2013 | 78* | TTNA 20-G | 86 | 100 | 86 | 0.7-3 | Some GGO |
| Ng (36) | 2008 | 47* | TTNA 22-G | 68 | 100 | 79 | ≤1 | |
| Zhuang (37) | 2013 | 102 | TTNA 18 or 20-G | 96 | 98 | 96 | 1-7 | Cavitary lesions |
| Kim (38) | 2008 | 43* | TTCNB 18 or 20-G | 92 | 100 | 91‡ (7) | 0.9-3.1 | GGO |
| Choi (39) | 2013 | 268* | Mixed, all 20-G | 93 | 99 | 95‡ (27) | <1 | Some GGO |
| Hayashi (40) | 1998 | 52 | TTCNB 18 or 20-G | 100 | 100 | 96 | <3 | |
| Li (41) | 2013 | 169 | TTCNB 20-G | 90 | 100 | 94 | ≤2 | |
| Lee (42) | 2014 | 1153 | TTCNB 18-G | 96 | 100 | 97 | 0.5-13 | |
| Choi (43) | 2012 | 173 | TTCNB 18-G | 97 | 100 | 98‡ (10) | ≤2 | |
| Choo (44) | 2013 | 107 | TTCNB 18-G | 97 | 100 | 98‡ (9) | ≤1 | Virtual CT scan |
| Lima (45) | 2011 | 89* | TTNA 25-G | 94 | 82 | 84 | Not reported | |
| Mesurolle (46) | 2003 | 85 | TTNA 18, 19, or 21-G | 82 | 100 | 81 | 0.9-9 | Head & neck CA |
| Yankelevitz (47) | 1998 | 48 | TTNA 20 or 22-G | 94 | 100 | 67 | <3 | Negative bronch |
| Yu (48) | 2002 | 52 | TTCNB 18 or 20-G | 97 | 100 | 97‡ (1) | 1.8-15 | |

**Table 1** (*continued*)

 

**Table 1** (*continued*)

| Study | Year | No. | Type of biopsy | Sensitivity (%) | Specificity (%) | Diagnostic accuracy (%) | Lesion sizes (cm) | Other |
|---|---|---|---|---|---|---|---|---|
| Floridi (49) | 2014 | 95 | TTCNB 20-G | 91 | 100 | 93‡ (5) | 0.7-14 | |
| Lu (50) | 2012 | 52* | TTCNB 20-G | 94 | 100 | 94 | ≤3 | GGO |
| Laspas (51) | 2008 | 409 | TTNA 21 or 23-G | 92 | 98 | 93‡ (40) | 0.6-10 | |
| Takeshita (52) | 2015 | 750 | Mixed | 91 | 99 | 93‡ (10) | 0.9-3.9 | |
| Uskül (53) | 2009 | 134 | TTNA 22-G | 83 | 100 | 84 | 1.3-11 | |
| Niu (54) | 2015 | 84 | TTCNB 20-G | 86 | 100 | 89 | 0.5-12 | Pleural lesions |
| Loh (55) | 2013 | 367* | Mixed | 96 | 100 | 97 | 0.6-12.3 | |
| Lee (56) | 2012 | 94 | Mixed | 93 | 100 | 91 | 0.8-12 | |
| Yaffe (57) | 2015 | 173* | TTCNB 18-G | 94 | 92 | 94 | 0.9-3.9 | |
| Jiao de (58) | 2014 | 110 | TTCNB 16-G | 97 | 100 | 97‡ (2) | 0.6-15 | |
| Pooled analysis | | | | 92.1 | | 92.1 | | |

*, subset of a larger population with adequate follow up; ‡, excludes nondiagnostic biopsies (number of biopsies excluded). CT, computed tomography; TTNA, transthoracic needle aspiration; TTCNB, transthoracic core needle biopsy; GGO, ground-glass opacities.

presence of emphysema (52,74), smoking history (59), lesion depth (52,63,72), lateral biopsy approach (72), posterior biopsy approach (72), number of pleural surfaces crossed (72), needle passing through a pulmonary fissure (75), and wider trajectory angle (63). However, many of these biologically plausible risk factors are only inconsistently associated with PTX and chest tube placement, likely owing to the heterogeneity of methods and lack of consistent controlling for confounding (15,37,42,56,61,62,67,68,73,74).

Clinically significant hemorrhage is the next most common complication with a pooled incidence of 2.8% (609/22,313) when defined as hemoptysis, hemothorax, hypotension, chest wall hematoma, or symptoms prompting imaging. These clinically significant hemorrhages were considerably less common than evidence of hemorrhage on screening post biopsy CT scan (41,56,68), and PTX (*Table 4*). Proposed risk factors for any hemorrhage included depth of lesion (41,55,68), number of times the pleura was punctured (68), GGO being biopsied (42,43), and size of the lesion (55,68). Other very rare complications such as cardiac or respiratory arrest, shock, seeding of malignant cells in the biopsy tract, and hemothorax have been reported (76-78). The dreaded complication of air-embolism occurs very rarely with an estimated incidence of 0.02% to 0.07% (52,79).

### *US guided TTNA*

#### Diagnostic accuracy

There is considerably less data available describing US guided TTNA for lung lesions. A total of ten studies met the inclusion and exclusion criteria for the pooled analysis (*Table 5*). Lesions amenable to US guided TTNA were abutting the pleura such that aerated lung did not reflect the US beams before the lesion was visible. The overall pooled diagnostic accuracy was similarly high at 88.7% (446/503), and the sensitivity for detecting malignancy was 91.5% (366/400). The specificity for the diagnosis of malignancy also approached 100% (*Table 5*).

Small lesions were biopsied with only mixed evidence that lesion size affected diagnostic yield (81,89). Pleural adhesion with a lack of lung sliding was also proposed as increasing diagnostic yield (89). As discussed above, a higher pretest probability of malignancy consistently increased the diagnostic yield as benign lesions were more difficult to definitively diagnose (83-89).

#### Safety

US guided TTNA was generally very well tolerated with a pooled incidence of PTX of 4.4% (22/503). This compared favorably to CT guided TTNA; however, US guided lesions are inherently more peripheral. Therefore, PTX is less likely regardless of biopsy method used. To our knowledge, the only comparison of US guided and CT guided TTNA reported retrospectively by Sconfienza *et al.* (90) did find a lower PTX rate with US guidance when biopsying consecutive peripheral lung lesions (14.7% *vs.* 5.8%). Pleural adhesions with a lack of lung sliding were proposed as protective against PTX (89).

 

**Table 2** Test characteristics for CT guided transthoracic needle biopsy for pulmonary lesions ≤2 cm

| Study | Year | No. | Type of biopsy | Sensitivity (%) | Specificity (%) | Diagnostic accuracy (%) | Lesion sizes (cm) | Other |
|---|---|---|---|---|---|---|---|---|
| Studies including data for nodules ≤2 cm | | | | | | | | |
| Yankelevitz (14) | 1997 | 69* | TTNA 20 or 22-G | 90 | 100% | NA | ≤2 | |
| Arslan (17) | 2002 | 20* | TTNA 22-G | NA | NA | 95 | 1 to ≤2 | |
| Wallace (20) | 2002 | 57* | TTNA 20 to 22-G | 82 | 100 | 88 | ≤1 | |
| Laurent (21) | 2000 | 66* | TTCNB 20-G | 91 | 100 | 91 | <2 | |
| Ohno (22) | 2003 | 162 | TTNA 22-G | 87 | 100 | 77 | ≤2 | |
| Hiraki (28) | 2009 | 582* | TTCNB 20-G | 94 | 100 | 95 | ≤2 | |
| Hur (30) | 2009 | 20* | TTNA 20 to 22-G | 69 | 100 | 80 | ≤2 | GGO |
| Yamauchi (31) | 2011 | 50* | TTCNB | 95 | 100 | 96 | ≤2 | GGO |
| Yamagami (33) | 2004 | 22 | mixed | 93 | 100 | 95 | 0.7-2 | Difficult lesions |
| Ng (36) | 2008 | 47* | TTNA 22-G | 68 | 100 | 79 | ≤1 | |
| Zhuang (37) | 2013 | 78* | TTNA 18 or 20-G | 97 | 93 | 96 | <2 | Cavitary lesions |
| Kim (38) | 2008 | 23* | TTCNB 18 or 20-G | 94 | 100 | 91 | <2 | GGO |
| Choi (39) | 2013 | 268* | Mixed, all 20-G | 93 | 99 | 95‡ (27) | <1 | Some GGO |
| Li (41) | 2013 | 169 | TTCNB 20-G | 90 | 100 | 94 | ≤2 | |
| Lee (42) | 2014 | 485* | TTCNB 18-G | 94 | 100 | 96 | ≤2 | |
| Choi (43) | 2012 | 173 | TTCNB 18-G | 97 | 100 | 98‡ (10) | ≤2 | |
| Choo (44) | 2013 | 107 | TTCNB 18-G | 97 | 100 | 98‡ (9) | ≤1 | Virtual CT scan |
| Takeshita (52) | 2015 | 391* | Mixed | NA | NA | 88 | ≤2 | |
| Jiao de (58) | 2014 | 17* | TTCNB 16-G | NA | 100 | 94 | ≤2 | |
| Pooled analysis | | | | 92.3 | | 92.8 | | |
| Studies reporting data for nodules ≤ 1 cm | | | | | | | | |
| Wallace (20) | 2002 | 57* | TTNA 20 to 22-G | 82 | 100 | 88 | ≤1 | |
| Laurent (21) | 2000 | 7* | TTCNB 20-G | 67 | 100 | 86 | ≤1 | |
| Hiraki (28) | 2009 | 151* | TTCNB 20-G | 90 | 100 | 93 | ≤1 | |
| Hur (30) | 2009 | 10* | TTNA 20 to 22-G | 67 | 100 | 80 | ≤1 | GGO |
| Yamauchi (31) | 2011 | 8* | TTCNB | 86 | 100 | 88 | ≤1 | GGO |
| Ng (36) | 2008 | 47* | TTNA 22-G | 68 | 100 | 79 | ≤1 | |
| Choi (39) | 2013 | 268* | Mixed, all 20-G | 93 | 99 | 95‡ (27) | <1 | Some GGO |
| Lee (42) | 2014 | 70* | TTCNB 18-G | 88 | 100 | 93 | ≤1 | |
| Choo (44) | 2013 | 107 | TTCNB 18-G | 97 | 100 | 98‡ (9) | ≤1 | Virtual CT scan |
| Pooled analysis | | | | 88.7 | | 92.6 | | |

*, subset of a larger population with smaller lesions; ‡, excludes nondiagnostic biopsies (number of biopsies excluded). CT, computed tomography; TTNA, transthoracic needle aspiration; TTCNB, transthoracic core needle biopsy; GGO, ground-glass opacities; NA, not available.

 

**Table 3** Test characteristics for CT guided transthoracic needle biopsy for GGO lesions

| Study | Year | No. | Type of biopsy | Sensitivity (%) | Specificity (%) | Diagnostic accuracy (%) | Lesion sizes (cm) | Other |
|---|---|---|---|---|---|---|---|---|
| Inoue (29) | 2012 | 66* | TTCNB 20-G | 95 | 100 | 95 | 0.5-3.5 | Pure GGO |
| Hur (30) | 2009 | 28 | TTNA 20 to 22-G | 71 | 100 | 82 | 0.8-2.8 | GGO |
| Yamauchi (31) | 2011 | 67 | TTCNB | 97 | 100 | 97 | 0.6-4.7 | GGO |
| Yamagami (32) | 2013 | 85 | TTCNB | 88 | 100 | 91 | 0.4-3 | GGO |
| De Filippo (35) | 2013 | 78* | TTNA 20-G | 86 | 100 | 86 | 0.7-3 | Some GGO |
| Kim (38) | 2008 | 43* | TTCNB 18 or 20-G | 92 | 100 | 91 | 0.9-3.1 | GGO |
| Choi (39) | 2013 | 268* | Mixed, all 20-G | 93 | 99 | 95 | <1 | Some GGO |
| Lu (50) | 2012 | 52* | TTCNB 20-G | 94 | 100 | 94 | ≤3 | GGO |
| Pooled analysis | | | | 91.4 | | 92.5 | | |

*, subset of a larger population with adequate follow up. CT, computed tomography; TTNA, transthoracic needle aspiration; TTCNB, transthoracic core needle biopsy; GGO, ground-glass opacities.

### *Electromagnetic navigational-transthoracic needle aspiration (E-TTNA)*

Although CT and US guided TTNA have been proven safe and effective they do not provide mediastinal staging which is essential in providing prognostic information as well as selecting appropriate surgical and oncologic treatment. A novel thoracic navigational system recently developed by Veran Medical Technologies (St Louis, MO, USA) allows operators to perform a virtual CT guided electromagnetic navigational TTNA using a CT scan of the chest obtained prior to the procedure which is virtually paired with the patient using a tracking pad placed on the chest. This allows the operator to perform mediastinal lymph node staging with convex endobronchial ultrasound (EBUS), navigational bronchoscopy if needed and a navigational E-TTNA all in one setting.

#### Diagnostic accuracy

A single center safety and feasibility trial of 24 patients using the above system was recently completed showing a diagnostic yield of 83% for E-TTNA (91), which is comparable to the above cited yield using real time imaging. Of note, when EBUS TBNA of mediastinal lymph nodes as well as navigational bronchoscopy using the same system was completed in the same study the diagnostic yield was raised to 92%.

#### Safety

Using the pilot study cited above, safety of E-TTNA appears to be equivalent to conventional CT guided TTNA. There were five pneumothoraces (20%) after the combined procedure with only two patients requiring pigtail chest tube catheters and admission. There was no other incidence of bleeding, hemoptysis, prolonged intubation or other complications reported.

Although this data is promising, the above pilot data only involves a single center with 24 patients. Further multi-centered, randomized trials with larger enrollment need to be completed before drawing conclusions about the diagnostic accuracy and safety of E-TTNA alone and in comparison to conventional image guided TTNA.

## Conclusions

Image guided TTNA remains an important modality in the diagnosis of thoracic diseases, particularly malignancies. This review has shown a high overall diagnostic yield, sensitivity and specificity for pulmonary nodules using CT and US guided imaging after analysis of 75 published articles. E-TTNA was also examined using data from a recent single center pilot study that showed similar diagnostic yield to the two previously mentioned imaging modalities. However, as this is a small, single center study, this data must be taken in context, with further large multi-center trials needed before this modality can be accepted as an alternative to CT or US guided TTNA.

Regarding safety, both CT and US guidance were extremely safe with the two most common complications reported being PTX, a large proportion of which can be managed conservatively with observation rather than tube

 

**Table 4** Safety profile of CT guided transthoracic needle biopsy

| Study | Year | Number | PTX rate (95% CI if available) (%) | PTX with chest tube (95% CI if available) (%) | Hemorrhage (95% CI if available)* (%) |
|---|---|---|---|---|---|
| Wiener (59) | 2011 | 15,865 | 15.0 (14.0-16.0) | 6.6 (6.0-7.2) | 1.0 (0.9-1.2) |
| Geraghty (13) | 2003 | 846 | 26.7 | 8.7 | NA |
| Kazerooni (60) | 1996 | 121 | 44.6 | 14.9 | NA |
| Nakamura (61) | 2011 | 156 | 59.6 | 7.7 | NA |
| Laurent (62) | 1999 | 307 | 19.9 | 2.0 | NA |
| Saji (63) | 2002 | 289 | 26.6 | 14.2 | NA |
| Yamagami (64) | 2002 | 134 | 34.4 | 2.2 | NA |
| Yeow (65) | 2001 | 117 | 12 | 0 | 3 |
| Yeow (66) | 2004 | 660 | 23.4 | 1.4 | 3.9 |
| Yildirim (67) | 2009 | 225 | 26.2 | 7.6 | 12.9 |
| Khan (68) | 2008 | 135 | 17 | 2.2 | 6.7 |
| Nour-Eldin (69) | 2015 | 650 | 25 | 4.3 | NA |
| Dennie (70) | 2001 | 506 | 22.9 | 6.5 | NA |
| Haramati (71) | 1991 | 131 | 27.4 | 4.6 | 3.8 |
| Kuban (72) | 2015 | 4,262 | 30.3 | 15 | NA |
| Chami (73) | 2015 | 163 | 36.2 | 5.5 | NA |
| Schulze (74) | 2015 | 664 | 21.7 | 6 | NA |
| Kim (75) | 2015 | 1,227 | 21.4 | 2.9 | NA |
| Larscheid (11) | 1998 | 130 | 43 | 18.5 | NA |
| Lopez Hänninen (12) | 2001 | 79 | 24 | 5.1 | 0 |
| Yankelevitz (14) | 1997 | 114 | 20.2 | 5.3 | 0 |
| Charig (15) | 2000 | 183 | 26.2 | 2.2 | 7.1 |
| Hirose (16) | 2000 | 50 | 42 | 12 | NA |
| Arslan (17) | 2002 | 294 | 8.2 | 1 | 3.1 |
| Lucidarme (18) | 1998 | 91 | 34 | 3.3 | 9.9 |
| García Río (19) | 1994 | 84 | 14.3 | 4.8 | 1.2 |
| Wallace (20) | 2002 | 61 | 62.2 | 31.1 | NA |
| Ohno (22) | 2003 | 162 | 28.4 | 2.5 | NA |
| Heyer (23) | 2008 | 172 | 26.2 | NA | NA |
| Yeow (25) | 2003 | 631 | 23.5 | NA | NA |
| Bladt (27) | 2006 | 72 | 9.7 | NA | 1.7 |
| Hur (30) | 2009 | 28 | 17.9 | 7.1 | 10.7 |
| Yamauchi (31) | 2011 | 90 | 15.6 | NA | 14.4 |
| Yamagami (33) | 2004 | 22 | 31.8 | 4.5 | 4.5 |
| Yang (34) | 2015 | 311 | 17.7 | 0.9 | 11.6 |
| Ng (36) | 2008 | 55 | 52.7 | 9.1 | NA |
| Zhuang (37) | 2013 | 102 | 8.8 | NA | 14.7 |
| Kim (38) | 2008 | 55 | 18.2 | 1.8 | 12.7 |
| Li (41) | 2013 | 169 | 14.8 | 1.8 | 6.5 |
| Lee (42) | 2014 | 1,153 | 17 | NA | 6.9 |

**Table 4** (*continued*)

 

**Table 4** (*continued*)

| Study | Year | Number | PTX rate (95% CI if available) (%) | PTX with chest tube (95% CI if available) (%) | Hemorrhage (95% CI if available)* (%) |
|---|---|---|---|---|---|
| Choi (43) | 2012 | 173 | 31.8 | 1.7 | 14.5 |
| Choo (44) | 2013 | 107 | 6.5 | NA | 5.6 |
| Lima (45) | 2011 | 97 | 27.8 | 12.4 | 2 |
| Yu (48) | 2002 | 52 | 11.5 | 0 | 5.8 |
| Floridi (49) | 2014 | 95 | 21.1 | 0 | NA |
| Lu (50) | 2012 | 55 | 47.3 | NA | 20 |
| Laspas (51) | 2008 | 409 | 4.2 | 0.2 | 0.2 |
| Takeshita (52) | 2015 | 750 | 36.8 | NA | 12.1 |
| Uskül (53) | 2009 | 134 | 16.4 | NA | NA |
| Niu (54) | 2015 | 84 | 16.7 | 2.4 | NA |
| Loh (55) | 2013 | 399 | 34.8 | 3 | 3.8 |
| Lee (56) | 2012 | 94 | 25.5 | 1 | NA |
| Yaffe (57) | 2015 | 181 | 26.5 | 1.1 | 9.4 |
| Jiao de (58) | 2014 | 110 | 12 | NA | 6.5 |
| Pooled analysis | | | 20.5 | 7.3 | 2.8 |

*, includes the subset of clinically apparent bleeding only: hemoptysis, hemothorax, hemorrhagic shock, chest wall hematoma, or symptoms prompting imaging. CT, computed tomography; PTX, pneumothorax; CI, confidence interval; NA, not available.

**Table 5** Test characteristics for US guided transthoracic needle aspirations for pulmonary lesions

| Study | Year | No. | Sensitivity (%) | Specificity (%) | Diagnostic accuracy (%) | Pleural based lesion | Other | PTX (%) |
|---|---|---|---|---|---|---|---|---|
| Knudsen (80) | 1996 | 134 | 100‡ (15) | 94‡ (15) | 98‡ (15) | Y | | 3.7 |
| Targhetta (81) | 1993 | 64 | 91 | 100 | 86 | Y | | 3.1 |
| Yuan (82) | 1992 | 30 | 92 | 100 | 90 | Y | Lesions <3 cm | 3.3 |
| Yang (83) | 1985 | 25 | 100 | 100 | 84 | Y | | 8 |
| Chen (84) | 1995 | 40 | 97 | 100 | 88 | Y | | 5 |
| Chen (85) | 1996 | 34* | 96 | 100 | 88 | Y | ≤3 cm | 2.5 |
| Dallari (86) | 1999 | 45 | 92 | 100 | 80 | Y | | 0 |
| Khosla (87) | 2009 | 21 | 90 | 100 | 95 | Y | | 0 |
| Hsu (88) | 1993 | 16 | 94 | 100 | 94 | Y | Apical lesions | 0 |
| Meena (89) | 2015 | 109 | 80 | 90 | 83 | Y | 6.4% hemoptysis | 8.3 |
| Pooled analysis | | | 91.5 | | 88.7 | | | 4.4 |

*, subset of a larger population with adequate follow up; ‡, excludes nondiagnostic biopsies (number of biopsies excluded). US, ultrasound; TTNA, transthoracic needle aspiration; TTCNB, transthoracic core needle biopsy; Y, yes; N, no; PTX, pneumothorax.

thoracostomy, as well as hemorrhage. Serious complications including hemothorax, air embolism, or cardiopulmonary arrest have been reported, but are extremely rare. There is a higher reported PTX rate using CT guided imaging as compared to US guidance. This is likely secondary to the fact that US guided biopsies are only performed on nodules and masses that are directly abutting the pleura. E-TTNA also appears to have an equivalent safety profile compared to CT guided TTNA, but again this data must be taken in context as discussed above.

 

One disadvantage with percutaneous biopsy of potential lung malignancies is the inability to simultaneously stage the mediastinum as is possible with bronchoscopic lung biopsy with simultaneous convex EBUS trans-bronchial needle aspiration of mediastinal lymph nodes. However, as diagnostic yield for bronchoscopic biopsies of peripheral lung nodules remains significantly lower than with CT guided TTNA even under navigational guidance (92), a combined modality of performing EBUS staging, attempted bronchoscopic biopsy and if unsuccessful E-TTNA biopsy of the suspected nodule may provide an efficient and convenient pathway to lung cancer diagnosis and staging for patients in the near future.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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Interventional Diagnostic Technique

# Ultrasound-guided central vascular interventions, comments on the European Federation of Societies for Ultrasound in Medicine and Biology guidelines on interventional ultrasound

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**Abstract:** Central venous access has traditionally been performed on the basis of designated anatomical landmarks. However, due to patients' individual anatomy and vessel pathology and depending on individual operators' skill, this landmark approach is associated with a significant failure rate and complication risk. There is substantial evidence demonstrating significant improvement in effectiveness and safety of vascular access by realtime ultrasound (US)-guidance, as compared to the anatomical landmark-guided approach. This review comments on the evidence-based recommendations on US-guided vascular access which have been published recently within the framework of Guidelines on Interventional Ultrasound (InVUS) of the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) from a clinical practice point of view.

**Keywords:** Guidelines; intervention; ultrasound-guidance (US-guidance); vascular access; central venous catheters; anatomic landmarks

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## Introduction

Sonographic imaging of potential target vessels to determine the most appropriate vessel, the ideal puncture site and the best patient position, is a reasonable approach to identify anatomical variations known to occur in a substantial portion of veins (1-5).

Ultrasound (US) guided catheter placement into the subclavian and internal jugular veins (IJVs) was first described in 1975 (6,7). The first attempts to use a Doppler-controlled needle director as an aid for percutaneous angiography were reported in 1973. More recently US guidance for vascular access has been introduced

 

more widely also as quality parameter to minimize complications (8). Real time ultrasound (RTUS) has proven beneficial in guiding interventional procedures under many circumstances, becoming standard in clinical practice for many years (9). Through technical advances and improvements of image quality, RTUS allows identification of vessel localisation the best target vessel and optimised puncture site (10). Anatomical variations can be easily identified (1-5) and vein thrombosis excluded which is not only of importance in oncological patients (11,12). It is important to exclude vein catheter associated thrombosis in, for example, critical care patients.

The aim of this paper is to summarize and comment on the recently published European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) on interventional ultrasound (INVUS), part VI, US-guided vascular interventions (13), to give practical advice and to illustrate the procedures. We refer also to the current EFSUMB guidelines on INVUS (13-18) on contrast enhanced ultrasound (CEUS) (19-21), elastography (22,23), and comments on the guidelines (24-29).

## Basic principles

The three cornerstones for US guided vascular interventions are the patient, the interventionalist and US equipment.

### *Indications and contraindications*

Most importantly the right indication for each kind of vascular access should be justified; this is especially true for central vascular access. The information provided to the patient depends on the situation (emergency) and on their level of consciousness (13).

Establishing central venous access is fundamental for emergency physicians in order to monitor the hemodynamics, central venous pressure (CVP) and pulse contour cardiac output (PiCCO), to deliver vasoactive drugs, hyperosmolar fluids and volume resuscitation (30). In oncological and haematological patients, central venous access is often required for blood sampling and for peripheral stem cell preparation, as well as for administration of blood products, chemotherapy or other drugs (11). Advantages of US-guidance for central venous access have been proved in a variate patient population, including critically ill patients (31,32), ventilated patients (33), both oncological and haematological patients (11,34-37), in situations when a parental nutrition was needed (37) or in haemodialised patients (38,39). Outcomes are improved for experienced as well as inexperienced operators (40). Given a clear indication, there is no absolute contraindication for US-guided vascular access and interventions.

### Which central venous access?

Due to coagulation disorders, thrombocytopenia (disease- or therapy-associated) and hemostasis disorders, oncological and hematological patients belong to the high-risk group for central venous access (11,41). Additionally, anatomical changes may be encountered in patients with the primary tumor, metastases or lymphoma in the puncture region (11).

One of the advantages of the subclavian/axillary approach is that it can be used for central venous catheter placement in patients with severe burns on the face, neck, and/or proximal shoulders (42). Still, there are drawbacks related to the smaller diameter and deeper location of subclavian and axillary veins (43).

### Risks and complications

The complication rates using the traditional landmark technique range from 0.3% to 18.8%, depending on multiple factors, such as patient population, site of insertion, time taken, number of needle passes and the specific definition of complications used (44-48). Evidence from meta-analyses of RCTs shows that RTUS-guided access to the IJV and subclavian vein (SV) in adults has a significantly lower failure rate as compared to the traditional 'blind' access and that it is associated with a decreased rate of complications, requires a shorter access time and fewer attempts for successful access (30,38,39,49-52). In the meta-analysis of Hind *et al.*, commissioned by the British National Institute for Clinical Excellence (NICE), the relative risk of complications, of failed attempts, and failed first attempt were reduced by 57%, 86%, and 41%, respectively (49). The two most important improvements associated with US guided technique versus landmark technique are lower risks of inadvertent arterial puncture and of local hematoma (37). It is important to recognise however that adverse events may occur also under RTUS-guidance. In particular, improper catheter placement, arterial puncture, hematoma at the puncture place, air embolism, or nerve lesions have been reported (53,54). Pneumo- and/or hemothorax are very rare events if central venous puncture is performed under RTUS-guidance (50,51). Furthermore, catheter misplacement or pneumo-/hemothorax in most cases are recognized by US at the time of intervention (54-63). Thrombosis, arteriovenous fistula and pseudoaneurysms represent possible mid-/long-

 

term complications of central venous catheter placement and all can be easily detected by means of US (64-70). In the study of Kaye *et al.* (n=325 patients undergoing cardiovascular surgery), complication rates after central vein catheterization (including carotid artery puncture and pneumothorax) were significantly higher for the group who received catheter placement without US-guidance, as compared to the group having catheter placement with US (71). Using US-guidance for central venous catheter placement, Cavanna *et al.* reported symptomatic deep-vein thrombosis of the upper limbs in 2.4% of the cases and catheter related infections in 10% of the catheters inserted. Removal of the catheter due to complications was necessary only in 2.9% of cases. No major bleeding, nerve puncture or pneumothorax was reported (34).

Despite US-guidance, posterior vessel wall puncture may occur as a complication of venous catheterisation (72,73). Factors influencing the risk of posterior wall penetration are the particular access technique (transverse *vs.* longitudinal approach), the speed of needle insertion, the distance between needle entry and transducer, and the angle of insertion (74).

**Tips and tricks (how to avoid risks and complications)**

Here are some important points to avoid unsuccesful punctures:

- Check the equipment and its function during preparation;
- Optimise the B-mode picture of the target vessel;
- Optimise positioning of the patient (e.g., Trendelenburg position), of the examiner and of the US device relative to the puncture site (aim for a comfortable working environment for the interventionalist);
- Choose the most appropriate head position in order to locate the target vein laterally rather than anterior to the artery;
- Skills training on appropriate phantoms and in normal patient conditions prior to emergency situations;
- In hypovolemic patients: give intravenous fluid before puncture;
- The indication for central lines must be well considered—sometimes peripheral vascular access meets the needs of the condition.

### *Patient informed consent*

Each procedure intended for diagnosis or treatment must be undertaken only after informed consent has been obtained from the conscious patient (75) or legal representative, after receiving comprehensible and understandable information about the procedure's goal and benefits, potential risks, alternatives and complications (76). There is no legal requirement for consent to be written, or be in a particular setting, however, a signed written consent form provides documentary evidence. Consent may be withdrawn at any time, even after the form has been signed, and should lead to immediate discontinuation of a procedure. It is the responsibility of the doctor to be aware of the valid legislation and ethical guidelines in their region. The European Society for Cardiovascular and Interventional Radiology and the Society of Interventional Radiology provide information on many interventional radiology procedures on their website (www.cirse.org). The Royal College of Radiologists (UK) and the British Society of Interventional Radiology has similar information at www.rcr.org.

### *Interventionalist*

Adequate teaching, education and training are necessary for a successful procedure. The degree of US experience significantly influences complication rates (71,77). Several studies have shown that simulation-based learning of US-guided central venous access increases skills in simulated central venous catheter insertion and is more effective than traditional bedside teaching (78-81). Moreover, a recent meta-analysis of 20 comparative studies gave proof of significant improvement in performance not only at simulators but also in some clinical outcome parameters, in particular number of needle passes to achieve central venous access and frequency of pneumothorax (82). Comparable results were reported in a meta-analysis of prospective comparative cohort-studies (83). Therefore, simulation training should be included in training programs for RTUS-guided central venous access to improve the real clinical performance of trainees.

### *Which US equipment?*

The US equipment should allow good to excellent near field resolution. Particular presets for e.g., cervical, brachial and femoral vessels are helpful.

### *Which transducer?*

High frequency (5–17 MHz, in practice 7–12 MHz) linear transducers with a relatively small aperture of less than 4–6 cm are recommended for superficial locations. In

 

**Figure 1** Sterile covering of the transducer before US-guided vascular access. US, ultrasound.

deeper locations (e.g., femoral vessels), particularly in obese or oedematous patients, the use of a curved array abdominal probe may be necessary.

### *Transducer guides*

Transducers may offer vendor-dependent needle guides but only a limited number of transducers are useful and most punctures will be done free hand.

### *Hygiene*

#### Sterile covers

For vascular access under US-guidance, after probe decontamination, a sterile barrier is needed, which must cover both the transducer and the cable (43). Sterile covers are mandatory according to hygiene recommendations and to avoid contact of the transducer membrane with alcohol or other disinfection fluids. It is generally required to use sterile, disposable probe covers made of latex-free material and applied under aseptic conditions, following manufacturers' instructions (84) (*Figure 1*). Random testing of the batch may be done in order to assess package integrity (85). If no sterile transducer covers are available, a sterile glove may be used. In a similar fashion contact gel will be placed inside, and the flat palm surface of the glove will be used to cover the scanning surface of the transducer. Attention must be paid to eliminate any air bubbles possibly interposed between the scanning surface of the transducer and the cover or glove (43).

#### Sterile US gel

Only sterile US gel should be used in interventional procedures, packed in small packages matching the gel requirement for one examination and a new sachet should be used for each patient (86-94). Residual product should not be used on further patients since it may be a potential vehicle for nosocomial infections. Disposable probe covers filled with sterile gel are also available (84,86-89,91,93-95). Alternatively, disinfectant solutions may be used to ensure acoustical coupling between the skin surface and the covered transducer.

#### Transducer decontamination

Sterile transducer covers do not eliminate the need for transducer decontamination (96-98). Sterilization of the transducer after use is necessary in procedures with a high risk of contamination. The cleaning technique of transducers using disinfection varies between manufacturers. For more details see the EFSUMB guidelines on interventional procedures (13-18,24,99).

## US guiding techniques

### *Definition*

US-guidance for venous cannulation can be performed using different approaches. Therefore, some definitions will be discussed in the following paragraphs including "landmark technique", "direct" and "indirect" methods, US-assistance and US-guidance, free hand technique, puncture transducers and transducer mounted devices. The "direct" technique implies needle placement under permanent real-time RTUS control (US-guidance). The needle is visualized on the US monitor as an echogenic line with ring-down artefact and the cannulation process can be monitored completely by US (43). "Indirect" (or static) techniques (US-assistance) imply that US is used to locate the appropriate target vessel, to examine its topographical relations to surrounding structures and to assess its dimensions and depth from the skin. This is therefore a simplified technique, with the advantage that sterile covers are not necessary for the transducer and there is less equipment to manipulate during the sterile line insertion. Optionally, marking might be drawn or placed on the skin corresponding to the vessel's position just at the point where the center of the transducer overlies the center of the vessel (43). Another method which has proved to be beneficial, especially for inexperienced operators, is the mechanical US-guided approach. This implies the use of an attachment to the transducer which provides a fixed needle trajectory. The method has better success rate, improved venous access time, improved average number of attempts to success and was associated with fewer complications when compared to the traditional landmark approach (43,100). Doppler US can also be used to facilitate vessel visualization.

 

## Comparison of access techniques

### *Review of the literature*

#### US-assistance *vs.* landmark approach

Two randomized control trials (RCTs) have demonstrated that with US-assistance ("static ultrasound" for pre-procedural evaluation) IJV catheterisation can be performed quicker in comparison to the traditional landmark technique (101,102). Furthermore first attempt success rate was higher with US assistance (101). In one RCT comparing landmark and US-assisted techniques in ventilated patients with respiratory jugular venodilation, results of cannulation did not differ with respect to first attempt cannulation, overall success rate or the incidence of arterial puncture. However, in the patients without respiratory jugular venodilation, those outcome parameters were significantly improved in the US-assisted group (33).

A further RCT comparing complications and failures of SV catheterization using the standard landmark technique and US-assisted technique found no significant differences between the two methods (45). There are no data comparing US-assistance and landmark technique for femoral venous (FV) access (13).

#### US-guidance versus landmark approach

US-guidance versus landmark approach has been discussed in detail in the EFSUMB guidelines (13). There is convincing evidence from meta-analyses of RCTs that RTUS-guided access to the IJV and SV in adult patients is associated with a significantly lower failure rate both overall and on the first attempt, a shorter access time, and decreased rates of arterial puncture and hematoma formation compared to the traditional anatomical landmark approach (30,38,39,49-51,103,104). These advantages were shown for particular patient groups and clinical situations, e.g., for adults requiring emergent central venous catheter placement (51,52), ventilated patients (33), critical care patients (31,32), in oncological and haematological patients (34-36), in elective situations for parenteral nutrition (37), and for placement of hemodialysis catheters (13,38,39).

#### US-assistance versus US-guidance

The results of RCTs comparing US-assistance and RTUS-guidance for central venous access are conflicting (13,102,104,105). A prospective randomized study was conducted by Nadig, in order to assess if the rate of unsuccessful attempts in puncturing the IJV for the placement of dialysis catheters can be reduced with the use of RTUS-guidance. In 36 punctures with RTUS-guidance only 10 unsuccessful attempts occurred, as compared to 87 unsuccessful attempts in 37 punctures using only a skin mark determined by US. Also, a reduced time to successful puncture in favour of RTUS guidance (3.4±0.9 versus 4.8±2.2 min) has been registered (106).

#### Conclusions

Based on this evidence, RTUS-guidance for central venous catheter placement has been endorsed as a key safety measure by both the Agency for Healthcare Quality and Research in the United States and the National Institute for Health and Care Excellence (NICE) in the UK (8,13,107-114).

### *Real time US guidance, examination technique*

The fundamental technique of InVUS (the puncture principle) is an alignment of two planes, namely the "scan plane" that shows the target vessel on the US screen and the "needle plane" containing the needle (or other InVUS device) approaching the target. Real-time visualization of the needle tip is possible using US due to the reflection from the metal in the needle (115). The intensity of the display of echoes from the "needle plane" will depend on the needle size, the scanning depth, angulation and the US system (116). The RTUS-guidance technique can be divided into three different approaches, the longitudinal, transverse and oblique techniques.

Using the longitudinal technique, the target vessel is delineated in a long-axis view (referring to the needle: in-plane approach). With the transverse technique the target vessel is approached in a short-axis (transverse) view (referring to the needle: out-of-plane approach). Both techniques may be combined (oblique technique) (43). There is conflicting evidence with regard to the particular US-guidance technique (short-axis view/out-of-plane approach *vs.* long-axis view/in-plane approach), which precludes recommendation in favour of either of the two approaches (14,15,74,117-122).

#### Longitudinal technique

In the longitudinal technique the transducer is placed parallel to the vessel and the needle at the greatest anterio-posterior diameter of the targeted vessel. The puncture of the skin has to be close to one end of the transducer under an angle of approximately 30° from the skin surface depending from the skin-vessel distance (43). The course of the target vessel and the complete process of insertion and

 

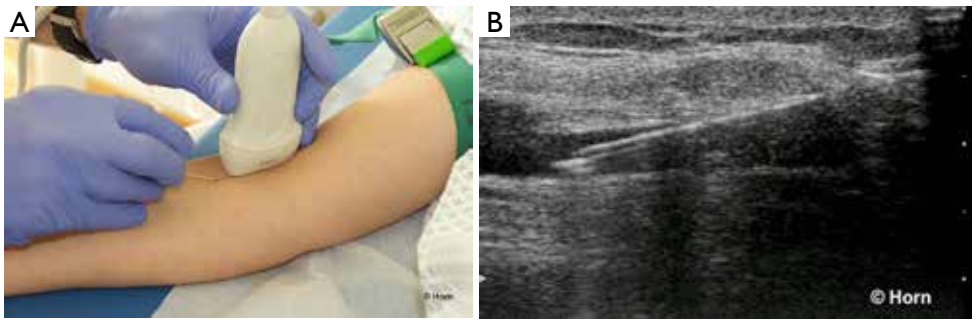


**Figure 2** Longitudinal approach. (A) Insertion of the needle along the long axis of the US transducer; (B) RTUS visualization of the needle course. US, ultrasound; RTUS, real time US.

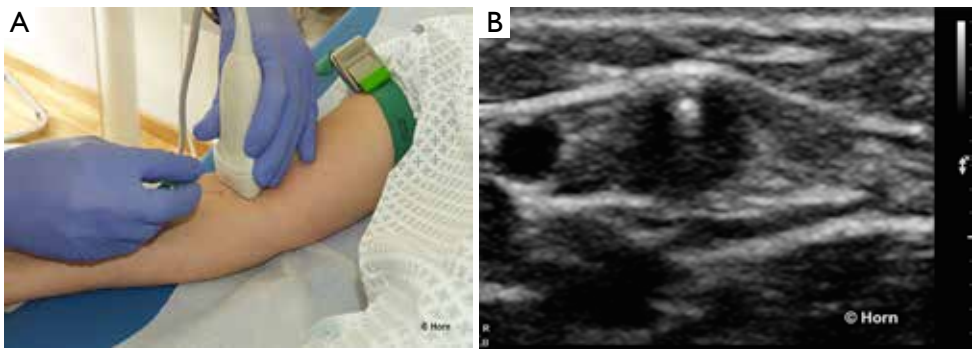


**Figure 3** Transversal approach: the US transducer is placed transversally to the target vessel. (A) Needle insertion in the middle of the transducer; (B) RTUS-guidance of the course of the needle tip. US, ultrasound; RTUS, real time US.

advancement of the needle are visualized in real-time in the long axis of the transducer (*Figure 2*).

The advantage of this technique is the view of the whole needle which allows the operator to define the optimal insertion angle. By doing this the posterior wall of the vein will not be penetrated (123). However, in particular anatomical situations it may be difficult to show the course of the target vessel.

### Transverse technique

In the transverse technique, also called the short-axis view, the position of the transducer is transversally placed to the vessel and the needle. The puncture of the skin should be performed exactly in the middle of the probe with an angle of approximately 45° to the skin. By tilting the probe during insertion, the tip of the needle is followed (*Figure 3*). The advantage of this technique is the reliable positioning of the needle tip according to the course of the vessel, preventing a deviation from the vessel's axis to the right or left. The transverse technique is useful in anatomical areas with limited access space and for cannulation of smaller vessels. It offers more confidence for inexperienced users. In the case of unsuccessful puncture, visualisation of needle tip deviation is easy. Disadvantages are possible loss of control over the needle tip with the risk of posterior wall penetration. Posterior vessel wall penetration is a frequent event in short-axis approach to IJV cannulation (72). Moreover, it is difficult to determine the most appropriate angle for insertion.

### Oblique technique

In particular anatomical conditions, like puncture of the SV, the oblique technique may be helpful. It combines advantages of the short and long-axis approaches, respectively better visualisation of the anatomical structures provided by the short-axis view and better needle tip visualization provided by the long-axis view (124).

In this approach, the position of the probe is parallel to the needle and oblique to the vessel. The view of the whole needle is maintained, while the vessel is only partially visible.

 

### Comparison of long-axis versus short-axis vascular access

The prospective trial of Stone *et al.* (74) proved that the long-axis access allows improved visualization of the needle tip at the time of puncture, a result which is consistent with standard approaches of other procedures done under US-guidance (e.g., regional nerve anesthesia under US-guidance) (125,126). In this study no statistically significant differences of the time to vessel access were observed between inexperienced and experienced interventionalists (74). A recent RCT demonstrated that the long-axis access approach to the IJV and SV was more time efficient than the short-axis access. The long-axis approach to SV catheterization was also associated with fewer posterior wall penetrations (118). Disconcordantly, Blaivas *et al.* reported that emergency medicine residents without previous experience in US-guidance in an inanimate model were able to complete the procedure faster using the short-axis approach as compared to the long-axis approach (123).

## US imaging techniques

### *B-mode*

In preparation of an US-guided procedure, it is important to choose the appropriate transducer, imaging program (presetting/application) and the correct interventional apparatus (14,15). Before puncture, it is mandatory to clearly identify the vein and to rule out thrombosis, which is often done by the compressibility test using B-mode. However, in patients with very low blood pressure the artery may also be compressible. The threshold for arterial compressibility is assumed to be <60 mmHg. In patients with a very low blood flow, blood stasis may look like thrombosis using B-mode. The compressibility test may be helpful but sometimes colour Doppler imaging (CDI) and rarely CEUS are necessary to prove or rule out thrombosis (*Figures 4-6*). Surgical emphysema, for example in thoracic trauma, reduces the visibility of vessels. Other artifacts

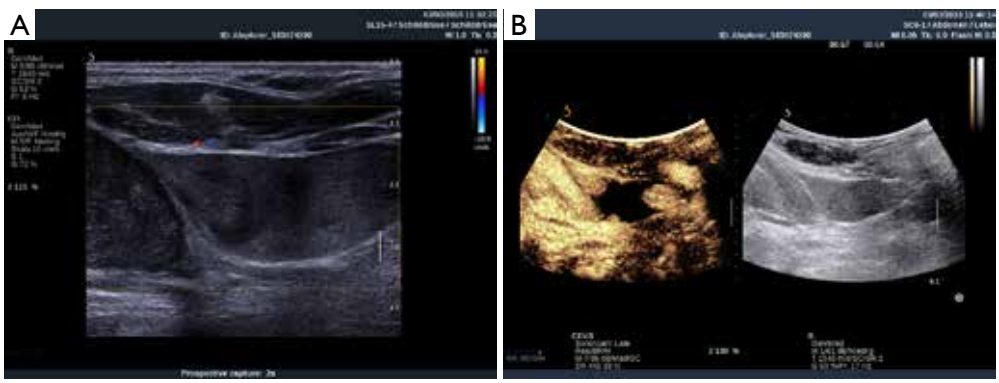


**Figure 4** Difficult venous access due to a hypoechoic tumor (Schwannoma). (A) B-mode US; (B) delineation of the tumor and the target vessel using CEUS. US, ultrasound; CEUS, contrast-enhanced US.

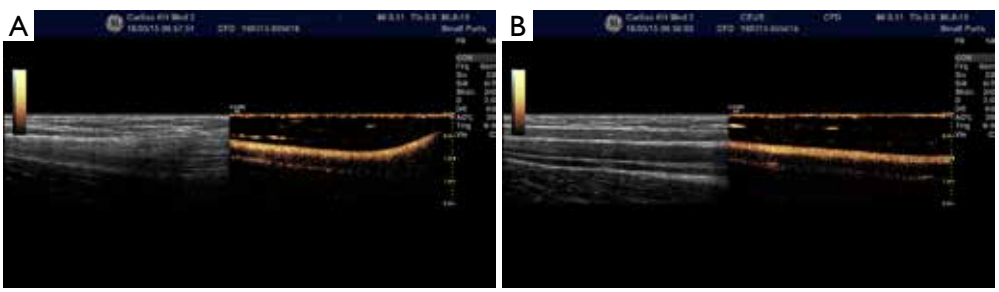


**Figure 5** Proof of intravasal position of a venous catheter using contrast-enhanced ultrasound. (A) Site of catheter insertion; (B) delineation of the vessel lumen by the injected contrast agent.

 

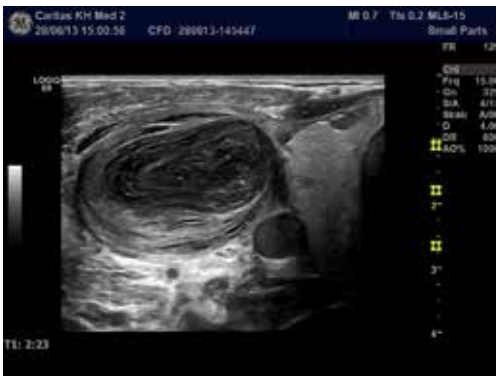

**Figure 6** Ultrasound image of thrombosis of the right internal jugular vein.

may be caused by circumscribed sclerosis of the arterial walls.

### *CDI*

CDI may be helpful to differentiate arteries and veins and might help to identify anatomical variants and pathological findings. Compared with the landmark technique, Doppler-guidance increases the first-attempt success rate of central venous catheter placement by 58% (103). The meta-analysis of Rabindranath *et al.* (39) included RCTs in patients requiring hemodialysis catheter insertion. Compared to the landmark approach, RTUS Doppler-guidance significantly decreased catheter placement failure, first-attempt failure rate, time to canulation, and number of attempts per catheter insertion. Associated complications such as arterial puncture or hematoma formation were also significantly decreased. They concluded that RTUS-guidance using Doppler US should be strongly recommended for hemodialysis catheter placement.

### *CEUS*

With the use of RTUS-guidance for catheter placement, the canulation of a thrombosed or of a small vein can be prevented (49).

CEUS is helpful:

- To diagnose thrombosis;
- To exclude thrombosis;
- For catheter tip position control;
- For detection of catheter obstruction;
- To detect pericatheter leakage.

### *Additional imaging*

All available imaging results should be used to reduce the associated risk of vascular access. Mainly in oncological patients computed tomography and easily available US findings (21,127-129) but also the endoscopic US reports should be known (130-135).

## Central venous access

### *General remarks*

The most common used central veins for vascular access are the IJV, the femoral vein (FV) and the SV. The most appropriate central venous access site depends on the particular circumstances of the patient. As a first step, thrombosis should be ruled out. Especially for access through the IJV, it is mandatory to examine the contralateral veins since thrombosis is a contraindication to catheterisation. The IJV is the easiest central vein to puncture. On the other hand, SV access is associated with the lowest infection rate. For intravascular temperature management the FV is also a good choice. A traditional 'blind' approach reported failure rates of 30% or higher in emergent or cardiopulmonary arrest cases (44,136-138). In 2001, RTUS-guidance for central venous access was listed in guidelines published by the American College of Emergency Physicians as one of the primary applications for emergency US (139). Skin disinfection should be performed according to local hospital guidelines for surgical disinfection. For normal central lines, chlorhexidine is often recommended. We refer to the EFSUMB guidelines (14,15).

#### Anatomy

RTUS allows determination of anatomical variants, such as small diameter, medial or lateral displacement. Valsalva maneuver response, or lack thereof, needs to be correctly assessed and evaluated in order to avoid further complications.

#### Ultrasonographic vessel screening and imaging before vascular access

US vessel screening and imaging of the target vessels should be performed to determine the most appropriate anatomical site and the optimal patient position for central vascular access (13). In order to successfully cannulate a vessel, understanding of the technical issues is necessary. A decision upon the best approach for US-guidance (direct, indirect, free-hand, mechanical guide, Doppler) should be made by

 

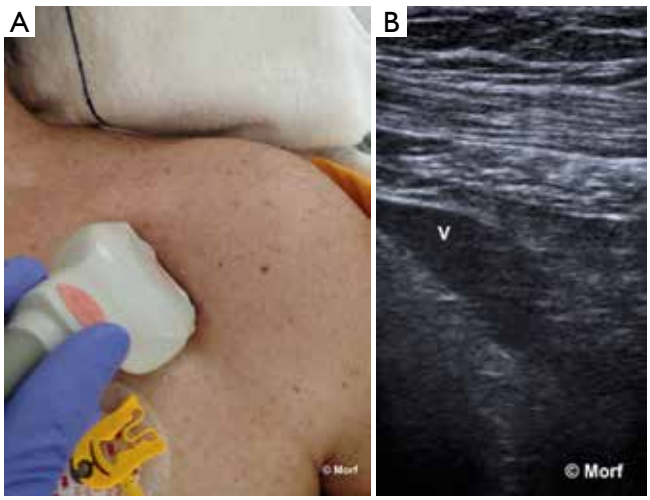


**Figure 7** Sonographic visualization of the subclavian vein: transducer position (A), corresponding US image (B). US, ultrasound.

the operator, according to patients' characteristics, equipment used and operator expertise (43). Changes in head position may influence the vein diameter and the relative position of surrounding vessels (3,140), so care must be taken (141).

**Procedure**

As central line insertion is painful, local anesthesia is recommended. The Seldinger procedure is normally performed. In brief, for the initial puncture a needle with attached syringe, half filled with sterile fluid, is used. After blood aspiration a guide wire is advanced under RTUS control. For the beginner, we recommend learning this procedure with another interventionalist present to aid. The second step is to perform it alone, as good coordination is required to perform the puncture with just one hand whilst manipulating the US probe with the other.

### *Jugular vein*

Central venous access through the IJV is preferred in many cases. Due to its larger diameter it is easily accessed with wider catheters, as for hemodialysis or plasmapheresis. The rate of delayed complications, such as stenosis, is lower than for other central veins (11).

**Anatomy**

The IJV usually lies anterior and slightly lateral to the carotid artery, being usually larger (3), however variants are common.

**Review of the literature**

Denys *et al.* found IJV anatomical variants in 8% of the 200 patients assessed (2). Of 1,009 patients assessed by Troianos *et al.*, in 54% of cases the IJV overlaid the carotid artery, predisposing to arterial puncture (5). Docktor *et al.* found the same anatomical variant in 25% of 150 patients (141). Benter *et al.* investigated 113 patients with haematological or oncological diseases, examining sonographically potential target regions for placement of a central catheter via the IJV and found anatomical variations of the IJV location and surrounding tissues in 36% of the patients (*Figure* 7). They concluded that the use of US-guided techniques for central venous catheters placement, particularly in haematological and oncological patients, is of particular importance in order to avoid arterial puncture (11). Particular attention must be payed to this group of patients because they may present a partially or completely thrombosed IJV, in up to 6% of cases according to the study of Benter *et al.* (11), whilst 4.4% of those investigated by Denys *et al.* had either thrombosed or absent IJV (2). A small IJV diameters ≤7 mm has been reported in 12–15% of the cases (142,143) and is associated with a catheterization failure rate of 14.9% (as compared to 3.9%, if IJV diameter is >7–10 mm) and a complication rate of 8.5% (as compared to 3.8%, if the IJV diameter is >7–10 mm) (143). The right IJV is as big, or bigger than the left IJV in about 74% of the patients, and offers a straighter and more direct path to the superior vena cava and the right atrium. Its cannulation is associated with a lower risk of pneumothorax, since the right lung apex is lower than the left one (142). It is worth noting that the diameter of the IJV expands during the Valsalva maneuver (144).

There might be differences in neonates and infants (105). Using variable degrees of head rotation, Lorchirachoonkul *et al.* proved that at 30° head rotation there is a potential for difficult catheterisation in 15%, with more difficulty on the left as compared to the right IJV (20% versus 10%). Head rotation did not significantly influence neither the risk of difficult catheterization, neither the size of the IJV nor the average distance between mid IJV and the skin. However, the degree of head rotation influences the position of the IJV relative to the carotid artery on both sides, with an increased overlap as the head is rotated further from the midline (142). These results have been recently confirmed by Maecken *et al.* only for the left IJV. These authors did not observe a significant impact of head position on the position of the right IJV (3). Therefore because anatomical variations

 

**Figure 8** Equipment preparation for sterile vessel puncture.

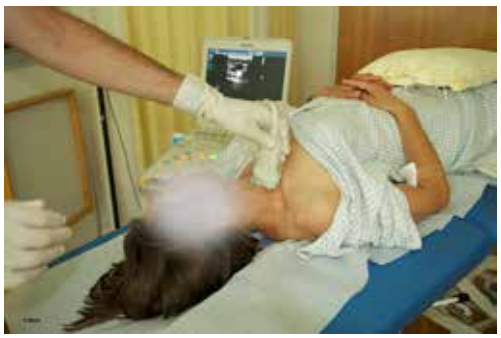

**Figure 9** Position of the interventionalist for RTUS-guided IJV access. RTUS, real time ultrasound; IJV, internal jugular vein.

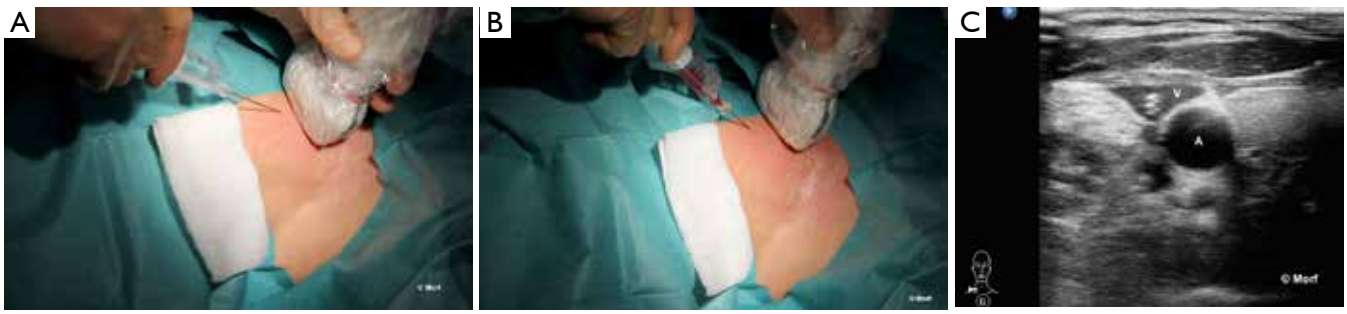


**Figure 10** RTUS-guided central venous access technique. (A) Puncture; (B) aspiration of blood; (C) sonographic visualization of the needle tip with the vessel lumen (V: internal jugular vein; A: common carotid artery). RTUS, real time ultrasound.

impact on the success of IJV catheterization, as well as the incidence of associated complications, the use of RTUS-guidance is also recommended in patients with seemingly normal neck anatomy (142).

### Technique and results

IJV catheterisation with RTUS-guidance can be performed faster, with a higher success rate (101,102) and fewer complications (33) than the traditional landmark technique (*Figures 8-10*).

### Risks and complications

Adverse events can occur even under RTUS-guidance in about 20% of the cases of IJV central line attempts (53). Complications can be classified in three categories: mechanical (with anatomical variations an important risk factor), infectious and thromboembolic (142). The most frequently encountered complication is placement of the catheter tip within the right atrium, which occurs in about 6–14% of the cases. Cardiac malposition is associated with a mortality risk due to possible cardiac perforation and subsequent tamponade (54). Pneumothorax and hemothorax are very rare if RTUS-guidance is used for central venous access (50,51). Puncture of the carotid artery is a common complication as well (*Figure 11*).

### Tips and tricks (how to avoid risks and complications)

Where the IJV overlays the carotid artery, arterial puncture may occur due to the so-called "double wall puncture" phenomenon. This occurs in cases of low IJV pressure, allowing the anterior wall to be pushed against the posterior wall and the IJV to be completely compressed before the needle punctures it (100,141). A common solution is to advance the needle a little deeper and then slightly retract, until the tip lies within the IJV lumen. Exclusion of an underlying carotid artery however, is of utmost importance with this technique (100).

## *SV*

The size of the SV allows placement of central access catheters.

 

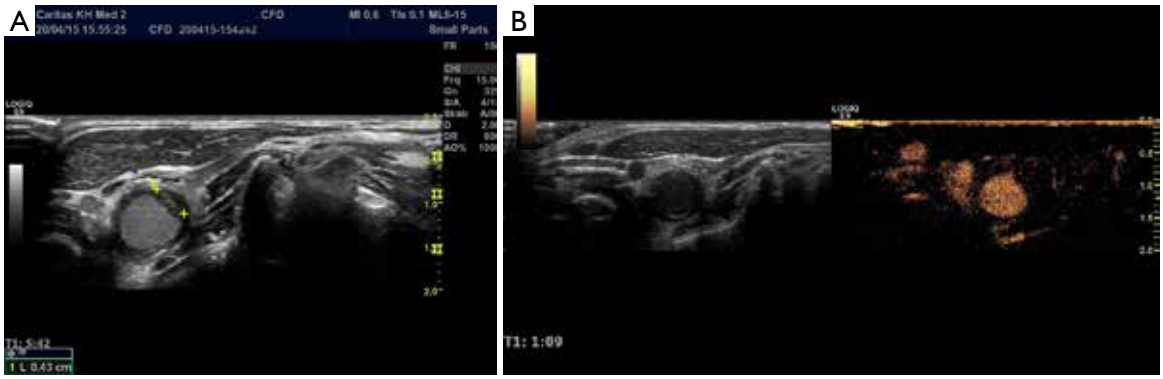


**Figure 11** Small hematoma of the vessel wall following inadvertent puncture of the common carotid artery. (A) B-mode; (B) CEUS: the vessel lumen is not occluded. CEUS, contrast-enhanced ultrasound.

**Anatomy**

The SV is deeply located and partially hidden under the clavicle bone. This hinders access to some of its portions. Its mid-portion can be cannulated using US guidance; however, it is difficult to obtain short-axis images at this level. Additionally, the lung apex is closely located, less than 1 cm (145), as is the subclavian artery and brachial plexus (43) with the risk of associated complications and morbidity.

**Technique and results**

RTUS-guidance is challenging due to the limited space available for both placement of the transducer and needle insertion. Two alternatives can be used with RTUS-guidance. One is the "low-IJV approach", with a safer and direct route to the superior vena cava and right atrium (146). The other alternative is to access the SV further laterally on the shoulder by cannulating the axillary vein, offering a better approach under RTUS-guidance and a lower complication rate (147,148). This "axillary approach" is possible also in patients with a cervical collar or neck trauma (43). The axillary landmark approach has been proven to be safe and efficient in adults (149) and in critically ill pediatric patients (150). Using the axillary vein approach under RTUS-guidance, Gualtieri *et al.* obtained a higher success rate and less complications as compared to the landmark technique (92% versus 44% and 4% versus 41%, respectively), with lower mean numbers of attempts and insertion kits used (1.4 versus 2.5 and 1.0 versus 1.4, respectively) (151). In patients with relative contraindications to SV catheter placement using the landmark approach, Fry *et al.* (152) reported 100% success rate with RTUS-guidance.

**Risks and complications**

No complications were been reported by Silberzweig *et al.* (146) using the low-IJV approach in 116 patients. The average number of attempts needed for success was 1.2. These results have been confirmed also by the study of Milone *et al.*, who reported no complications for the RTUS-guided cannulation of the SV, while 13% of the patients cannulated using the landmark approach developed mechanical complications (e.g., pneumothorax or arterial puncture) (153). The knowledge of surrounding structures is of main importance (154).

***Detection of complications of venous access***

As the EFSUMB INVUS guidelines (13) state, central venous catheter misplacement into the right heart may be detected by transabdominal US using a subxiphoidal approach or by echocardiography (55-61). Moreover, transthoracic US may be used to detect or to rule out pneumothorax related to central venous access in the critically ill patient. Therefore, routine chest radiography is dispensable after central venous line placement (54-57,62,63). Moreover, US has a very high accuracy for the detection of vascular complications of venous and arterial access, in particular of thrombosis of the target vessel (64,65), arterial pseudoaneurysm and arteriovenous fistula (66-70). Therefore, US should not only used to guide central venous access, but also to check correct placement of the line and to rule out the most common complications in the intensive care unit (13,155-157). The role of endoscopic US for catheter placement has not been examined so far (130,131,158).

 

## Conclusions

According to the available evidence in literature it is strongly recommended to use real-time US guidance for central venous access.

## Acknowledgements

None.

## Footnote

*Conflicts of Interest*: The authors have no conflicts of interest to declare.

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# Navigation bronchoscopy for diagnosis and small nodule location

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**Abstract:** Lung cancer continues to be the most common cause of cancer death. Screening programs for high-risk patients with the use of low-dose computed tomography (CT) has led to the identification of small lung lesions that were difficult to identify using previous imaging modalities. Electromagnetic navigational bronchoscopy (ENB) is a novel technique that has shown to be of great utility during the evaluation of small, peripheral lesions, that would otherwise be challenging to evaluate with conventional bronchoscopy. The diagnostic yield of navigational bronchoscopy, however, is highly variable, with reports ranging from 59% to 94%. This variability suggests that well-defined selection criteria and standardized protocols for the use of ENB are lacking. Despite this variability, we believe that this technique is a useful tool evaluating small peripheral lung lesions when patients are properly selected.

**Keywords:** Electromagnetic navigational bronchoscopy (ENB); diagnosis; lung nodule

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## Introduction

Lung cancer is the most common cause of cancer death among men and women in the United States (1). Unfortunately, the diagnosis is usually made at advanced stages with reported 5-year survival rates of approximately 15% (2). An early diagnosis and timely surgical resection is essential to improve outcomes and decrease mortality (3,4). Survival rates as high as 70% can be achieved in patients who undergo surgical resection at the earliest stage of disease (5,6).

Lung cancer screening programs with low-dose CT-scan have allowed detection of small lung nodules (7). Nevertheless, an accurate diagnosis from these small, peripheral lung lesions can still be challenging with the use of conventional procedures. Options available to diagnose newly identified lung lesions include: flexible fiberoptic bronchoscopy (FFB), CT-guided transthoracic biopsy, bronchoscopy with endobronchial ultrasound (EBUS) and thoracoscopic or open thoracic surgery.

FFB is useful for visible endobronchial and central lesions, with an overall sensitivity of roughly 88% (8,9). However, its performance as a diagnostic tool for small peripheral lesions is limited and has been reported to be between 19% and 62% (10,11). In nodules measuring less than 20 mm the diagnostic yield can be as low as 14% (12).

On the other hand, CT-guided transthoracic procedures display a higher diagnostic yield. CT-guided fine-needle aspiration has an overall sensitivity of 82% and an accuracy of 88%, but its performance might vary depending on lesion size and location (13). A sensitivity of over 90% has been reported for CT-guided transthoracic core needle biopsies, but the rate of complications is not negligible, with hemorrhage and pneumothorax occurring in as many as 30% of the cases (14-16).

The rate of accurate diagnosis for solitary pulmonary nodules using bronchoscopy with radial ultrasound probe is around 70–77% (17). This technique is operator dependent

 

**Table 1** Diagnostic yield of ENB across studies

| Study | Diagnostic yield (%) |
|---|---|
| Gildea, 2006 | 74 |
| Makris, 2007 | 62.5 |
| Eberhardt, 2007 (trial) | 59 (ENB alone) |
| | 88 (ENB + EBUS) |
| Eberhardt, 2007 | 67 |
| Lamprecht, 2009 | 76.9 (ENB + ROSE) |
| Eberhardt, 2010 | 55 |
| | 90 |
| Seijo, 2010 | 67 |
| Mahajan, 2011 | 77 |
| Lamprecht, 2012 | 83.9 (ENB + ROSE) |
| Brownback, 2012 | 74.5 |
| Odronic, 2014 | 63 |
| Loo, 2014 | 94 |
| Al-Jaghbeer, 2016 | 60 |
| Average | 72.7 |

ENB, electromagnetic navigational bronchoscopy; EBUS, endobronchial ultrasound; ROSE, rapid on site cytopathologic examination.

and involves blind navigation through the bronchial tree. Consequently, difficulty localizing the lesion is present in about 20% of cases (18,19). Although Kurimoto *et al.* (20) found no difference in the diagnostic rates amongst different lesion sizes, Eberhardt *et al.* reported a decrease in diagnostic yield, in lesions smaller than 20 mm (21).

The highest diagnostic yield (close to 100%) is achieved with thoracoscopic and open surgery (22). However, these approaches are more invasive and may be limited by poor pulmonary reserve in some patients (23). Electromagnetic navigational bronchoscopy (ENB) is a novel technique that offers a less invasive procedure for the diagnosis of small, peripheral lung nodules. It may also be a better option in certain circumstances (severe emphysema) where CT guided biopsy would be associated with a greater risk for complications.

ENB combines virtual and conventional bronchoscopy for the localization of lung nodules and allows the guidance of diagnostic and/or dye marking instruments (10,24). The most widely used and reported system is the SuperDimension system (Medtronic, Minneapolis, MN, USA) The planning phase is performed using the patient's CT scan that is loaded onto a computer prior to the procedure. The target lesion is identified and the most appropriate bronchial pathway is carefully chosen for guidance during navigation. The system has an extended working channel (EWC), that is passed through the working channel of the bronchoscope and a locatable guide (LG) that is placed within the EWC. The LG is trackable on the navigation system providing the link between the real-time and virtual bronchoscopy. At the start of the procedure a standard bronchoscopy is performed and landmarks from this bronchoscopy registered on the software of the system. The standard bronchoscopy and virtual bronchoscopy created from the initial CT will then be linked. The surgeon or pulmonologist will then navigate towards the target lesion using both the standard and virtual images. At some point the bronchoscope will wedge within a segmental bronchus. The surgeon or pulmonologist will then advance the EWC and LG towards the target lesion using the virtual image only. Once the target lesion is reached, the LG is removed allowing placement of biopsy forceps, cytology brushes and aspiration needles through the EWC. It is also possible to obtain washings, place fiducials to guide stereotactic body radiation therapy and inject dye to mark small lesions for minimally invasive resections.

Two other navigation systems are commercially available, namely The LungPoint Virtual Bronchoscopic Navigation System (Bronchus Technologies, Inc., Mountain View, CA, USA) and the SPIN Drive System (Veran Medical Technologies, St. Louis, MO, USA). A potential advantage of the Veran system is that this uses "trackable" instruments that may improve accuracy as biopsies are performed. Currently, data with these other systems are limited and no comparative information is available (25,26).

## ENB for the diagnosis of small lung nodules

ENB has been shown to aid in the diagnosis of lung lesions with a lower rate of complications compared with more invasive techniques. However, the diagnostic yield for small, peripheral lung nodules is variable and clear selection criteria for patients that may benefit from this intervention have not been well defined.

The diagnostic yield of ENB has been reported between 59% and 94% (24,27-37) (*Table 1*). This large variability across several studies highlights the need to define systematic selection criteria and standardized protocols for

 

the use of ENB.

Several variables that affect the performance of ENB have been evaluated. The presence of a bronchus sign on CT-scan (38), the use of rapid on-site cytopathologic examination (ROSE) (30,34), combining ENB with endobronchial radial ultrasound (28,31), PET scan (30), and the use of general anesthesia and fluoroscopy could improve the diagnostic yield of ENB. Moreover, the experience of the operator given by the number of procedures performed is a good predictor of success. The diagnostic yield of ENB has been shown to increase from 63% during the first year of work to 90% after two years of experience (33,34).

One of the first studies conducted to assess the utility of ENB was performed by Gildea *et al.* (27). The overall diagnostic yield was 74%. However, when analyzed by lesion size, the diagnostic yields ranged between 66.6% and 72%. Although all the nodules were considered peripheral, the distance from the pleural surface to each nodule was not reported, probably confounding the results since higher diagnostic yields could be expected for centrally located lesions.

On the other hand, Eberhardt *et al*. carried out a randomized controlled trial, finding a diagnostic yield of 59% that did not change with nodule size or location (28). This trial compared the use of EBUS with that of ENB alone or EBUS plus ENB for the diagnosis of peripheral lung lesions. The diagnostic yield with the combination of both tests was higher (88%) than either one alone, proving the adjunctive effect of endobronchial ultrasound. A more recent study by the same group showed different diagnostic rates depending on the biopsy technique. The overall diagnostic yield was 75.5%. Samples acquired using suction catheter had higher yields compared to forceps, where the diagnostic rates dropped to 55% (31). Again, this study found that the combination of ENB and EBUS achieved a higher diagnostic yield (93%) compared to 48% when the lesion was not visible under ultrasound (31).

In another study conducted by Eberhardt *et al*. there was a nonsignificant trend towards an increase in the diagnosis of lesions located within the right middle lobe compared with other locations (24). Similarly, Chen *et al*. showed that lesions located within the lower lobes may be more challenging to reach via ENB due to greater movement during respiration compared with upper lobe nodules (39).

Other diagnostic tools used in combination with ENB have shown favorable results. ROSE has been used immediately after ENB tissue sampling, although this technique is not readily available at all centers.

Loo *et al.* showed an overall diagnostic yield of 94% with the use of ENB and fine needle aspiration, and a diagnostic yield of 87% for lung lesions <2 cm, which was attributed to the use of ROSE (36). Similarly, Lamprecht *et al.* (34) showed diagnostic rates of over 80% with the combination of ENB, PET-scan and ROSE. The diagnostic yields varied depending on size. A correct diagnosis was achieved in 76% of lesions smaller than 20 mm and 90% of those larger than 20 mm. However, these differences were not statistically significant and both studies showed false-negative and false-positive results, affecting the sensitivity and specificity of ROSE.

As mentioned above, the biopsy technique could also affect the probability of obtaining a definitive diagnosis after ENB. Diagnostic yields of 55% to 77% have been reported with the use of biopsy forceps and 54% for bronchial brushing (29,31-33,35,38). Combining ENB with fine needle aspiration biopsy (FNA) has allowed surgeons to achieve diagnostic yields as high as 87% for lesions <20 mm and 100% for those >20 mm (36). The concurrent use of bronchial brushing and transbronchial biopsies did not improve these outcomes (36). Furthermore, Odronic *et al.* also found that the sensitivity of ENB-FNA was higher when compared to the use of biopsy forceps and bronchial brushings (35). However, they suggest that that the combination of these techniques could improve sensitivity. Our own preference is to use a number of techniques including biopsy forceps, bronchial brushing and washings, and needle aspiration.

CT-scan findings have also been shown to influence the diagnostic performance of ENB. Seijo *et al.* (38) found that the diagnostic yield of ENB improved significantly from 31% when a bronchus sign on CT scan was absent to 79% when such sign was present. Size of lesion was also a variable that significantly affected the rates of definitive diagnosis in that study (38). In contrast, Brownback *et al.* found a 13.9% absolute increase in the diagnostic yield when a bronchus sign was identified on CT scan, but this finding was not statistically significant. Lesion size did not affect the diagnostic rates significantly either in this study (33).

In our own analysis of 100 ENB's performed in 95 patients (data not published), the diagnostic yield of this technique was associated with lesion size, location and the presence of a bronchus sign on CT-scan. Lesion size ≥2 cm, location within the central and intermediate regions, location within the upper and middle lobes and the presence of a bronchus sign were all factors associated with an increased probability of obtaining a definitive diagnosis.

 

The large range in diagnostic yield reported among studies could be explained by differences in study design, lesion size, location, biopsy techniques employed, the inclusion of adjunctive resources such as radial EBUS and ROSE, and differences in learning curve/operator experience. This variability has led to the conflicting findings reported. As further studies and experiences are reported, it is hoped that factors that impact the performance of ENB will be better defined, improving selection criteria for ENB rather than an alternative diagnostic modality. It is also important to note that all studies consistently demonstrate lower complication rates with ENB compared to that reported by CT guided techniques.

## Additional uses of ENB

### *Fiducial placement for SBRT*

Besides the diagnostic potential of ENB for small peripheral lung nodules, this technique is also useful for the placement of fiducials and dye marking for subsequent stereotactic body radiation therapy (SBRT) and minimally invasive surgical resection.

It has been shown that the use of ENB for the placement of fiducial markers is a safe and feasible procedure for subsequent SBRT (40). The deployment of these fiducials showed lower rates of complications compared to transthoracic placement, and higher retention rates in close proximity within the tumor or the location of initial placement, allowing successful completion of radio surgical treatments (40,41).

### *ENB-guided dye marking for minimally invasive resection*

The increased number of small lung lesions detected by CT scan has also increased the number of cases referred for surgical resection. The surgical approach of these lesions may be challenging since visualization and palpation of small nodules is limited during minimally invasive resection.

ENB-guided dye marking has shown to be a safe and feasible procedure for the identification of lung nodules during video-assisted thoracoscopic (VATS) and robotic-assisted thoracoscopic resection (RATS) (42,43). This potentially has great utility for thoracic surgeons performing these procedures.

Krimsky *et al*. used ENB-guided dye marking for the localization of 21 lung nodules with a median size of 13.4 mm (range, 7–29 mm) (43). Indigo carmine and methylene blue were used. In 81% of the cases the dye was identified close to the lesions, in one case the dye marking extravasated into the pleural space, and in 3 cases the dye was not identified. No complications related with ENB were reported.

Recent studies have also shown a good performance of ENB-guided dye marking with significantly less rates of complications when compared to other percutaneous marking procedures (44-46). Marino *et al*. reported a success rate of 97% for the localization of 70 lung lesions with a median lesion size of 8 mm (range, 4–17 mm) and a median distance from the pleural surface of 6 mm (range, 1–19 mm). The failure rate was 2.9%, which is significantly lower than that of transthoracic methylene blue marking and hook-wire localization (46). Similarly, Awais *et al*. (45) found a success rate of 100% for the localization of 33 lung nodules with a median size of 10 mm (range, 4–27 mm) and a median distance from the pleural surface to the center of the lesion of 13 mm (range, 3–44 mm). Complications were reported in two patients, which seemed to be independent of the ENB procedure.

## Conclusions

Electromagnetic Navigational Bronchoscopy is a novel technique that has proven to be useful for the diagnosis of small lung nodules. This technique increases the likelihood of obtaining tissue samples from lesions that were unreachable with the use of standard bronchoscopy. It is also of great utility for the localization of small, non-palpable lung nodules for subsequent minimally invasive resection, as well as for the placement of fiducial markers for therapeutic purposes in patients with advanced stage disease.

There is variability in diagnostic yields from ENB with an average of 72% (*Table 1*) reported. Although not statistically significant, the majority of the studies have shown differences in the diagnostic rates related to lesion size (24,28,29,32,34-36) suggesting that bigger lesions are more likely to be diagnosed with ENB. Other variables that have been suggested to improve the performance of ENB include presence of bronchus sign on CT scan and location in the middle and upper lobes.

Future studies should focus on establishing well-defined selection criteria for ENB that will help guide the selection of optimal diagnostic approach when evaluating a new lung nodule. Additionally, methods to improve the performance of ENB, such as the biopsy technique (e.g., brush, fine-needle, core or cup biopsy) and adjunctive approaches (such as the use of radial EBUS) will need to be established.

 

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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Interventional Therapy Technique

# Indications and interventional options for non-resectable tracheal stenosis

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**Abstract:** Non-specific presentation and normal examination findings in early disease often result in tracheal obstruction being overlooked as a diagnosis until patients present acutely. Once diagnosed, surgical options should be considered, but often patient co-morbidity necessitates other interventional options. Non-resectable tracheal stenosis can be successfully managed by interventional bronchoscopy, with therapeutic options including airway dilatation, local tissue destruction and airway stenting. There are common aspects to the management of tracheal obstruction, tracheomalacia and tracheal fistulae. This paper reviews the pathogenesis, presentation, investigation and management of tracheal disease, with a focus on tracheal obstruction and the role of endotracheal intervention in management.

**Keywords:** Airway stent; laser therapy; rigid bronchoscopy; tracheal stenosis; large airway obstruction

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## Introduction

Large airway obstruction, particularly tracheal disease, is widely believed to be under-diagnosed and under-reported. Recognition of the precipitants to tracheal obstruction and of the common clinical manifestations and investigation findings will facilitate prompt and appropriate management. Rigid bronchoscopy is increasingly popular for the diagnosis and management of tracheal obstruction, and has a role in the delivery of interventional bronchoscopy. Surgical management is often definitive, but patient selection and preparation is essential for surgical success.

This paper reviews the pathogenesis, presentation, investigation and management of tracheal disease, with a focus on tracheal obstruction and the role of endotracheal intervention in the management of non-resectable disease. It is intended that this paper will provide guidance for those involved in the care of patients with tracheal disease.

## Tracheal anatomy and physiology

The trachea extends from the lower body of the cricoid cartilage to the carina and is normally between 110 and 130 mm in length. The tracheal diameter is typically up to 22 mm in males and up to 18 mm in females. Air is a fluid which flows down a pressure gradient, from higher to lower pressure. Airflow can be laminar or turbulent, with the flow rate defined as the amount of fluid moving per second. When flow is laminar, the airflow rate is directly proportional to the pressure gradient but when flow is turbulent, the airflow rate is proportional to the square root of the pressure gradient. Turbulence thus increases airflow resistance, necessitating a higher pressure difference to maintain a given flow rate. Reynolds number is a non-dimensional parameter that governs the change from laminar to turbulent air flow. It is calculated by multiplying mean fluid velocity, density and airway diameter then dividing by fluid viscosity. The diameter of the trachea affects airflow by this equation and any abrupt variation in tracheal diameter produces a transition point which also predisposes to turbulence.

## Tracheal obstruction

Congenital or acquired tracheal narrowing may result from intrinsic tracheal stenosis and/or external compression, at

any anatomical level. Variation in the tracheal diameter alters the airflow dynamics in the direction of increased airflow resistance. Tracheal stenosis often results in varying degrees of distortion along the vertical plane in addition to airway narrowing. When the trachea becomes pulled away from or twisted within its normal anatomical path, this further predisposes to airway turbulence and increased resistance.

### *Congenital*

Tracheal stenosis is rarely congenital but may result from posterior fusion of the tracheal rings. By contrast, congenital tracheal webs are well recognised, with 75% occurring at the level of the glottis. Tracheal webs differ from tracheal stenosis due to the absence of a cartilaginous framework. Both may present in adult life.

Congenital cardiovascular anomalies can result in extrinsic compression of the trachea. Most commonly, early bifurcation of the innominate artery compresses the anterior tracheal wall, appearing pulsatile at bronchoscopy. Other causes include anomalies of the subclavian artery and vascular rings, such as congenital double aortic arch, which encircle the trachea causing circumferential compression.

### *Acquired*

#### Trauma

The cartilaginous trachea has a natural tendency to narrow and fibrose in the face of injury. Tracheal trauma is the most common cause of benign tracheal stenosis and is a feared complication of prolonged endotracheal intubation or tracheostomy tube placement. The presence of tracheal stenosis can necessitate re-intubation and delay respiratory weaning in intensive care unit patients or can present many years later.

The reported incidence of tracheal stenosis following endotracheal intubation ranges from 6-21% and following tracheostomy ranges from 0.6-21% (1-3). With the trend towards early tracheostomy as an aid to respiratory weaning, and increasing numbers of successful discharges from intensive care units, the incidence of tracheal complications is rising.

Stenosis occurs when pressure and friction on the mucosal surface stimulates inflammation and pressure necrosis. Granulation tissue formation is followed by fibroblast proliferation, scarring and contracture. Stenoses can develop after as little as 36 hours of endotracheal intubation but the risk of stenosis rises with duration of intubation. Most strictures occur at the site of the tube cuff, with reduced incidence following the introduction of compliant, large volume, low-pressure cuffs (4).

After tracheostomy, stenosis most commonly occurs at the stomal site (3,5). Wound sepsis is a predisposing factor (6). Pre-existing chronic lung disease and airway infection are also associated with tracheal stenosis post endotracheal intubation or tracheostomy (7).

Trauma may also arise from thermal or chemical burns (including chemical warfare agents), resulting in localised stenosis.

#### Infection

Airway infection alone can result in the development of tracheal stenosis. Tuberculosis is the most common cause of post-infective stenosis but diphtheria, syphilis and fungal infection (e.g., histoplasmosis, blastomycosis) are also recognised causes.

#### Non-infectious inflammation

Non-infectious inflammatory conditions causing tracheal stenosis include collagen vascular disorders (e.g., Wegener's granulomatosis), sarcoidosis, amyloidosis and chronic atrophic polychondritis. Diffuse inflammatory and infective processes often result in multi-level tracheobronchial stenoses.

#### Neoplastic

Airway obstruction develops in 20-30% of lung cancer patients (8); however, tracheal compromise occurs in less than 1% of all malignancies (9). Direct tumour invasion of the trachea by a bronchogenic malignancy is more common than metastatic involvement of the trachea. Primary benign tumours of the trachea such as chondromas, fibromas, hemangiomas, and squamous papillomas are rare causes of tracheal stenosis. Extrinsic compression of the trachea can occur from malignant lymphadenopathy, thyroid and mediastinal tumours.

#### Iatrogenic

The insertion of a tracheal stent (e.g., for tracheobronchomalacia) can, paradoxically, lead to stenosis due to tracheal irritation and the formation of granulation tissue at either end of the stent. Cervico-mediastinal radiotherapy is another recognised cause of stenosis.

 

### Other

Tracheopathia osteochondroplastica is a rare, but increasingly recognised condition in which there is the idiopathic development of focal or diffuse, osseous and/or cartilaginous nodules in the submucosa of the trachea and bronchial walls. The posterior membranous portions of the trachea are characteristically spared. Significant tracheal stenosis and/tracheomalacia can result.

Superior mediastinal pathology can cause extrinsic tracheal compression. Most frequently this arises from lymphadenopathy secondary to infection, inflammation or neoplasia, but abnormalities of the aortic arch such as dissection or aneurysm can also compress the trachea (10). Thyroid goitre may also cause extrinsic compression, particularly if there is retrosternal extension.

### Idiopathic

Idiopathic tracheal stenosis is rare, representing 3-5% of cases. Most commonly these stenoses develop at the level of the cricoid cartilage and are restricted to young women (11). Pathologically there is extensive keloidal fibrosis and mucus glands dilation which may represent a form of fibromatosis (12).

## Tracheal fistulae

Any aggressive tracheal pathology can disturb the integrity of the tracheal wall resulting in communication with the mediastinum. Iatrogenic, traumatic and malignant cases are the most prevalent. Infection as an aetiological factor (tuberculosis, HIV infection, mediastinitis) has reduced in recent years. Communication may also be established between the tracheobronchial tree and the oesophagus, resulting in tracheo-oesophageal (or bronchial-oesophageal) fistulae. Acquired tracheo-oesophageal fistulae are frequently the result of mediastinal malignancy. Tumours arising from the oesophagus, trachea, lungs, larynx, thyroid and lymph glands have all been reported to cause fistula formation. Tracheo-oesophageal fistulae can also be congenital. These typically present in the neonatal period but may rarely present in adulthood.

## Tracheomalacia

Tracheomalacia is characterised by flaccidity of the tracheal cartilage, leading to airway collapse during expiration. The condition may extend to involve the bronchi (tracheobronchomalacia). Significant airway malacia is defined as a greater than 60% reduction in luminal diameter.

Congenital tracheomalacia results from a developmental defect in the cartilage of the tracheal wall. Tracheomalacia may also develop in the context of congenital conditions such as cystic fibrosis, Mounier-Kuhn syndrome, Marfan syndrome, Ehlers-Danlos syndrome, and congenital trachea-oesophageal fistulae.

Acquired tracheomalacia is associated with prolonged endotracheal intubation and tracheostomy, trauma, head and neck surgery, radiotherapy, and inflammatory conditions such as polychondritis. Intrinsic tracheal disease such as tracheal stenosis and previous tracheal stenting may also contribute to weakening of the airway support and malacia. When tracheomalacia occurs in the absence of a clear pathophysiology, these patients are often obese, with smoking-related lung disease or recurrent/chronic airways infection.

## Diagnosis of tracheal disease

The diagnosis of tracheal disease is a recognised challenge because of the broad range of aetiologies and the non-specific nature of presentation, which often has an insidious onset at first. Thus, a detailed patient history and examination is imperative to guide further investigation and management. Sometimes when the patient presents in extremis, this is not possible or appropriate, and rapid intervention in a controlled environment with appropriately skilled personnel is central to a successful outcome.

### *History and examination*

Symptoms depend on the location and degree of airway narrowing, additional airway distortion and concurrent thoracic pathology. Most commonly, patients report shortness of breath on exertion, which may progress to dyspnoea at rest. Symptoms occur on exertion when the tracheal diameter is significantly reduced to 8 mm (13). Cough and wheeze are common. Airway obstruction may lead to difficulty with sputum clearance and recurrent infection. The combination of exertional dyspnoea and wheeze is frequently mistaken for chronic bronchitis or asthma. Failure to respond to bronchodilators should not be overlooked.

It is not uncommon for patients with tracheal disease to present with acute respiratory distress, even in benign disease. These presentations are usually triggered by the partial or complete occlusion of the abnormal airway by

 

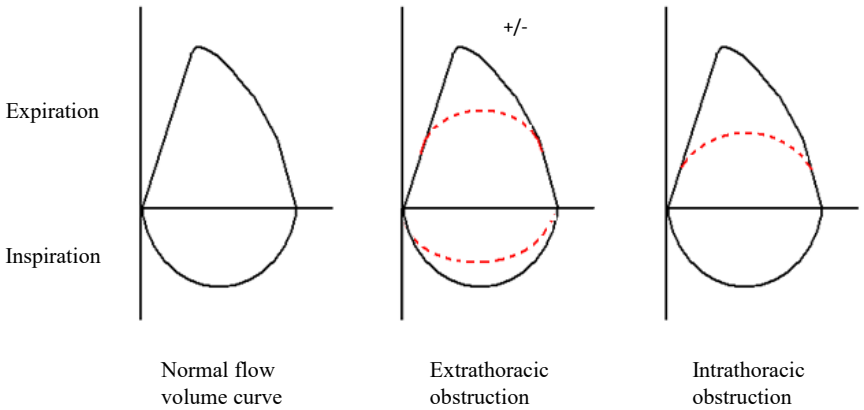


**Figure 1** Flow volume curves showing upper airway obstruction.

sputum or haemorrhage.

History taking should focus on potential tracheal insults such as intensive care admission, hoarseness after general anaesthesia (suggestive of traumatic injury), or respiratory tract infections. A full systems enquiry may also reveal information relevant to the underlying diagnosis.

Respiratory examination is often normal until there is severe tracheal stenosis or secondary airway occlusion due to sputum or haemorrhage. Stridor occurs when the tracheal diameter is less than 5 mm (13). Examination should explore the underlying diagnosis, looking carefully for signs such as a tracheostomy scar, goitre, lymphadenopathy or the classical nasal changes of Wegener's granulomatosis.

### *Investigation*

When tracheal disease is suspected, first line investigations should include targeted blood tests to look for the underlying diagnosis (e.g., inflammatory markers, autoimmune screen), pulse oximetry and/or arterial blood gas analysis and standard chest radiography. These investigations are often normal.

#### Lung function testing

When spirometry results are interpreted correctly, ensuring technical requirements are met, they can be the first investigation to suggest the diagnosis of tracheal obstruction. Flow volume diagrams provide an indication of the severity of airflow obstruction and the location of airway obstruction, i.e., intrathoracic or extrathoracic (14).

The pressure surrounding the intrathoracic airway approximates to pleural pressure, which changes during the respiratory cycle. During inspiration, negative intrapleural pressure causes the intrathoracic airway to be splinted open. During expiration, positive intrapleural pressure compresses the intrathoracic airway. Therefore, in intrathoracic airway obstruction (for example in lower tracheal stenosis) typically there is upper airway collapse during expiration and flattened expiratory flow volume curves, but the inspiratory flow-volume curve remains normal.

The reverse is true in the fairly compliant extrathoracic airway that is not exposed to intrapleural pressure. Inspiration results in collapse of the extrathoracic upper airway, as the airflow acceleration into the lungs reduces intraluminal pressure. Extrathoracic airways obstruction (upper or mid tracheal obstruction) therefore typically causes airway collapse during inspiration, with flattening of the inspiratory flow-volume curve. The force of expiration opens the extrathoracic airway usually resulting in a normal expiratory curve. The expiratory curve may become flattened when there is significant extrathoracic obstruction, resulting in reduced peak airflow rates. Schematics of the classical flow-volume diagrams are displayed in *Figure 1*.

#### Radiological imaging

Computed tomography (CT) is the radiological modality most often used to image the trachea. Dedicated tracheal protocols allow the acquisition of thin slices through the upper airways. With standard chest protocols, tracheal disease is easily underestimated. "Virtual endoscopy" procedures can be performed using CT images constructed during post-processing, with no additional radiation burden (*Figure 2*). The advantages of virtual endoscopy include the capability to view non-traditional perspectives, to

 


**Figure 2** Virtual bronchoscopy images of the normal proximal (A) and distal (B) trachea and tracheal stenosis (C).

provide volumetric analyses and to apply automatic feature recognition software (15).

CT is useful for diagnosing tracheal disease, identifying the precise anatomical location, the characteristics of the lesion and the extent of disease, including distal airway patency and local vascular anatomy. When tracheal lesions are visualised in cross section, it is possible to assess whether they are circumferential or incomplete, in a single plane (web like) or in three dimensions, like a cork-screw. CT windows also include the wider chest and may provide supportive evidence of an underlying diagnosis.

The combination of axial imaging, multiplanar reformating, and 3-dimensional rendering is useful prior to tracheal intervention, especially when there is significant anatomical distortion or airway narrowing (16).

### Bronchoscopy

Flexible bronchoscopy is often performed in the diagnostic work up for symptoms that are subsequently identified as tracheal in origin. Flexible bronchoscopy is, however, best avoided due to the risk of precipitating acute, complete airway obstruction or proximal haemorrhage. Rigid bronchoscopy is preferred for evaluating stenotic lesions in the trachea and the advantages over flexible bronchoscopy for diagnosis and therapy which will be discussed further below.

## Management

### *Non-acute airway obstruction*

In the non-acute setting, initial management should target ongoing tracheal insults such as inflammation or infection, to retard disease progression. Inflammatory conditions such as collagen vascular disease may respond to steroid or immunomodulatory therapies. Airway infection can be difficult to control and identification of the pathogenic organism is key. Recurrent pathogen isolation may prompt long term antibiotic prophylaxis as oral or nebulised therapy. Airway clearance is crucial and can be enhanced by the use of mucolytic agents such as carbocysteine, nebulised therapy with saline and/or N Acetyl Cysteine and chest physiotherapy.

### *Acute airway obstruction*

When patients present acutely with significant upper airways obstruction, supportive measures may be necessary and include the commencement of an inspired Helium-oxygen (Heliox) mixture. Heliox is less dense than oxygen and nitrogen. In accordance with Reynold's equation, reducing the density of the inspired gas has the effect of predisposing to laminar flow and this can be used to improve airway dynamics in the short term.

### *Definitive management*

Most significant tracheal stenoses necessitate interventional bronchoscopy or surgical resection. Definitive management should be planned with the input of the multi-disciplinary team. It is the nature of patients with tracheal pathology that their underlying disease or history of intensive care admission may make them high risk surgical candidates; thus, endotracheal intervention is often preferable (17). All patients should, however, be considered for tracheal surgery.

Interventional bronchoscopy does not preclude future surgery in most cases and may optimise potential surgical candidates. Lower surgical success rates are evident if the patient has had previous tracheal surgery, but previous laser therapy does not affect surgical outcome (3).

The most frequent complication of tracheal resection and reconstruction is granulation tissue formation at the anastomotic site. Since the introduction of novel suture

 

materials in 1978, the complication rate has fallen to 1.6% (18). It is possible to treat granulation tissue at the anastomotic site with endotracheal therapy.

## Interventional bronchoscopy

### *Background*

Interventional bronchoscopy should ideally be performed in specialist centres, with the support of experienced, consistent multi-disciplinary teams. Globally, interventional bronchoscopy is most commonly performed using intravenous awake sedation, local anaesthesia and the flexible bronchoscope. Rigid bronchoscopy under general anaesthesia has increased in popularity over the last two decades (19,20) but widespread adoption of the technique is limited by relative operator inexperience and a lack of available training. Rarely, if a tracheal stenosis is high, in close proximity to the vocal cords, a laryngeal mask and flexible bronchoscopy is indicated to visualise and treat the trachea.

### *Strengths and potential limitations of rigid bronchoscopy*

Unlike flexible bronchoscopy, which relies upon the patient's own, potentially unstable airway and ventilation, rigid bronchoscopy offers a controlled, ventilated airway under general anaesthetic, with the support of a cardiothoracic anaesthetist (21). Rigid bronchoscopy is therefore preferable for patients with severe respiratory disease who can be poorly tolerant of flexible bronchoscopy. The use of general anaesthesia also has the benefit of creating an immobile field, free from cough, allowing intervention to be performed more safely (22).

Biopsy or airway intervention during flexible bronchoscopy risks airway haemorrhage with potential compromise of both lungs, rendering the patient hypoxic. Rigid bronchoscopy offers a potentially safer means of obtaining a tissue diagnosis (23). Using the rigid bronchoscope it is possible to apply direct pressure to bleeding lesions, and to apply adrenaline soaked gauze using rigid forceps to tamponade the bleeding source, if direct application of adrenaline solution is not sufficient. Single lung isolation with the rigid bronchoscope can also be used to protect the non-bleeding lung if significant haemorrhage occurs.

The bronchoscope barrel can be used to dissect tissue or dilate tracheal stenoses directly, with excellent access for instrumentation with dilators or stents under direct vision. Rigid bronchoscopy minimises procedure times for endotracheal intervention. The median time to stent deployment is 12 minutes at our institution using rigid bronchoscopy (24).

In a specialist centre with a highly trained and experienced team, low complication rates are seen with rigid bronchoscopy. Potential complications include dental trauma, vocal cord trauma/inflammation and airway haemorrhage. Pneumothorax is a risk due to tracheal instrumentation and positive pressure ventilation but our local experience suggests rates of pneumothorax are less than 1% (based on review of >500 rigid bronchoscopy procedures) (24).

### *Performing rigid bronchoscopy*

The rigid bronchoscope is a hollow, tapered metal tube, with distal side-holes along the body for optimal ventilation. The patient is positioned supine with their neck extended. The pharynx, larynx and trachea are aligned in order to insert the rigid tube, taking care to protect the teeth and vocal cords from trauma.

The lumen of the rigid bronchoscope is used for direct vision. Intervention is performed using rigid instruments passed through the rigid bronchoscope. A flexible bronchoscope is passed through the lumen of the rigid bronchoscope to better visualise segmental airways or to see beyond a narrowed trachea. Some centres use special thin flexible bronchoscopes for this purpose (25). The flexible bronchoscope is also utilised for laser therapy.

### *Endotracheal intervention*

There is an overlap between the techniques used to treat tracheal and bronchial obstruction (26). Options include airway dilatation, tissue destruction and stent insertion, each of which is detailed below.

#### Airway dilatation

Dilatation is achieved with lubricated bougies of increasing diameter applying radial pressure circumferentially to the narrowed airway. Balloon dilatation is an alternative method. The flexible then rigid bronchoscope can also be used to perform blunt dissection and dilatation of stenosed areas under direct vision.

With all dilating techniques, it is imperative to identify the path of the true airway lumen. It is easy, especially when

 

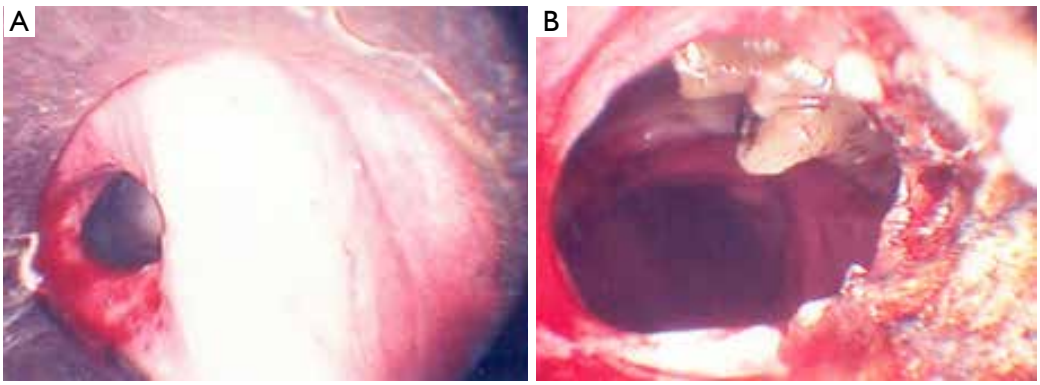


**Figure 3** The endoscopic images of tracheal stenosis before (A) and after (B) Nd Yag laser therapy.

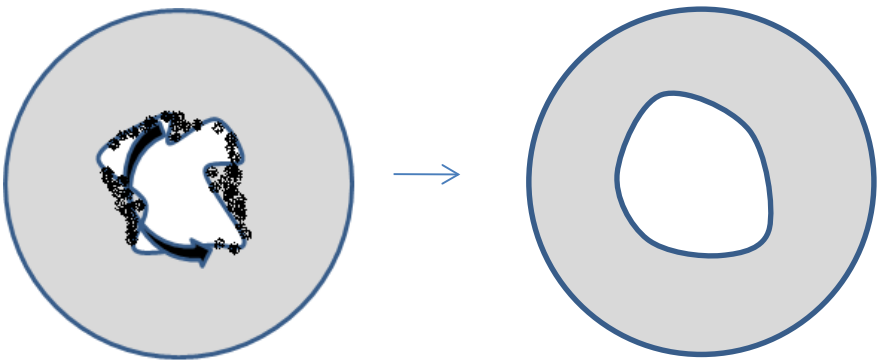

**Figure 4** The technique of Nd Yag laser therapy. The laser fibre is moved in a circumferential fashion, starting from the centre of the airway.

the trachea is distorted, to lose sight of the true lumen, risking airway perforation. Pre-operative imaging is useful to define patient anatomy.

Dilatation alone is very rarely a definitive therapy and re-stenosis usually occurs. Dilatation may be used in combination with other therapeutic techniques such as laser ablation and stent insertion, and can be repeated as necessary (NICE guideline IP938).

### Tissue destruction

Once the true airway lumen has been identified, it is usually preferable to destroy and physically remove diseased tissue (*Figure 3*). The most rudimentary method of tissue destruction uses forceps to mechanically remove tissue from the trachea. Techniques used to effect tissue destruction include laser therapy, argon plasma, brachytherapy, electrocautery and cryotherapy. Most centres prefer laser therapy, of which the neodymium: yttrium-aluminum-garnet (Nd Yag; Nd: Y3Al5O12) laser is the most commonly used (19,27-29).

Nd-Yag laser energy is delivered via fibres inserted into the working channel of the flexible bronchoscope, using the rigid bronchoscope as a stable airway. The fibres can either be contact or non-contact and are used to devitalise or resect diseased tissue whilst assisting with haemostasis. Nd-Yag laser has a wavelength of 1,064 nm, which is in the invisible photo spectrum. A red light is therefore used to direct application. The bronchoscopist should always apply laser energy parallel to the central airway to avoid unintended trauma to local structures. Energy should be applied in a circumferential motion (*Figure 4*), using 1-5 seconds laser pulses. A circumferential as opposed to radial approach is preferred to open the airway in malignant and benign disease, to ensure good visualisation of the distal airway whilst improving airflow. The lowest possible power is recommended. Our recommended practice is to use a power of 15-20 watts in the trachea, and lower power distally.

 

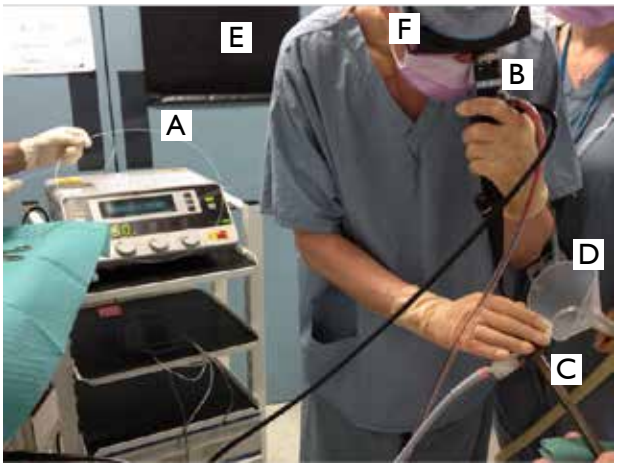


**Figure 5** Nd Yag laser therapy. Laser fibre (A) to be inserted through the working channel of the flexible bronchoscope (B), passed through the lumen of the rigid bronchoscope (C). Laser fume extraction device (D), protective curtain (E) and eye wear (F) can be seen.

**Table 1** Potential complications of endotracheal stent insertion (27,31-39).

| Potential complications of endotracheal stent insertion |
|---|
| Mucous plugging |
| Stent migration |
| Halitosis |
| Cough |
| Obstructing granulation tissue formation |
| Stent fracture (*Figure 6*) |
| Bacterial colonisation/recurrent infection |
| Fistula formation |
| Airway malacia (after removal) |

Following laser treatment, the airway lumen may still appear narrowed. The effects of the treatment continue for days to weeks after the initial application. The bronchoscopist must, therefore, refrain from being too aggressive with laser therapy. During and after laser treatment, it is important to clear devitalised tissue from the trachea and distal airways. Aspiration is usually sufficient, but manual forceps can also be used. The patient will cough up any remaining or further tissue that sloughs away over the coming days.

Personnel should be trained in the use of laser and a committee responsible for laser usage, maintenance and safety should be established and meet regularly. All staff within the potential laser field should wear protective eyewear. The operating room should be adapted for laser therapy with protective curtains, barriers and warning signs at all entry points, and a laser fume extraction device used (*Figure 5*). Inspired oxygen concentration should be less than 40 percent and ventilation should be ceased during laser pulses to reduce the risk of airway fire. If a laryngeal mask is used during laser therapy this should be inflated with saline rather than air, to reduce fire risk.

Reported complications of laser treatment include haemorrhage, airway perforation and airway fire. However, published case series report overall complication rates below 1% in approximately 7,000 treatments (27). With safety measures in place, laser therapy is an excellent and reliable way of treating tracheal stenosis.

There is no limitation to the amount of times laser therapy can be performed. Nearly all patients require more than one endotracheal treatment to achieve long-term airway patency. Tissue regrowth can be significantly slowed or halted by serial treatments, with the chance of success increasing after each treatment (30).

## Endotracheal stenting

Endotracheal stents are used to provide structural support to the airway and to maintain airway patency. They are, however, foreign bodies in the airway and disrupt mucociliary clearance. The complications of stent placement are listed in *Table 1* and stent fracture is displayed in *Figure 6*.

Metal and silicone stents are available. Metal stents come with or without a silastic or polyurethane covering which is used to minimise tissue growth when intrinsic tracheal disease is present. The covering is purposefully absent at either end of the stent to allow the stent to anchor to the mucosa and reduce stent migration but re-growth or new tissue growth may occur in these areas.

Historically, metal stents expanded in an unpredictable and uneven manner, resulting in local airway ischaemia, granulation tissue formation, airway perforation and stent migration. The titanium stents in current use are lighter, easier to insert and demonstrate more uniform self-expansion. The application of a more consistent radial force to the airway means perforation, ischaemia and migration are less common and stronger forces can be withstood. There is also a greater availability of stent sizes.

Silicone stents result in a lesser local inflammatory response

 

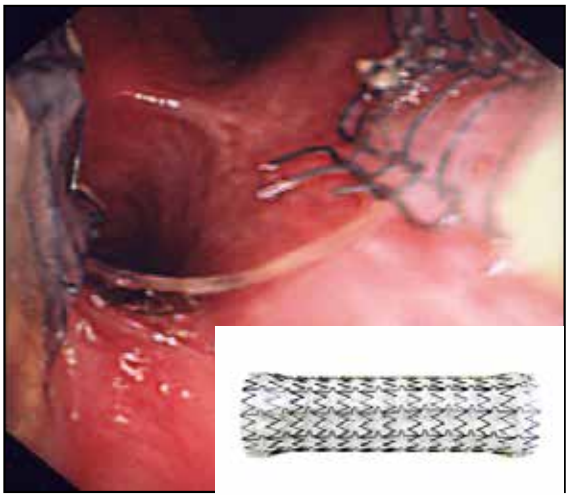

**Figure 6** Tracheal metal stent fracture. Endotracheal view of a fractured covered metal tracheal stent and inset picture demonstrating an expanded metal airway stent.

than metal stents, reducing granulation tissue formation. Silicone stents are therefore easier to remove but have a high risk of stent migration which limits their use (40,41).

When selecting a tracheal stent, it is desirable to use the greatest diameter stent possible. Selection will depend on patient size and disease extent after optimal airway remodelling. In general, airway stents deployed in tracheal disease are between 40-120 mm in length and 14-24 mm wide.

A stent should not be placed when there is active infection as this will promote granulation tissue formation. Treatment of bacterial colonisation in long-term airway stents appears useful (42). Our centre routinely offers five days prophylactic oral antibiotics post stent placement.

Stent migration, especially in proximal lesions approaching the vocal cords, can acutely threaten the airway. External fixation of silicone stents has been trialled but with limited success and use, mainly due to cumbersome techniques (43,44). With careful prospective surveillance of metal tracheal stents there is usually minimal risk of migration and no requirement for stent fixation.

Concurrent tracheal and bronchial disease can be managed using Y-shaped silicone stents. The use of Y-shaped stents is limited by recurrent stent obstruction and infection. It is believed the stent structure results in excessive airway friction and mucociliary clearance disruption, with granulation tissue overgrowth and mucus impaction (45). Simultaneous stenting of the trachea and bronchi can be performed with metal stents, when necessary.

Following stent insertion, surveillance bronchoscopy is indicated in both malignant and benign disease (46). This facilitates early identification and management of complications. Relying on history and examination alone for surveillance is potentially hazardous due to the paucity of symptoms and signs before severe tracheal disease development. Treatment of peri-stent granulation tissue is most commonly addressed by laser therapy (20,31). Timely identification and treatment of airway infection is also crucial.

**Indications for stent insertion**

In malignant tracheal disease, stenting (with a covered stent) is used to reduce the occurrence of rapid, life-threatening disease progression (47). Stenting is also indicated in malignant tracheal fistulae, even if there is no luminal compromise due to tumour bulk. Stents are used to physically obstruct the fistulae, palliating symptoms and protecting the large airway. Stenting for benign tracheal fistulae may be performed in non-operable disease.

Indications for tracheal stent placement in benign disease are less clear than for malignant disease, with varying practices seen worldwide. This is due to the better long-term prognosis of individuals with benign pathology, the difficulty removing airway stents, and the reported complications of their use. Endotracheal stent insertion for benign disease should only be considered after airway remodelling by tracheal dilatation and/or tissue destruction has failed to effectively sustain airway patency.

The US Food and Drug Administration recommended in 2005 that metal stents should not be used for benign disease unless absolutely necessary (48). A major concern raised was turning operable cases into inoperable cases (36). Nevertheless, stenting does have a role as a bridge to surgery, enabling optimisation of a patient's functional and physical state prior to surgical intervention.

Tracheal stents for airway malacia should only be considered when patients are symptomatic and airway collapse is greater than 60%. The dynamic radial forces in malacia lead to higher stent complication rates, including metal fracture (49). A further problem with stenting these patients is recognising where to stent, as often long segments are involved. Extensive airway stenting risks higher occlusion rates due to widespread disruption in mucociliary clearance. When a stent is too short for the involved segment this risks displacing airway collapse to the distal unsupported airway, failing to improve or worsening airway dynamics and symptoms.

**Stent removal**

Metal stents should be considered permanent as they

 

remodel into the airway by granulation tissue growth and epithelialisation (9,32,50). The longer a stent remains *in situ*, the lower the chance of successful removal. Nevertheless, stent removal has been performed successfully in tracheobronchial disease using both rigid bronchoscopy (51-53) and flexible bronchoscopy (54).

Silicone stents are more easily removed than metal stents and so may lend themselves to short-term placement if planned, despite their high migration rates. Research is ongoing to produce a fully degradable tracheal stent which can remain *in situ* (55).

**Airway management with a tracheal stent *in situ***

Great care should be taken to avoid damaging any tracheal stent if intubation is necessary. It is recommended to use a flexible bronchoscope to ensure that the endotracheal tube is sited above or within the stent lumen (56).

Strong consideration should be given to using rigid bronchoscopy to guide placement of percutaneous tracheostomy in complex tracheal disease (including tracheal stenosis or when a tracheal stent is *in situ*). Percutaneous tracheostomy using rigid bronchoscopy has been previously described (57,58) including where the endotracheal tube is removed and replaced by the rigid bronchoscope (59). The benefits to this approach include better visibility of the complex airway and/or stent, guide wire location, reduced risk of cuff rupture during cannulation and ease of haemostatic control.

## Long-term tracheostomy

Long-term tracheostomy may become necessary for patients with complex tracheal disease. Commonly a Montgomery T tube is placed through a tracheostomy which serves as both a tracheal stent and tracheostomy tube. Tracheostomy is usually reserved for non-surgical candidates, after endotracheal therapy has become complicated and/or requires too frequent procedures, produces suboptimal clinical response or is anatomically too complex to perform safely. Tracheostomy can also be used as a bridge to tracheal surgery or as an adjunct to surgery. Our practice suggests patients are disinclined to tracheostomy, mainly due to negative cosmetic effects, and consider this a last resort.

## Interventional outcomes in tracheal obstruction

### *Malignant disease*

There is no randomised controlled trial evidence regarding the use of tracheal intervention in malignant disease due to the ethical challenges in patients requiring life-saving intervention or palliation. The impact of tracheal intervention on survival cannot, therefore, be quoted accurately. Studies have, however, consistently demonstrated that stenting can improve symptoms of breathlessness, quality of life and lung function in malignant disease. Data supports the use of metal covered stents to achieve success rates from 82-97% in these parameters (9,34,40,46,50, 60-64). Importantly, improvements in performance status following stenting can open avenues to other therapies for malignancy, potentially improving outcomes further.

### *Benign disease*

Successful short and long-term outcomes using a combination of controlled dilatation and/or Nd-Yag laser therapy to destroy endotracheal tissue in tracheal stenosis have been published (28,30,65-68). Despite concerns regarding the use of tracheal stents in benign disease, there are a number of supportive case series and reports in the literature (31,32,35,68,69).

Early studies suggested that endotracheal treatment was less effective for circumferential disease and for stenoses greater than 1 cm in length (70). Recent studies have demonstrated that involvement of the cricoid cartilage and stenoses over 3 cm are associated with a reduced chance of success (71). Time from tracheal stenosis development to first intervention is also important. One study in post intubation tracheal stenosis established that 90% of patients who had intervention within six months of extubation had a positive outcome compared to 61% of those with a longer delay before intervention (72).

Galluccio *et al.* proposed the classification of tracheal stenosis into simple and complex, with simple stenoses defined as those less than 1 cm in length with no associated tracheomalacia or loss of cartilaginous support. Using this classification, silicone stent insertion as part of an endoscopic approach achieved airway patency in 96% of simple lesions at two years follow up but only 69% of complex lesions (30). When considering the removal of short-term silicone stents, higher success rates have been seen when sizeable air pockets (longer than 1 cm) between the stent and tracheal wall are visualised at CT (in post tuberculosis tracheobronchial stenosis) (73).

Although our centre strongly advocates the use of rigid bronchoscopy for endotracheal intervention, other centres have described using flexible bronchoscopy to intubate,

 

dilate and stent patients with tracheal stenosis without complication, in limited patient series (74).

Patient selection for airway stenting in tracheobronchomalacia is crucial as there must be limited disease and a strong enough, supported airway distal to the stent to avoid collapse. As discussed the complication rates of stent insertion in tracheomalacia are higher and when there is malacia from loss of cartilaginous support in tracheal stenosis this reduces the chance of a successful outcome (30,70). However, when patients are carefully selected, studies have demonstrated that patients can achieve relief from breathlessness and an improved quality of life (75,76).

Benign tracheal stenosis has been successfully treated with tracheostomy at long-term follow up, including tracheostomy tube placement through tracheal stents remodelled into the airway (36,77).

## Summary

Tracheal disease resulting in upper airways obstruction can be life threatening and is an important diagnosis to consider early. A thorough history to identify predisposition to tracheal disease is necessary, with a high clinical index of suspicion directing comprehensive investigation. Prompt treatment of concurrent airway infection is crucial.

Due to the aetiology of tracheal obstruction, the patients are often poor surgical candidates and patients seldom wish to pursue long-term tracheostomy. Fortunately, non-resectable tracheal disease can be successfully treated with interventional rigid bronchoscopy to restore airway patency using debulking and/or dilatation techniques. Tracheal stenting is often performed in malignant disease to protect the airway but should be carefully considered in benign disease as stent removal can be difficult. We advocate the use of covered metal stents when stenting is required for tracheal stenosis, due to their infrequent migration ahead of silicone stents. With regular follow up, including surveillance repeat bronchoscopy, endotracheal intervention can achieve long-term success for patients with tracheal disease.

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## Footnote

*Conflicts of Interest*: The authors have no conflicts of interest to declare.

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Interventional Therapy Technique

# Rigid bronchoscopy and silicone stents in the management of central airway obstruction

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**Abstract:** The field of interventional pulmonology has grown significantly over the past several decades now including the diagnosis and therapeutic treatment of complex airway disease. Rigid bronchoscopy is an invaluable tool in the diagnosis and management of several malignant and non-malignant causes of central airway obstruction (CAO) and has become integral after the inception of airway stenting. The management of CAO can be a complicated endeavor with significant risks making the understanding of basic rigid bronchoscopy techniques, ablative technologies, anesthetic care and stenting of utmost importance in the care of these complex patients. This review article will focus on the history of rigid bronchoscopy, the technical aspects of performing a rigid bronchoscopy as well as the use of silicone stents their indications, complications and placement techniques.

**Keywords:** Rigid bronchoscopy; silicone stenting; central airway obstruction (CAO); ablative technologies

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## Introduction

Rigid bronchoscopy has been an invaluable tool for over a century in the diagnosis and management of innumerable pulmonary diseases. Since its inception by Dr. Gustav Killian in the late 1800's the use and popularity of this technique has waxed and waned. However, with advances in flexible bronchoscopy, ablative technologies and stenting over the past two decades rigid bronchoscopy has again become an integral tool in the management of malignant and non-malignant central airway disease by thoracic surgeons and interventional pulmonologists.

## History of rigid bronchoscopy

Dr. Gustav Killian performed the first rigid bronchoscopy in the late 1800's. This innovative procedure provided physicians with a new glimpse into human anatomy and sparked the growth of pulmonary medicine. Using a metal tube, a light, and topical cocaine anesthesia, Killian removed a pork bone from a farmer's airway in 1897 (1). Prior to the invention of rigid bronchoscopy, over half of the patients who aspirated foreign bodies died, mostly of a post obstructive pneumonia. Rigid bronchoscopy with foreign body removal quickly evolved into the treatment of choice in these patients, with a clinical success rate above 98% (2). During the early 1900's, Killian published extensively and lectured throughout the world. He further went on to adapt his bronchoscopes, laryngoscopes and endoscopes, and first described techniques such as using fluoroscopy and X-ray to define endobronchial anatomy. The design and functionality of the rigid bronchoscope was improved further in 1904 when Chevalier Jackson, who is regarded as the father of American bronchoesophagology first equipped

 

his bronchoscope with a suction channel and a small light bulb at the distal tip to provide illumination.

The rigid bronchoscope quickly became an indispensable piece of equipment for otolaryngologists across the world and remained the only medical instrument to access the airways until 1963 when Shigeto Ikeda from the National Cancer Center Hospital in Tokyo, Japan introduced the flexible fiberoptic bronchoscope (3,4). For the next 30 years the use of rigid bronchoscopy declined as flexible bronchoscopy quickly gained worldwide acceptance and almost completely replaced the rigid bronchoscope as the diagnostic instrument of choice for pulmonary disease. In a survey performed in 1989, 8% of responders were performing rigid bronchoscopy (5). In a repeat survey in 1999 this number had declined to only 4% (6).

It was not until the lung cancer epidemic of the late 1900's and the associated increase in central airway obstruction (CAO) that the utility of the rigid bronchoscope reemerged. In addition, recognition of certain advantages that rigid bronchoscopy has over flexible bronchoscopy such as airway control and ventilation during intervention as well as the ability to simultaneously use larger forceps, suction catheters and tumor excision techniques have led to the increase in rigid bronchoscopies being performed today.

## Central airway obstruction (CAO)

The majority of rigid bronchoscopies done today are for the diagnosis and management of CAO. CAO is generally split into malignant and non-malignant disease. Malignant disease outnumbers non-malignant disease due to the rising incidence of primary lung cancer as well as countless types of malignancies that can metastasize to the lung (7). Non-malignant causes of CAO are often iatrogenic and secondary to endotracheal intubation or prior tracheostomy as well as inflammatory and connective tissue disorders (8). Although less prevalent, it is important to diagnose and treat these appropriately as patients with non-malignant CAO often have a longer life expectancy and can live with their disease for years to decades, as opposed to their malignant counterparts.

The incidence of CAO is difficult to estimate, but does appear to be on the rise in large proportion due to the increase in primary lung cancer. It is estimated that about 20-30% of patients with primary lung cancer will develop CAO, many of which may benefit from palliative measures to relive dyspnea caused by the obstruction (9). While less prevalent, non-malignant cases also appear to be on the rise. It is unclear whether this is due to increased availability of bronchoscopy leading to increased discovery versus the increase in ICU care, endotracheal intubation and tracheostomy (8).

The causes of malignant and non-malignant CAO are listed in *Table 1*. Primary tracheobronchial tumors are extremely rare consisting of adenoid cystic carcinomas [600-700 cases per year (10)], bronchial carcinoid tumors which are slightly more common with an incidence of 2 cases per 100,000 globally (11) and primary squamous cell and adenocarcinomas of the trachea. Much more common are metastasis of primary lung cancer, breast, renal cell, melanoma and thyroid cancers.

The anatomy of malignant CAO is generally classified into three groups. The first consisting of tumors that are purely intra-luminal and do not erode outside of the tracheal wall or cartilage. The second category of CAO is extrinsic compression from either parenchymal metastasis or mediastinal adenopathy. Finally, the most common category of CAO is a mixed extrinsic/intrinsic stenosis. These forms of stenosis generally originate outside of the airway and erode into the lumen. Differentiating between these three types of CAO is important as therapeutic options can differ for each category (*Figure 1*).

Non-malignant CAO is most frequently caused by iatrogenic injury post endotracheal intubation or tracheostomy placement. However, inflammatory and connective tissue disorders including Wegener's granulomatosis, sarcoidosis, amyloidosis, relapsing polychondritis and tracheobronchopathia osteochondroplastica can also be the etiology of CAO. Another large category of non-malignant CAO is lung transplantation and stenosis at the anastomotic site. As mentioned previously the treatment intent in malignant CAO is almost always palliative in nature. This is certainly not the intent in many cases of non-malignant CAO where the intent should be curative. Rigid bronchoscopy with dilation and stenting should be used as a trial for improvement in symptomatology and as a bridge to curative surgical repair. Long-term stenting of benign stenotic airways may cause extension of the stenotic area due to granulation tissue, which may actually hinder future surgical repair.

As mentioned above the primary goal for rigid bronchoscopy is to relieve dyspnea and improve quality of life (QOL) caused by CAO in malignant as well as non-malignant disease. There have been a small number of papers published looking at the subjective improvement of dyspnea after bronchoscopy and relief of CAO, the

 

**Table 1** Etiologies of central airway obstruction

| |
|---|
| Non-malignant |
| Lymphadenopathy |
| Sarcoidosis |
| Infectious (i.e., tuberculosis, histoplasmosis) |
| Cartilage |
| Relapsing polychondritis |
| Granulation tissue from |
| Endotracheal tubes |
| Tracheostomy tubes |
| Airway stents |
| Foreign bodies |
| Surgical anastomosis |
| Wegener's granulomatosis |
| Pseudotumor |
| Hamartomas |
| Amyloid |
| Papillomatosis |
| Hyperdynamic |
| Tracheomalacia |
| Bronchomalacia |
| Webs |
| Idiopathic |
| Tuberculosis |
| Sarcoidosis |
| Other |
| Foreign body goiter |
| Mucus plug |
| Blood clot |
| Malignant |
| Primary airway carcinoma |
| Bronchogenic |
| Carcinoid adenoid cystic |
| Mucoepidermoid |
| Metastatic carcinoma to the airway |
| Bronchogenic |
| Renal cell |
| Breast |
| Thyroid |
| Colon |
| Sarcoma |
| Melanoma |
| Laryngeal carcinoma |
| Esophageal carcinoma |
| Mediastinal tumors |
| Thymus |
| Thyroid |
| Germ cell |
| Lymphadenopathy |
| Associated with any of the above malignancies |
| Lymphoma |

largest being a multicenter registry study of 947 patients at 23 centers undergoing therapeutic bronchoscopy for CAO (12). Technical success was achieved on average in 93% of cases which was defined as opening of >50% of the airway. Dyspnea and QOL were measured using the Borg score and SF-6D in a portion of the study patients (187 and 183 respectively) with dyspnea subjectively improved in 48% of cases and QOL improved in 42%. Greater dyspnea at baseline as well as endobronchial obstruction was associated with greater improvement in dyspnea and QOL. American Society of Anesthesia (ASA) scores >3, renal failure, lobar obstruction, and tracheoesophageal fistulas were associated with less improvement.

The above trial like many of the other papers published on this topic, generally use a validated dyspnea or QOL score as the primary outcome. A recent prospective case series examined 53 patients undergoing therapeutic rigid bronchoscopy over a 3-year period and measured QOL and dyspnea scores as well as changes in pulmonary function testing (13). The population examined was predominantly malignant (45%) and post-transplant stenosis (43%) related CAO. Patients were found to have a subjective improvement of dyspnea and QOL measured by the University of San Diego Shortness of Breath Questionnaire and the SF-36 respectively, both validated tools to assess dyspnea and QOL in lung disease patients. Besides subjective improvements this study also showed a statistically significant improvement in $FEV_1$ as well as FVC. There has yet to be any data showing improvement in survival after relief of malignant CAO.

## Rigid bronchoscopy

### *Equipment*

The rigid bronchoscope is a simple piece of equipment that has not significantly changed since its invention. Rigid bronchoscopes generally come in two forms; rigid tracheal scopes and rigid bronchoscopes. Both are hollow metal tubes with beveled distal edges available in several different diameters. The rigid bronchoscope is longer allowing access into the right and left bronchial trees as well as having distal fenestrations to allow ventilation of the contralateral bronchial tree. All scopes come with a built-in or attachable port for jet or conventional ventilation. The light source can either be attached to the barrel, or more commonly directly to the camera. Scopes come in various sizes and length depending on the manufacturer, but all have an inner

 

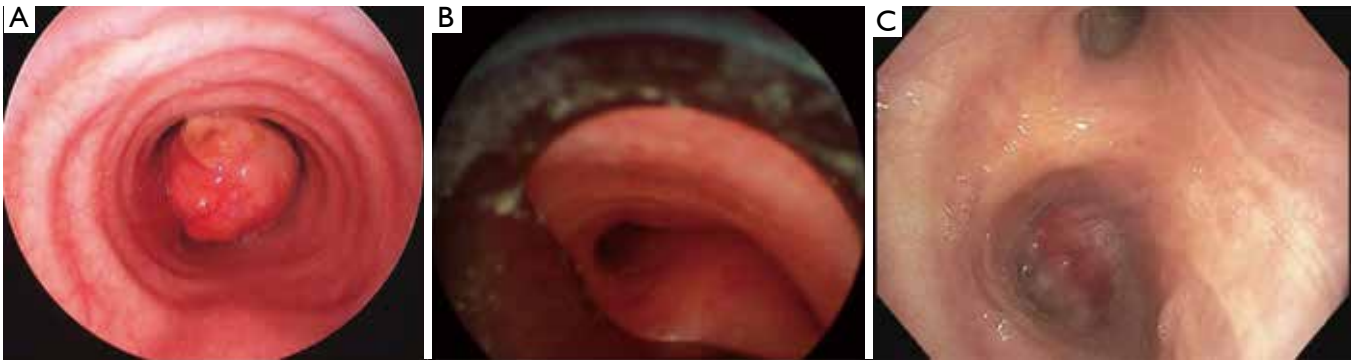


**Figure 1** Three categories of central airway obstruction (CAO). (A) Intrinsic CAO: patient with mucoepidermoid carcinoma; (B) extrinsic CAO: patient with metastatic osteosarcoma with compression of RMSB; (C) combined intrinsic and extrinsic CAO. Patient with compression of the bronchus intermedius by a right sided primary lung malignancy as well as endobronchial tumor. RMSB, right main stem bronchus.

and outer diameter varying from 7-13 mm and 8-14 mm respectively.

Although there have not been significant advances in the rigid bronchoscope itself, countless types of instruments have been developed to use through the working channel. The first and most commonly used being the flexible bronchoscope. Once the airway has been secured with the rigid scope a flexible scope is often passed through the working channel and into segmental airways to lavage, suction secretions or blood as well as cannulate past smaller obstructions prior to coring, excising or stenting. A multitude of other instruments are now also available to pass down the working channel of rigid scopes including rigid and flexible suction catheters, different types and sizes of forceps, scissors, rigid and balloon dilators, multiple types of lasers, electrocautery, argon plasma coagulation and cryotherapy catheters, snares, loops, baskets, microdebriders, and stent deployment devices (14). Finally, a manual or automated jet ventilator is needed for oxygenation and ventilation during cases. If preferred or necessary the patient can also be ventilated by packing the mouth, placing silicone caps on the end of the rigid bronchoscope and using conventional positive pressure ventilation through a ventilator circuit adaptor placed on the proximal end of the rigid scope.

### *Rigid intubation and anesthetic considerations*

Prior to rigid intubation the operator must discuss induction with the anesthesiologist, including medication choice and paralysis as well as a backup plan in case difficulty is encountered with rigid intubation. They must also ensure all equipment is ready and functional as well as properly position the patient to optimize first attempt success. Rigid bronchoscopy requires careful planning, cooperation and communication between the operator and the anesthesiologist to ensure patient safety.

Choice of induction agent is generally left to the anesthetist, depending on the patient's medical history and clinical stability. Rigid intubation, similar to endotracheal intubation is extremely stimulating and generally deep sedation is required to blunt the gag reflex. Total intravenous anesthesia (TIVA) is almost exclusively used for rigid bronchoscopy, as a fully closed system required for inhaled anesthetics is rare. Generally a combination of a hypnotic administered simultaneously with a narcotic is used with the most common drugs being propofol (40-200 μg/kg/min) and remifentanil (0.05-0.5 μg/kg/min) (15). Similar to endotracheal intubation paralysis is not required during rigid intubation but can be helpful especially in patients with anterior or difficult airways. If paralysis is going to be administered the choice of agent should be discussed with the operator. When a short case is expected a shorter acting agent such as succinylcholine should be considered as a one-time dose or as an infusion. Otherwise, longer acting agents such as cisatracurium, vecuronium or rocuronium can be administered (15).

Once a plan for induction has been established and all equipment is ready the patient should be positioned with a shoulder roll or the head of the bed dropped to allow maximal extension of the neck without allowing the head to float. A tooth guard should be placed to protect the

 

upper teeth, however, if proper technique is used minimal to no pressure should be placed on the patient's teeth. The operator should then scissor the patient's mouth open in standard technique and carefully insert the rigid scope initially visualizing the tongue and hard palate. The operator's thumb should be used to support the bottom of the rigid scope just outside of the oral cavity with the index and possibly the middle finger placed in the patient's mouth resting on the hard palate. The scope is carefully inserted into the mouth with the bevel up or towards the tongue. The scope should then be carefully advanced further into the oral cavity until the uvula is visualized. Once the uvula is visualized the dominant hand holding the rigid scope and camera should be lowered using the thumb as a fulcrum and advanced further until the epiglottis is seen. The bevel of the rigid scope should then be used in a similar fashion as a Miller laryngoscope to lift the epiglottis anteriorly exposing the arytenoids, vocal cords and the glottis. If the patient's glottis is anterior the thumb should be used to apply anterior and upward force on the rigid scope to expose the glottis. Care should be taken not to use the patient's teeth as a fulcrum as this can cause significant damage. Once a good view of the glottis is achieved the scope is then rotated 90 degrees to allow the bevel to pass a traumatically through the vocal cords. The scope is then rotated another 90 degrees with the bevel rested on the posterior membrane of the trachea (16).

Once intubation is complete the jet ventilator is attached or the mouth is packed and ventilation is initiated and ensured by watching for chest rise prior to the initiation of any diagnostic or therapeutic interventions. The patient is monitored using continuous pulse oximetry, EKG tracing and blood pressure monitoring. Placement of an arterial line for blood pressure and blood gas analysis is generally not required unless the patient is unstable or a longer case is expected.

### *Ventilation techniques*

Once rigid intubation is complete and the patient's airway has been secured the operator must turn their attention to ensuring adequate oxygenation and ventilation. These are achieved with either jet ventilation or less commonly through conventional positive pressure ventilation. Sanders originally described open system manual jet ventilation in 1967, a technique still currently in use (17). The jet ventilator is connected to a 100% oxygen source and has a pressure-limiting device peaking at 50 PSI or less. The jet is connected through a catheter to the ventilation port of the rigid scope being used. Breaths are delivered to the patient at a rate of 12-18 per minute with the breath length and expiratory time being controlled by the anesthesiologist who is monitoring chest rise and vital signs to ensure adequate ventilation. The tidal volume of delivered air is dependent on the length of the breath given, the inspiratory pressure (PSI), the compliance of the patient's respiratory system and the resistance of the patient's airways (18). The advantage of jet ventilation is the ability to keep the working channel of the rigid bronchoscope completely open allowing easy passage of instruments. Disadvantages include the ability to only use 100% oxygen (unless an ambient air blender is available) as well as difficulty in oxygenating and ventilating sicker patients with severe parenchymal or obstructive lung disease.

A second type of jet ventilation commercially available is the automated jet ventilator. This is a computerized ventilator where the operator or anesthesiologist is able to set the applied pressure, respiratory rate, $FiO_2$ and inspiratory time. The advantages of an automated system is the ability to free the anesthesiologist from holding the manual jet throughout the case as well as the ability to vary the $FiO_2$ to enable the use of thermal ablative techniques without completely holding ventilation.

Closed system ventilation is achieved by attaching a ventilator circuit adaptor onto the distal end of the bronchoscope and using the rigid scope as an endotracheal tube. All of the proximal ports of the scope must be covered with silicone caps and the patient's mouth must be packed with gauze to ensure minimal air leak. The advantage of this system is the ability to give positive pressure breaths through an automated ventilator circuit as well as positive end-expiratory pressure (PEEP). This may allow improved ventilation and oxygenation in sicker patients with less respiratory reserve. A closed system also allows the use of inhaled anesthetics without significant exposure to those in the operating room. The disadvantages are the labor-intensive nature of packing the mouth as well as covering the proximal ports of the rigid scope with silicone caps, which can make the passage of multiple instruments difficult.

### *Tumor excision, coring and airway dilation techniques*

After the patient has been successfully intubated with the rigid scope and ventilation has been initiated attention can be turned to relieving the CAO. Several different

 

techniques can be utilized at this time and depends on the category of CAO encountered; extrinsic, intrinsic or mixed. For pure extrinsic compression without any mucosal or endobronchial involvement, therapeutic intervention relies on CRE balloon and rigid dilation followed by silicone or covered metal stent placement to maintain a patent airway.

In the setting of intrinsic or mixed obstructions, the initial goal is to establish patency of the airway. It is of critical importance that the operator maintains good visualization of the airway as well as appropriate spatial orientation to avoid perforation of the airway and invasion into the surrounding mediastinal structures. Once the operator has established good visualization, appropriate spatial orientation and a parallel axis to the central airway a decision can be made on how to remove the obstructing lesion. The first option is coring with the rigid scope, this allows one rotary forward motion to remove the lesion from the wall and simultaneously allows the scope to provide hemostasis at the site. Ensuring spatial and parallel axial orientation is of utmost importance during this method as one can easily core through an airway into the mediastinum (16). The next option includes mechanical excision with optical cup forceps, free forceps, loop cautery, microdebrider or a cryoprobe.

Microdebriders are powered instruments that consist of a hollow shaft with a rapidly rotating blade and suction. This device has been used for many years by the otolaryngology community for sinus and tracheal surgery (19). More recently, the procedure has been used as an alternative to or in conjunction with other modalities such as laser excision or electrocautery. Airway debulking with the microdebrider is accomplished by shaving and suctioning tissue under direct telescopic guidance through the rigid bronchoscope.

In a study by Lunn and colleagues, 16 subjects were treated with the microdebrider for the management of CAO. The majority of patients (87%) suffered from benign airway disease and remaining three patients (13%) had malignant airway obstruction. Using the microdebrider, the obstructing airway lesions were rapidly removed in all patients. There was only mild bleeding that occurred and was easily controlled by utilizing the rigid bronchoscope to tamponade the affected area or instillation of oxymetazoline hydrochloride. In this study, there were no procedure-related or long-term complications of the microdebrider reported (20). A case report by Kennedy and colleagues reports the safe use of the microdebrider for more distal lesions due to the devices long length. The microdebrider was successfully used for relief of a distal left mainstem obstruction in a 59-year-old male with T3N2M1 non-small cell lung cancer followed by stent placement (21).

The oscillatory speed of the device and level of suctioning have varying adjustment levels and there have been reports in the literature of inadvertent resection of normal tissue with aggressive suctioning. There is one case report in the literature of pneumomediastinum and retroperitoneal air after the removal of tracheal papillomas with the microdebrider and jet ventilation. The author's hypothesize those micro-perforations occurred within the tracheal wall in conjunction with jet ventilation and allowed air entry into the mediastinum and retroperitoneum. In this case, spontaneous resolution ensued without the need for surgical or medical intervention (22).

The microdebrider requires a rigid bronchoscope or laryngoscope and due to its rigid structure is not amenable to the flexible bronchoscopic technique. The advantages of the microdebrider for management of CAO include the ability to rapidly destroy and excise tissue with minimal bleeding, the ability to maintain a clear working field due to the automatic suctioning of the debrided tissue and no risk of airway fire or perforation. Although the technology appears promising and a useful modality in the management of CAO, further studies are required to assess the long-term outcomes of the microdebrider compared with more conventional therapy (14).

Cryotherapy is another safe and effective tool for debridement, hemostasis and removal of clot in rigid bronchoscopy. The device releases nitrous oxide or carbon dioxide stored under pressure into the tip of the cryoprobe which rapidly cools to –89 ℃. The effectiveness of cryotherapy depends on the rapidity of the freezing and thawing process, the lowest temperature achieved the number of freeze-thaw cycles, and the water content of the tissue (23). Compared to other techniques for tumor destruction, the effects of cryotherapy are delayed, and frequently a repeat bronchoscopy to remove the necrotic tissue is required (24).

Cryotherapy has been used to successfully treat both benign and malignant CAO. It is effective in reducing or eliminating hemoptysis due to malignant disease in up to 93% of patients (25), and Maiwand and Homasson recommend cryotherapy as a first-line treatment in patients with post-transplant anastomotic strictures (26). As cartilage and fibrous tissue are relatively cryo-resistant, cryotherapy remains a very safe procedure. Bleeding is also uncommon because of the hemostatic effects of cryotherapy. Because of the lack of electrical current needed, cryotherapy is not

 

associated with the risk of airway fires, electrical accidents, or radiation exposure. Cryotherapy can be used via both the rigid and flexible bronchoscopes. When using the flexible bronchoscope, care must be taken to have the probe protrude outside the distal tip of the scope, so as not to freeze the video chip.

After relief of the CAO due to an intrinsic or mixed lesion the operator must decide whether to leave the airway as is or if a stent is needed to maintain patency and stabilization. The risk of stent migration, granulation tissue formation and mucostasis must be weighed with the benefit of continued patency provided by the stent. This will be discussed extensively in the following section.

## Silicone stenting

### *Introduction*

Dr. William Montgomery is credited with initiating the widespread use of airway stents after his development of a silicone T-tube in 1965, but it wasn't until 1990 that Dumon introduced that first completely endoluminal airway stent. The endobronchial stent remains the only tool available to alleviate extrinsic airway compression, but can be used in conjunction with other therapies to relieve CAO in those with intrinsic or mixed disease.

There are two main types of endobronchial stents available for use in the United States; silicone and metal. Silicone stents have been in use since the 1960's and have a long track record of safety. Metal stents continue to evolve from the original uncovered metal stents to a number of newly designed covered metal stents made of nitinol. Unfortunately, the "ideal stent" has not yet been developed. This stent would be easy to insert and remove, yet not migrate; of sufficient strength to support the airway, yet be flexible enough to mimic normal airway physiology and promote secretion clearance; biologically inert to minimize the formation of granulation tissue; and available in a variety of sizes.

### *Types of silicone stents*

Most of the commercially available silicone stents are based on the original Dumon stent, which is a silicone tube with external studs to decrease migration. The Dumon silicone stent comes in two main types' straight and Y. Both types of these stents come in various lengths, diameters and shapes. The shape can be a uniform diameter throughout the length of the stent or have an hourglass shape with a narrow central portion allowing optimal positioning around a stenotic airway. Silicone stents can also have one end with a smaller diameter for optimal positioning. Y stents come with multiple various tracheal and bronchial limb diameters. These stents generally come in a uniform length, which can be adjusted at that time of insertion by shortening each of the three limbs to the desired length using a scalpel during the procedure. Other modifications can also be made at the time of insertion including the cutting of holes to allow ventilation of lobar bronchi covered by the stent during placement. Silicone stents can be made of transparent non-radio opaque material, or melted with barium sulfate, which are white in color, non-transparent but radio-opaque (27).

Another type of silicone stent commercially available currently is the Polyflex silicone stent (Boston Scientific, Natick, MA, USA). This stent is made of polyethylene threads embedded in a layer of silicone. These stents have a thin wall resulting in a better inner to outer diameter ratio compared to a Dumon stent. However, as they are not studded on the outside may have a higher rate of migration. They are embedded with tungsten making them radio-opaque and are deployed out of a semi-rigid tube inserted down a rigid bronchoscope. There are a small number of other companies commercially producing other types of silicone stents such as those manufactured by Hood (Hood Laboratories, Pembroke, MA, USA) with similar properties as the Dumon stent.

Dynamic Y tracheobronchial airway stents are also commercially available. These were initially described by Freitag *et al.* in 1994 (28) and are composed of anteriorly placed U shaped metal rings in the tracheal limb, with a silicone posterior membrane that can be dynamically compressed during cough to physiologically mimic the human trachea and allow for better mucus clearance. Finally, there are also numerous types of T-tubes and T-tube Y stent combinations manufactured currently for different types of tracheal and carinal pathology. This review will primarily focus on endobronchial silicone stents (27).

### *Indications*

There are several indications for the use of silicone stents in the management of CAO. In general silicone stenting is indicated for maintaining central airway patency due to malignant and non-malignant disease causing greater than 50% stenosis of the trachea or bronchi. The first major indication includes stabilization of airways from malignant

 

CAO. This can be either due to extrinsic compression, endobronchial tumor or a combination as described above. Stents may be the only resource available to maintain airway patency in extrinsic compression, as simple dilation is extremely transient if successful at all. In terms of endobronchial disease and mixed obstruction, stents are generally placed after excision and destruction of tumor has occurred to maintain patency and attempt to avoid recurrent obstruction by tumor re-growth or until systemic chemotherapy or radiation treatment has time to take effect. Post obstructive pneumonia caused by malignant airway obstruction is another appropriate indication, which may be necessary to maintain patency and provide adequate source control of the infected lobe or segment (29).

The second major indication is treatment of benign CAO caused by intubation trauma, tracheostomy, connective tissue disease, cartilaginous disorders or benign adenopathy. Silicone stents play an even larger role in benign disease, as they are preferred over metal stents due to complications with granulation of metal stents into the airway, difficulty with removal and fistula formation. Another benign indication for silicone stenting is stabilization of collapsing airways secondary to tracheobronchial malacia or cartilaginous disorders such as relapsing polychondritis. Finally, the last category of disease necessitating silicone stenting is to cover airway-esophageal or airway-mediastinal fistulas caused by malignant disease, iatrogenic complications of esophageal stenting, radiation therapy, or dehiscence of transplanted airways (29).

### *Deployment*

Once a lesion has been dilated, excised or destroyed and the decision has been made to place a silicone stent several steps must be taken to ensure the appropriate stent is placed in a safe, accurate and timely manner. Deployment is still based on the original technique describe by Jean Francois Dumon in a 1990 paper published in Chest of 118 stents placed in 66 patients in Marseille, France (30).

The initial step prior to deployment is choosing the appropriate size and length of the stent to be placed. This is extremely important as proper sizing decreases the chance of migration (under-sizing) and the formation of granulation tissue, airway fistulization or difficulty in deployment (over-sizing). The length and diameter of a stent can be estimated using a chest CT prior to the procedure, but measurements during bronchoscopy are the only accurate way of sizing a stent. The diameter can usually be determined by choosing a size similar to the largest external diameter of the rigid bronchoscope used to maximally dilate the lesion in question. There are also commercially available stent sizers that can be placed down a rigid scope and used to measure the diameter of the stenotic airway. Once an appropriate size has been determined the length of the lesion should be measured using the rigid camera or flexible bronchoscope with the stent extending about 5-10 mm proximal and distal to the lesion. In sizing stents for fistulas, one should slightly oversize the stent as there is no endobronchial lesion to anchor the stent to, making migration more likely (27).

Once the appropriate stent has been selected it is loaded into a hollow metal stent deployment tube either manually or with a commercially available loading device. The rigid bronchoscope should then be placed slightly distal or within the stenosis. A prosthesis pusher is then placed through the hollow stent deployment tube and these are both placed down the rigid bronchoscope as ventilation is held. If the scope is positioned distal to the lesion, the rigid scope can be slightly withdrawn simultaneously as the stent is deployed to allow the stent to deploy within the stenosis. The deployment device is then removed and the camera alongside forceps should be placed back into the rigid scope. The stent may fully deploy, but generally requires being pulled back into optimal position, or slightly rotated to fully open. If manual rotation or adjustment does not fully open the stent the barrel of the rigid scope can be used to open the stent carefully without pushing it distally or a CRE balloon may be used to help expand the stent (30). If that is still unsuccessful, the stent is likely too large for the lesion and needs to be removed with a smaller diameter stent re-deployed.

Deployment of a Y silicone stent is slightly more difficult and can be accomplished through two general strategies. In both techniques the stent is loaded into the stent deployment device after lubrication with care taken to note the directionality in which the stent is folded in order to deploy the left and right limbs in the proper orientation. In the first technique the rigid bronchoscope is positioned above the carina based on the length of the tracheal limb. The stent is pushed out into the trachea in a similar fashion as described above and then using a camera, forceps and the rigid scope the stent is advanced and turned to position the left and right limbs appropriately in their respective mainstem bronchi flush with the carina.

In the second technique the stent is loaded in the same manner but deployed in the mainstem that will house the

 

longer limb of the Y stent or alternatively the mainstem with the more stenotic airway. In this technique a rigid bronchoscope must be used and intubation of the right or left mainstem must be possible. Once the mainstem has been intubated the stent deployment device is inserted into the bronchoscope and the stent is pushed out of the device. As the stent is being deployed the rigid scope is slowly withdrawn back into the trachea until the stent is fully out of the deployer. The rigid telescopes as well as forceps are then used to pull the stent back gently from the mainstem it was deployed in, allowing the shorter limb to fall into place in the contralateral bronchus. Again rotation of the stent may be necessary to allow snug seating on the carina.

Deployment of a dynamic Y stent described in the previous section must be done in an altogether different manner than the two techniques described above. After inspection of the airway with a rigid or flexible bronchoscope and measurements made to determine the size of the dynamic Y stent to be placed the scope is removed and the patient ventilated with a bag valve mask or laryngeal mask airway until the stent is ready to be deployed. The dynamic Y airway stent is loaded onto a specific deployment device, which is a modification of rigid foreign body retrieval forceps, with longer jaws onto which the right and left mainstem limbs are inserted over. The operator then using direct laryngoscopy with either a Macintosh or Miller blade inserts the stent at a 90 degree angle carefully through the vocal cords on top of the deployment forceps using their right hand. Once the stent is fully inside the trachea, the stent is rotated 90 degrees clockwise and advanced until slight resistance is met. At this point the jaws of the forceps are opened and the stent is pushed further forward onto the carina (using a device connected to the deployment apparatus) until further resistance is met. At this point the jaws are closed and the deployment forceps withdrawn from the glottis. The patient is then rigidly intubated and the rigid camera and forceps are used to adjust the stent if necessary by further pushing it forward or rotating it to optimally seat it on the carina. The patient does need to tolerate a certain amount of apnea during deployment of a dynamic Y stent and the operator must be confident in their ability to obtain a good glottic view and rapidly re-intubate the patient with the rigid bronchoscope in the case of poor deployment and obstruction of the trachea by the stent. To aid in intubation or for training purposes, placement of dynamic Y stents with a video laryngoscope can be done to allow both the trainee and instructor to have a view of the glottis (31).

### *Complications*

There are a wide range of complications related to rigid bronchoscopy and placement of silicone tracheal and bronchial stents ranging from as minor as mucostasis to death from hypoxic arrest during placement or migration of the stent. Complications from rigid bronchoscopy and stenting are in general very low, however when consenting a patient prior to a procedure a multitude of risks should generally be discussed including trauma to the oral cavity (lips, gums, teeth, tongue, pharynx), the vocal cords, the trachea and bronchi themselves, bleeding, infection, tracheal or bronchial rupture, hypoxia, respiratory failure requiring mechanical ventilation, tracheostomy, cardiac arrest and even death. If stenting is to be performed then the risks of stent placement are generally listed including mucus plugging, migration, formation of granulation tissue, bacterial overgrowth, halitosis and repeat procedures to inspect the stent, adjust if migrated and remove granulation tissue. Depending on the clinical stability of the patient different levels of emphasis can be placed on more serious complications such as respiratory failure and death. The overall risk and benefit of the procedure can then be discussed with the patient and family and an informed decision can be made to proceed, even in high-risk situations.

Most studies examining complications following bronchoscopic treatment of CAO have been retrospective in nature; however, a recent multicenter registry trial published by Ost *et al.* examines 1,115 procedures performed on 947 patients at 15 centers from 2009 to 2013 (32). These included flexible (34%) and rigid (66%) therapeutic bronchoscopy under both general anesthesia (86%) and moderate sedation (14%) with multiple interventions reported including dilation (40%), ablative technologies: cryotherapy (8%), APC (35%), laser (23%) or electrocautery (21%) and stenting (36%). Only 44 patients (3.9%) were reported to have complications, which were defined as: bleeding requiring intervention, pneumothorax, hypoxemia, clinically significant airway injury, hypotension, arrhythmia, cardiac arrest, respiratory failure requiring mechanical ventilation and death. Of those reported complications 61% of those patients required a higher level of care. There were six deaths reported within 24 hours, four of which were secondary to a complication of the procedure and two unrelated. Two more deaths >24 hours after the procedure, but thought to be secondary to a complication of the procedure, were also reported. This gives a total mortality rate of 0.5% due to

 

complications from therapeutic bronchoscopy.

Risk factors for complications included emergent procedures, ASA >3, re-do therapeutic bronchoscopy and the use of moderate sedation. Of note the use of neuromuscular blockade was associated with decreased rate of complications. This is likely due to the ability to oxygenate/ventilate better during the procedure as well as improved visualization due to lack of cough and patient movement. The study also examined risk factors for death at 30 days (14.8%) which were found to be associated with ASA >3, intrinsic or mixed obstructions or placement of a stent. The association with stenting and higher 30-day mortality is not likely due to the stent itself or stent complications, but rather to confounding factors including the fact that patients requiring stents likely have a higher level of disease burden are generally sicker and may not have other systemic treatment options remaining. Overall, the mortality/morbidity from therapeutic bronchoscopy is low when used in the appropriate setting.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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Interventional Therapy Technique

# Stents for airway strictures: selection and results

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**Abstract:** Airway stents can provide effective and timely relief in patients with central airway obstruction. Silicone-based stents are the most commonly used airway stents worldwide with a long track record of safety. Metallic stents continue to evolve from the earliest uncovered versions to a variety of newly designed covered stents. Despite the availability of a variety of stent materials and designs, minimal advances have been made towards innovation in stent technology and an ideal stent has unfortunately not yet been developed. Nevertheless, the first generation of biodegradable airway stents are available, work on drug-eluted stents is in the pipeline and three-dimensional printing of a customized airway stent may be the future. In this review, we discuss selection and results for most commonly utilized airway stents.

**Keywords:** Airway strictures; central airway obstruction; malignant strictures; benign airway stenosis; airway stenting; silicone stents; expandable metal stents

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## Introduction

Airway stents have been used for management of tracheobronchial pathologies since the second half of 20$^{th}$ century. A silicone-based T-Tube developed by Montgomery in the 1960's is one of the earliest airway stents (1). Dumon followed with the introduction of a 'stand alone' stent (2). Several variations of these polymer-based stents evolved and remained widely utilized until self-expandable metal stents (SEMSs) were introduced in the late 20$^{th}$ century. All currently available airway stents have certain limitations, and stent selection should be catered for specific disease processes. Airway stents remain an important therapeutic option to restore airway patency in selected patients especially in conjunction with other endoscopic modalities. Proper stent selection is crucial and requires consideration of multiple factors including properties, indication, and duration of stent placement. In this review, we discuss selection and results for the most commonly used airway stents.

## Indications for airway stents

Major potential indications for airway stenting include:

(I) Palliation of extrinsic compression and endoluminal intrinsic lesions in malignant airway disease;
(II) Treatment of benign airway stenosis;
(III) Treatment of airway fistulas and dehiscence;
(IV) Management of post lung-transplant (LT) anastomotic complications;
(V) Management of pediatric airway stenosis.

The two main types of airway stents are silicone stents and metallic stents. Results with their use are discussed below.

## Silicone stents

Silicone stents have a long record of safety, are relatively inexpensive and easy to manipulate. They are available in nonexpandable (Dumon, Hood, Dynamic airway) and expandable versions (Polyflex). Dumon and Hood stents are the most commonly used airway stents worldwide and are

developed in two designs: straight and Y-shaped (for carinal stenosis).

### *Silicone stents for benign airway strictures*

Silicone stents have established good efficacy in patients with tracheobronchial strictures, both benign and cancer-related. Earlier reports for their use demonstrated successful airway palliation in 85% to 95% cases, with good tolerance and infrequent complications resulting in their continued use to date (3-7).

The effectiveness of silicone stents has been re-validated in recent works. Jeong *et al.* investigated the utility of silicone stents in 19 patients who developed tracheobronchial stenosis following major thoracic surgery (8). A total of 50 stents were placed (Natural, 33; Y-stent, 13; Dumon, 3; and T-tube, 1) and symptomatic improvement was achieved in all cases. In addition, successful stent removal was possible in 7 (36%) patients within a median duration of 7 months. There was no procedure-related mortality. Common complications included restenosis (33%) and stent migration (32%).

Terra *et al.* (9) reported their experience in 92 patients with benign airway strictures using 258 silicone stents (T-tubes, 72%; DUMON, 15%; Polyflex, 12%; and Y-tube, 1%). Interestingly, the authors showed that decannulation was possible in 21% of cases who were considered inoperable before stenting. Mean follow-up after decannulation was 37.4 months. Granulation tissue formation (22%) and stent migration (5%) were the most common complications. Presence of tracheostomy before stenting was the only significant predictor of poor decannulation outcome.

### *Silicone stents for post-lung transplantation strictures*

Silicone stents have demonstrated good efficacy and safety in patients with post-LT anastomotic strictures. Dutau *et al.* examined their utility in 17 patients and observed symptomatic improvement following stent placement in all patients (10). The mean FEV1 increased by 672±496 mL and airway patency was maintained at a mean follow-up of 867 days. Complications occurred in 16 of 23 anastomoses including granulation tissue (n=10), mucus plugging (n=7), stent migration (n=7), and infection (n=4). Successful stent removal was achieved in 16 of 23 anastomoses (69.5%) at a mean of 362±126 days. Similar results were reported by Sundset and colleagues, who described their experience of silicone stent placement in 35 LT patients (11). Symptoms were relieved in all patients and 25 stents were successfully removed within 6 months (range, 1–22 months). Median $FEV_1$ was 2.3 liters after stent removal and remained 2.3 liters at 24 months.

Despite proven effectiveness for the treatment of tracheobronchial strictures, there are several limitations with silicone stents such as migration and the need of rigid bronchoscopy for stent placement etc. This has led to development of self-expanding stents most notably SEMS.

## Metallic stents

Commonly used metallic stents include uncovered/partially covered (Ultraflex and Wallstent) and covered stents (AERO Stents). They are relatively easy to place using fiber-optic bronchoscopy under fluoroscopic guidance. Covered metallic stents are manufactured with or without a silastic or polyurethane covering to minimize intrinsic tissue growth. Metallic stents have been studied in the management of both benign and malignant airway stenosis.

### *Metallic stents for malignant strictures*

In cancer-related strictures, airway stents can be used either for palliation to maintain airway patency following debulking or as a bridge to other procedures. In addition to providing excellent palliation, timely placement of an expandable metal stent improves survival in patients with malignant stenosis. This was reported by our group in a retrospective analysis of 50 patients with advanced metastatic airway obstruction (12). A total of 72 airway stents were placed. EMSs (Ultraflex and AERO) were inserted for tracheal and bronchial stenosis, while silicone stents (dynamic airway) were deployed for carinal stenosis. Symptomatic improvement was observed in 45 patients (90%). Overall complication rate was 20% (n=10) including mucus plugging (n=2), stent migration (n=2), and tumor ingrowth (n=1). The overall median survival was 117 days with 3-month and 6-month survival rates of 60% and 40%, respectively. Significant survival benefit was observed for patients who had intermediate performance (based on ECOG and MRC) compared with the poor performance group (233 versus 89 days, $P<0.05$).

### *Metallic stents for benign strictures*

Use of metallic stents for benign airway diseases is controversial. Given their ease of insertion compared to silicone stents, metallic stents use gained initial enthusiasm,

 

with encouraging short-term results. However, long-term results revealed significant complications associated with metallic stents for benign airway diseases that prompted the US Food and Drug Administration (FDA) to release a public health warning against the use of metallic stents in benign airway disease (13). Previous reports comparing the outcomes of metallic stents in benign and malignant strictures have reported a higher incidence of complications in the benign group (14). This has been validated in recent observations as well. Chung and colleagues reported their experience with 211 SEMSs insertion in 149 patients and observed a higher complication rate in the benign group (42.2% *vs.* 21.1%) including granulation tissue formation (19% *vs.* 10.5%) and stent fracture (16.4% *vs.* 1.1%) (15).

Besides a higher complication rate, metallic stents can be difficult to remove. Lunn *et al.* performed stent removal in 25 patients and reported significant complications including retained stent pieces (n=7), mucosal tear (n=4), re-obstruction requiring re-stenting (n=14), need for postoperative mechanical ventilation (n=6) and one tension pneumothorax (16). In the largest series of 55 SEMSs removals by Alazemi and coworkers, it was estimated that stent removal comes with an additional cost of approximately $11,000 dollars per encounter (17). In addition, there is a concern that EMSs may also limit future therapeutic options in some cases. This was observed in a series of 15 patients, where primary repair was judged to be possible in 10 patients before an EMS placement, yet only 5 patients had a successful repair afterwards (18).

### *Metallic stents for post-LT strictures*

Airway stents have been investigated in the setting of post-LT anastomotic strictures and while some initial reports observed high complication rates, significant benefits have been demonstrated in recent work. Gottlieb and coworkers inserted 111 SEMSs (91% uncovered) in post-LT recipients who developed anastomotic strictures (19). Clinical improvement was seen in 80% cases. Most frequent complications were restenosis (52%), bacterial colonization (40%), mucus plugging (11%) and migration (3%). In multivariate analysis, stent insertion within 3 months postoperative period was independently associated with an increased risk of re-stenosis (HR 3.29; 95% CI: 1.50–7.18; P=0.003). In patients who received stent placement, 5-yr survival rate was significantly lower than those who did not undergo stenting (60% versus 76%; P=0.02).

Recently, Abdel-Rahman *et al.* evaluated the short-term and long-term outcomes in 47 post-LT patients (20). The median follow-up was 54 months (range, 1–132 months). Immediate relief was achieved in 95% of patients. Granulation tissue mandating treatment was observed in 65%. Five-year survival rate for patients who underwent stenting was lower compared to those who did not receive stents (55.5% *vs.* 61.1%, P>0.05). Overall, the stent group had a significantly increased number of bronchoscopies to manage stent-related problems. They concluded that metal stents can be an acceptable option in this group of patients, but the need for more procedures in the follow-up must be accepted.

Other applications of metal stents include their utility in managing life-threatening post-LT anastomotic wound dehiscences (21). Metal stents are frequently associated with granulation tissue formation which can provide a platform for healing of the dehiscence. Ideally, the stent should be removed at 6–8 weeks by the time wound repair is achieved.

## Pediatric application of airway stents

Airway stenting may also represent an effective treatment in children with tracheobronchial strictures. Serio *et al.* described the largest cohort of 100 children with severe airway obstruction who underwent stent placement (22). A total of 235 stents were inserted (silicone 112, metallic 120 and biodegradable 3). Silicone stents were mainly placed in the trachea; stainless steel metallic stents were utilized for bronchial lesions. Clinical improvement was reported in eighty patients after stent insertion; furthermore, 17 patients were weaned off mechanical ventilation while 3 showed no significant clinical improvement. Silicone stents were more prone to granulation tissue formation (11.6% *vs.* 0.8%) and dislocation (39.2% *vs.* 4.1%) compared with metallic stents. At a median follow-up of 41.4 months (range, 1.1–145.4 months) complete resolution was registered for 60 (65.9%) patients (silicone 76.6% and metal 72.9%), 17 were still under treatment, 9 lost to follow-up, 8 underwent surgery and 6 died of non-stent related causes. Stent removal was performed in 26 (23%) patients with silicone stents and 6 (5%) patients with metallic stents.

Airway stenting is also potentially useful in the emergency management of pediatric airway pathologies such as congenital tracheal stenosis. Xu *et al.* reported using self-expanding metallic stents in 31 infants with congenital tracheal stenosis without observing any immediate stent-related complication (23). All patients had immediate improvement of respiratory obstruction and successful weaning from the breathing machine.

 

Granulation tissue was observed in three cases, managed successfully by cryotherapy. In a follow-up up to 24 months, stents remained functional in 29 patients. Only three patients required repeat stent replacement. Stent retrieval was performed in seven cases (range, 0 to 10 months) without any complications. Based on the literature and their own experience, the authors provided the following recommendations for stent removal:

(I) The stent has been in place for 2–3 months under a good follow-up program;
(II) The airway remains unobstructed as confirmed by fiber bronchoscopy and CT imaging;
(III) Absence of dyspnea and ventilatory dysfunction;
(IV) The stent could be removed by pulling gently using flexible bronchoscopy.

## Future perspectives in airway stenting

### *Biodegradable stents*

Biodegradable stents represent a novel alternative in stent technology. They are based on polydioxanone, a material used in sutures. Lischke *et al.* reported the first clinical application of custom-made biodegradable polydioxanone stents for the relief of anastomotic stenosis in 6 post-LT patients (24). Stents were inserted using a 13–15F introducer via endotracheal tubes over a guide wire. Airway relief was achieved in all patients. Restenosis occurred in four patients requiring biodegradable stent reinsertion (3–7 stents) with a median duration of 5 months (range, 2–15 months) between resenting. The stents dissolved at an average of 5 months. One patient died during the study period due to pulmonary embolism. All other cases remained clinically well throughout the follow-up period.

The research group of Fuehner recently reported a larger case series with biodegradable stents in post-LT patients (25). They inserted a total of 11 stents. All patients reported immediate relief of their clinical symptoms and patency was achieved in 9 stenoses (82%) at 1 year. Complete degradation was observed at a median of 141 days. Four patients developed in-stent stenosis which was successfully treated with a metallic stent (n=1), argon therapy, and/or balloon dilatation (n=3). Nine patients were treated with topical mitomycin as a result of granulation tissue during follow-up.

### *Three-dimensional (3D)-printing in airway stenting*

Other areas of interest include the possibility of designing customized airway stents. Cheng and colleagues reported successful insertion of a personalized T-tube designed from a virtual 3D model of the upper airway in a patient with tracheal dehiscence (26). Improvement in symptoms was observed after placement of the T-tube and the patient was able to phonate within 4 days. Follow-up CT scan and bronchoscopy revealed no granulation tissue at 4 weeks. Similarly, Morrison and colleagues reported the clinical application of a custom-made 3D printed external airway splint in three infants with severe bronchomalacia (27). The implant was able to provide immediate relief and continues to allow growth of the primary airways.

## Commentary

Management of central airway obstruction caused by malignant lesions and benign pathologies is an important clinical problem. Surgical reconstruction remains the preferred approach, but not all patients may be appropriate candidates for surgery. Thus, endoscopic management is important for palliative reasons and for patients deemed inoperable. Airway stents can provide timely and effective relief in these patients and remain an important modality especially in conjunction with other endoscopic therapies such as laser, debridement, photodynamic therapy, mechanical dilatation and cryotherapy.

There are important considerations that must be taken into account regarding the choice of a stent. Both silicone stents and metallic stents have advantages and disadvantages that should be considered before choosing the best stent option for an individual patient. Silicone stents are potentially retrievable and inexpensive. They can be repositioned as many times as needed. However, they are more likely to migrate and interfere with mucociliary clearance. In addition, placement of a silicone stent generally requires rigid bronchoscopy and general anesthesia. Conversely, metallic are technically easier to insert via flexible bronchoscopy under fluoroscopic guidance. They have a more favorable internal-to-external diameter and are less prone to stent migration (however migration does occur). Metallic stents often become embedded in the mucosa and thus are not easily removable. This is an important issue in patients with non-malignant airway strictures who live longer and may require several interventions during the course of their disease.

For malignant airway stenosis, both silicone and metallic stents appear to provide similar efficacy and safety profile (28,29). This is most likely due to the shorter life expectancy of these patients during which long-term complications

 

of stenting are not observed. In addition, stent removal is generally not a concern in these patients especially when palliation is the ultimate goal. Therefore the choice of a stent is often based on physician's expertise, patient's anatomy and stent availability.

Stent selection in patients with benign strictures is controversial. Significant complications occur with the use of metal stents and their use is strongly discouraged in this group. Silicone stents have shown low complication rates and can ultimately be removed and hence serve as first choice in these patients. Similarly in patients with post-LT strictures, silicone stents should be the first line stent option. We recommend stent removal between 6–12 months after insertion. With regards to the use of SEMSs in these patients, current data is promising with good short-term outcomes. However, due a high long-term complication rate, the need of more follow-up bronchoscopic procedures to manage complications must be accepted (19,20). In addition, Data on removal of SEMS in post-LT patients is very limited. Fruchter *et al.* reported the largest series of six stent removals in 24 patients. The cause of stent removal was excessive granulation tissue formation and stent obstruction. Stents were removed at a median of 30 months (range, 16–48 months) from insertion. No major complications were encountered during stent removal. They concluded that SEMS can be used in selected post-LT patients since their removal could be safely and effectively accomplished if needed (30). A recent area of interest is the use of biodegradable stents in these patients with reasonable initial results (24,25). However, additional data is needed before they can be adopted in the armamentarium of thoracic surgeons and interventional pulmonologists.

In conclusion, airway stenting offers palliation in patients with cancer and a minimally invasive endoscopic option in patients with benign airway disease. Although there are limitations associated with the use of airway stents, they are generally safe and effective in selected patients. We strongly advocate that stent insertion should only be performed at specialized centers by experienced physicians.

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## Footnote

*Conflicts of Interest*: The authors have no conflicts of interest to declare.

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Interventional Therapy Technique

# Current status of spray cryotherapy for airway disease

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**Abstract:** The use of liquid nitrogen to treat skin and mucosal lesions is well understood in the dermatologic and gastrointestinal literature. Direct spray cryotherapy (SCT) in the airway has shown promising results in the treatment of esophageal premalignant and even invasive lesions. In the airway, several studies have shown it to be a safe, effective treatment for both benign and malignant disease. It is easily administered in the outpatient setting and can be repeated several times without undue side effects. In this article, we review the current literature on the use of SCT for the treatment of endobronchial lesions and also describe our own institutional experience of the use of SCT in the airway. The use of proper technique and airway venting is important in mitigating the complications of barotrauma from massive expansion of nitrogen upon conversion from the liquid to gaseous state. We also review some of the basic science principals behind the use of the cryotherapy to treat lesions in different tissues. We feel that SCT is a potential area for further research at both clinical and basic science level.

**Keywords:** Spray cryotherapy (SCT); liquid nitrogen; bronchial stenosis; airway disease

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## Introduction

Extreme cooling for a therapeutic effect or cryotherapy is employed for different indications including ablation of benign and malignant neoplasms, ablation of granulation tissue, treatment of infections, nerve ablation for chronic pain, bronchoscopic biopsies, and even cosmetic surgery (1-6). The cooling temperature can range significantly from 0 ℃ to almost –200 ℃. The most common modes of application of cryotherapy are by direct contact with a probe [cryoprobe therapy (CPT)] or by catheter-based delivery or spraying of a liquid cryogen [cryospray therapy (CST)]. The effect on tissues can therefore also differ depending on the temperature and modality applied.

Direct contact cryoprobes are cooled using the Joule-Thompson effect. A compressed gas such as nitrous oxide is suddenly released into a closed tip causing a drop of temperature of this probe and can achieve cooling temperatures of down to –90 ℃. Directly adjacent tissues will become cooler and eventually freeze over a period of time, usually minutes. This causes freezing of extracellular water and actual dehydration of cells.

CST, on the other hand, relies on rapidly releasing a liquid with a low boiling point (BP) through a catheter in order to induce a hypothermic effect on the tissues. The most commonly used cryogens for CST are nitrogen and oxygen. Liquid nitrogen spray creates a non-contact cryogenic effect on tissues. The large difference in temperature between the BP of this liquid (–196 ℃) and normal body temperature (37 ℃) leads to a rapid flash freezing of tissue. This leads to intracellular ice crystal formation and aggregation with eventual rupture of intracellular organelles and cell death. Immediately upon release from the catheter, the liquid boils and evaporates, rapidly increasing in volume. It is therefore

also essential to evacuate or "vent" this gas in order to avoid complications of pressure buildup or barotrauma.

## Brief history of cryotherapy

The origins of cryotherapy can first be found in the literature dating back to 1850 when Arnott *et al*. first published the benefits of local application of a cooling solution used to treat pain. This initial solution was cooled by a mixture of a salt and crushed ice (1). The first use of liquid nitrogen in medicine was described by Allington in 1950 for treatment of dermatologic lesions (2). The liquid was applied by direct swabbing on the skin. Cooper and Lee introduced a cryosurgical probe in 1961 which was cooled by liquid nitrogen traveling down a hollow probe (3,4). This was used to directly ablate areas in the cerebral cortex for treatment of neurologic diseases such as Parkinsonism. The probe was inserted through a small craniotomy and local anesthesia in order to allow examination of the patient during the procedure (5).

The first successful delivery system of a cryoprobe into the airway was by Grana *et al*. using a direct contact cryoprobe which was advanced through a rigid bronchoscope for ablation of "unwanted tissue". In 1969 they described their technique in an animal model (7). In 1981, Sanderson *et al.* also described their experience with cryoprobe ablation using bronchoscopy and a nitrogen cooled cryoprobe in a series of patients with lesions that were deemed non-surgical. The procedure had a 3% operative mortality rate (3,8).

The first description of spray cryotherapy (SCT) was initially described using liquid nitrogen spray in 1997 by Pasricha *et al*. in a canine esophageal model (9). Later in 1999 Johnston *et al*. also described the endoscopic SCT system in a porcine model to examine its effects on the esophagus. They used the term "cryoburn" for the treated lesion, which was defined as the visualization of the white frost on tissues after initiation of the spray (10). In 2005, Johnston *et al*. then described the use of SCT clinically in humans for ablation of high-grade dysplasia in Barrett's esophagus. At the time of their 2005 pilot study, the only other endoscopic ablative method that was FDA approved for the treatment of high-grade dysplasia in Barrett's esophagus was photodynamic therapy. The authors were able to show in a series of 11 patients that the use of SCT for the ablation of high-grade dysplasia in Barrett's esophagus was efficacious, safe and easy to perform (11). This study paved the way for FDA approval for the first-generation device (TruFreeze system, CSA Medical Inc., USA) in 2007. Two subsequent studies by Greenwald *et al*. and Shaheen *et al*. using this same device showed that liquid nitrogen CST was able to eradicate 97% of cases of high-grade dysplasia in Barrett's esophagus and 72% of T1 esophageal cancers (12,13).

Au *et al*. showed in an animal study that SCT was feasible for intraluminal application to endobronchial tissue. They were able to reliably reproduce the effects of the SCT in order to cause superficial necrosis extending from the mucosa to the cartilage in the airway (14). Due to concerns about barotrauma, it was slower to adapt this technology in the airway. Krimsky *et al*. published a case series in 2010 where they used SCT for the treatment of three patients with glottic and subglottic stenosis which resulted in patency of the stenosed areas with some degree of normalization of the mucosa (15). In 2011 and 2012, Fernando and Finley described two multicenter studies using SCT with the first generation device in the treatment of benign and malignant airway disease.

The current commercially available device for liquid nitrogen delivery (G2 TruFreeze system, CSA Medical Inc., USA) shown in *Figure 1* has been modified from the first generation device by providing two adjustable flow rates at 25 watts (normal flow) and 12.5 watts (low flow). The current device received FDA approval for the destruction of unwanted tissue in 2012. The low flow rate may allow for slower delivery and slower buildup of pressure in case of inadequate venting. The first report of SCT for central airway disease using the new adjustable flow device was by Browning *et al*. in 2013 who reported a case series of four patients with malignant airway disease. It showed the feasibility of this treatment and some of its unique advantages such as in the presence of stents and its use to control bleeding (16).

## Mechanism of action

The mechanism of tumor ablation by cryotherapy is based on the freezing of extra and intracellular tissue water causing formation of ice crystals. Slower cooling such as by direct contact tends to cause mainly extracellular ice which leads to cell death by dehydration and electrolyte imbalance. SCT of liquid nitrogen on the other hand leads to very rapid cooling with intracellular ice crystallization and subsequent cell death by direct destruction of intracellular organelles (3).

Benign strictures, however, are acellular and the

 


**Figure 1** The G2 TruFreeze system for spray cryotherapy (SCT) (CSA Medical Inc., USA). (A) The G2 SCT console (Courtesy, CSA Medical®); (B) the spray catheter (Courtesy, CSA Medical®).

mechanism of action is therefore different. Dermatology literature has shown that cryotherapy can cause remodeling of the connective tissue matrix which subsequently may allow for a more easily dilated stricture (17,18). Kim *et al.* showed that the use of cryotherapy in benign bronchial lesions allowed for easier dilation of a softer scar which may help prevent the common complication of bronchial laceration during balloon dilation which may cause further scarring and stricture formation (19).

Studies have shown that with SCT, there is relative sparing of the extracellular matrix in tissues (3). This matrix can then form a scaffold for subsequent tissue healing without a severe fibrotic response (18,20) and thus less long-term scarring (3,19). It has also been shown that although the matrix remains intact, SCT has an immediate softening effect on the fibrotic stricture allowing easier and wider dilation with less chance of laceration. This may be due to a remodeling of the connective tissue (20,21).

## Technique of SCT

The truFreeze System (CSA Medical, Inc., Baltimore, MD, USA) is used to spray liquid nitrogen through a 7F catheter that is passed into an endoscope. In the esophagus, a sump tube is advanced into the stomach and attached to suction to perform active venting of the gas. However, in the airway, this cannot be performed as there is not enough room to place both a bronchoscope and a suction catheter in the airway while still allowing for ventilation of the patient. In addition, any active suctioning would deplete the lungs of air and cause severe atelectasis. The concept of passive venting is therefore, employed in the airway. It relies on the fact that gas will egress through the path of least resistance. As long as there is a patent and unobstructed opening of sufficient diameter, gas under pressure will vent through it. Ensuring adequate venting of the excess nitrogen gas to prevent barotrauma is essential during the procedure.

## Protocol for passive airway venting

- Deflate the endotracheal tube cuff;
- Disconnect the tube from the ventilator circuit;
- Visualize adequate passive egress (misting) of gas through the endotracheal tube or rigid bronchoscope;
- Confirm the absence of chest wall rise during the sprays;
- Remove bronchoscope between treatments;
- Closely monitor the heart rate, blood pressure,

oxygenation and EKG tracings;
- ❖ When treating multiple strictures, the more proximal lesion is treated first in order to allow adequate proximal venting when treating the distal lesion;
- ❖ If at any time there is concern that passive venting is compromised, SCT is immediately aborted and the bronchoscope is immediately removed.

The use of this protocol is essential to help prevent the potentially catastrophic complications of tension pneumothorax, pneumomediastinum and nitrogen gas embolism.

The procedure is done under general anesthesia with a large bore endotracheal tube (>8 mm) or rigid bronchoscope. Glottic or subglottic lesions can be treated through a laryngeal mask airway (LMA) or suspension laryngoscopy although this is not recommended in more distal lesions where venting may be compromised.

The spray is applied in intervals of 5 seconds, timed from when visible frost formation has covered at least 50% of the target area. Complete thawing for at least 30 seconds is allowed after each application.

As mentioned previously, the current device can generate two flow rates; normal flow and low flow. Whereas the low flow rate may allow for slower delivery and buildup of pressure in case of inadequate venting, it also requires longer periods of apnea while administering the treatments. In the authors experience it is preferable to use the normal flow rate once adequate venting is confirmed in order to avoid potential hypoxia from the longer treatment times.

The number of cycles of spray and thawing is based on disease burden and response. Usually, four cycles are administered followed by dilation and/or debridement then a final two cycles.

There is usually no immediately visible effect after CST. For this reason, all patients undergo an additional procedure to SCT including balloon dilation, stent placement, and/or mechanical debridement depending on the nature of the lesion.

## Adjunctive modalities

While CST does show promise in treating both malignant and benign pathology of the central airways, it is not a sole treatment modality. It appears to be most successful when used in conjunction with mechanical dilation methods such as balloon dilation, mechanical debridement of tissue and stent placement. Browning *et al.* utilized adjunct modalities in 39% of their procedures which included mechanical debulking, electrocautery or argon beam coagulation, laser, cryoprobe and stent placement (22). Fernando *et al.* used the balloon dilation universally in their treatment of non-malignant strictures of the airway (20).

The safe use of the CST in the vicinity of stent placement, covered or uncovered, is an important benefit of this modality. Many of the patients that are being treated have had prior intervention and attempts at maintaining their airway. In our experience, we had a number of prior lung transplant patients who were treated for anastomotic complications with stents. This is becoming a more common technique and is particularly important at transplant centers. Dutau *et al.* showed in a single institution, retrospective study that the use of stents to treat lung transplant associated airway complications was both feasible and provided significant improvement in patient symptoms and outcomes (23). In our experience, we utilize adjunct treatments universally and have found no ill effects of such practice.

## Advantages of SCT

SCT is technically quite simple and can be performed as an outpatient procedure, similar to any other routine bronchoscopy. The therapy compared to thermal or mechanical modalities is painless and may actually have an analgesic effect on nerve fibers. In addition, due to its vasoconstrictive effect, it is beneficial in achieving hemostasis on bleeding granulation tissue or tumors.

Since there is no heat delivery, there is also no combustion risk. It is therefore possible to administer high concentration oxygen during treatments and it is therefore ideal when performing ablations on patients who require high oxygen delivery. For the same reason, it can be used in cases with indwelling tracheobronchial stents, as opposed to other thermal modalities which can cause damage or combustion of stent material

In CPT, the tissue is cooled in a radial fashion from the area of contact. In contrast, SCT allows a more even and linear distribution of the hypothermic effect over a larger area with a more uniform effect on the entire treated lesion

## Risks of SCT

Despite these advantages and the relative simplicity of the procedure, there is also a risk for severe barotrauma if the gas is not vented. When liquid nitrogen is released into the warm airway, there is almost instantaneous conversion

 

**Table 1** Complications of SCT

| Author | Number | Morbidity | Mortality |
|---|---|---|---|
| Fernando *et al*. (study of benign strictures) (20) | 35 patients; multicenter | 5.7%: tracheostomy, pneumothorax | None reported |
| Finley *et al*. (study of malignant strictures) (24) | 80 patients; multicenter | 19.3%: hypotension, bradycardia, massive hemoptysis, desaturation, pneumothorax | 2 intra-op deaths, 3 post-op deaths (comfort care) |
| Browning *et al*. (study of malignant strictures) (22) | 27 patients; single center | 5%: transient hypoxia | No intra-operative deaths |
| Janke *et al*. (study of benign and malignant strictures) (6) | 22 patients; single center | 1.5%: benign stricture; 0%: malignant stricture | No intra-operative deaths: 1 post-op death with benign stricture, 3 deaths within 30 days in patients with malignant stricture* |

*, all malignancy related deaths were due to patients succumbing to their illness. SCT, spray cryotherapy.

to gas with resultant volume expansion on the order of 1:645. The main risks are therefore those of unrecognized barotrauma and although rare, can be serious and fatal. They include pneumothorax, pneumomediastinum, and nitrogen gas embolism. Other risks are those associated with the necessary apnea while holding ventilation during the treatments including hypoxia, hypercarbia, respiratory acidosis and bradycardia. *Table 1* compares the complications of different studies in using this modality.

## Indications and contraindications of SCT

The indications for CST in the airway are mainly stenotic lesions, whether benign or malignant. There have also been reports of its benefit in treatment of cough associated with malignant disease and chronic bronchitis (22).

Contraindications for SCT, however, include all situations where venting may be inadequate or where there is a potential for escape of nitrogen gas outside the airway and into the body. Venting may be compromised when treating distal lesions due to the relatively large diameter of the bronchoscope in relation to the smaller airway. In general; it is not recommended to treat strictures distal to the bronchus intermedius or left main-stem bronchus

In addition, extremely tight strictures (>90%) may cause gas to become trapped distally. It is safer to dilate such strictures prior to SCT.

Transmural bronchial invasion by tumor is a situation which may subsequently lead to fistula formation after cryospray ablation of the tumor. If there is obvious destruction of the wall of the airway and invasion by an extrinsic tumor, it may be safer not to treat such lesions with this modality. Of course, a stricture in the presence of an established bronchial fistula or anastomotic dehiscence should not be treated with SCT which may cause pneumomediastinum or pneumothorax in these situations.

## Outcomes of SCT

In contrast to its use in esophageal disease, the published literature on the use of SCT in the treatment of airway diseases is still quite limited. In order to grade the degree of stenosis, we used the system described by Finley and Fernando which grouped stenoses into four quartiles; <25%, 26–50%, 51–75% and >75% and each quartile was given a score of 1–4.

Fernando *et al*. first published a multi-institutional study of the feasibility of CST and balloon dilation for benign strictures of the airway in 2011. They showed a statistically significant improvement of stricture diameter from 3.5 pre-treatment to 2.03 post-treatment (20). They also showed a complication rate of 5.7% with no reported mortalities in their series (18,20). Their complications included tracheostomy in a patient who developed glottis edema and pneumothorax which was thought to have developed due to treatment of a distal lesion prior to treating a more proximal one. Finley *et al*. followed with a similar study on a series of 80 patients treated with SCT for malignant airway disease in 2012. In this series, pretreatment airway occlusion was graded as more than 75% in 74% of patients, but only eight

 

**Table 2** Comparison of results of SCT treatment of malignant and benign stenosis (n=22)[†]

| Comparative parameter | Malignant (n=12) | Benign (n=10) | P value[‡] |
|---|---|---|---|
| Initial grade of stenosis[†] | 4 [1-4] | 3.5 [1-4] | 0.28 |
| Final grade of stenosis[†] | 2 [1-4] | 1 [1-2] | 0.28 |
| Number of treatments[†] | 2 [1-4] | 4 [1-9] | 0.04 |
| Change in grade of stenosis[†] | −2 [−3–0] | −2 [−3–0] | 0.79 |
| Improved | 10 (83%) | 9 (90%) | 1.00 |
| Day 90 mortality | 6 (50%) | 1 (10%) | 0.06 |

Table entry = n (%) for categorical variables and median [range] for continuous variables. [†], grade of stenosis defined as 1 (<25%), 2 (26–50%), 3 (51–75%) and 4 (>75%); [‡], by Chi-square/Fisher's exact test for categorical variables or Wilcoxon test for continuous variables; NS: P value ≥0.10 between the two groups. SCT, spray cryotherapy.

patients had more than 75% narrowing after treatment (24). They reported a 19.3% complication rate which included two intraoperative deaths. There was one emergent chest tube placed for a pneumothorax, one airway tear during mechanical debridement treated without intervention, one episode of massive hemoptysis treated with SCT, and one cardiac arrest (24). The two intraoperative deaths both had similar events which consisted of bradycardia, ST segment changes, hypoxemia and PEA arrest. There were also three postoperative deaths which included patients who were transitioned to comfort care.

Browning *et al*. described an institutional experience treating malignant airway disease with SCT in a recent publication in 2015. They quoted a 5% complication rate which included only episodes of transient hypoxia that resolved and did not lead to any measurable morbidity or mortality (22).

We have recently completed a single institution study to review our own experience with SCT (6). Our study included 22 patients, who underwent 66 bronchoscopies with 87 lesion-treatments. The patients were predominantly male (64%), with a median age of 61.5 [28–75] years. The cause of airway stenosis was benign in 10 (45.5%) and malignant in 12 (54.5%) patients. The majority of the benign lesions were anastomotic strictures for lung transplant while most of the malignant lesions were secondary to primary lung cancer.

At initial bronchoscopic evaluation, the median grade of stenosis was 4 for malignant disease and 3.5 for benign disease. The median final post-treatment grade of stenosis was 2 for malignant and 1 for benign disease. The median improvement in grade of stenosis after treatment was 2 for both malignant and benign causes (Wilcoxon test P=0.92). Final patency of Grade 1 was achieved in 42% of malignant stenosis and 80% of benign. Overall, 86.4% of patients had an improvement in grade of stenosis after treatment. *Table 2* shows our results and compares our outcomes between patients with benign and malignant disease. Patients with benign disease generally required four treatments over 6–8 weeks, while those with malignant disease required 3–4 treatments over 2–3 weeks, in order to achieve adequate patency. Benign disease appears to require more treatments in order to achieve the same results as malignant tumors. This is likely based on the cellular and structural differences between the benign and malignant diseases.

In our study, there were no intraoperative deaths. In the benign group, there was one death (10%) within 90 days in a patient with preexisting ventilator dependent respiratory failure 3 months after double lung transplant. Ninety day mortality in the malignant group was 50%, with all deaths related to progression of disease. The rate of procedure-related morbidity was 1.5% (1 complication in 66 procedures performed). The single complication occurred in a lung transplant patient, who was 7 months post-transplant and had an anastomotic stenosis in addition to a pre-existing, small anastomotic dehiscence. This patient required re-intubation for pulmonary edema prior to eventual recovery and discharge.

We believe that these results support the use of SCT in both benign and malignant airway strictures. They also highlight the need for appropriate protocols as defined above in order to prevent, mitigate, and treat the potential complications as well as provide appropriate informed consent for the prospective patients who are to undergo this new treatment. We also believe that an established diagnosis of airway perforation or dehiscence is a contraindication to SCT.

## Areas for research

SCT is a relatively new procedure in the field of endobronchial ablative therapies. Published studies have helped define feasibility and safety for the use of the SCT delivery system in the airway and have outlined potential protocols to be followed. However, all the studies on this topic have been retrospective case reports and case series.

 

There is, therefore, a need for both clinical and basic science research. Since the major risk of this procedure is barotrauma, animal research is necessary in determining the correlation of treatment to airway pressures and gas content. Also, little is known about the cellular and subcellular effects of this modality on tissues. More research is therefore needed on the molecular level in order to fully understand the effects of extreme hypothermia have on malignant tumors, benign strictures and normal tissues. Additionally, it would be interesting to determine whether there are any systemic effects, e.g., immune, from the ablation of tumors in these patients.

More information is also necessary on determining the best protocol in different situations, e.g., optimum duration of treatment cycle and number of cycles. In addition, it is important to determine the need and timing of follow-up endoscopic evaluation and re-treatment.

Ultimately, a randomized controlled study comparing SCT to other endoscopic treatment such as cryoprobe, laser or argon plasma coagulation would help determine the best approach to bronchial lesions in an arena with numerous available modalities but no clear guidelines as to which is the best approach.

## Summary

Patients with endobronchial or endotracheal strictures have been shown to benefit from CST. It can be safely performed as an outpatient procedure by flexible bronchoscopy to most targets in the central airway.

Surgeons with experience in the delivery system have developed their own protocols based on their individual experience. Our own experience has shown that the use of the SCT delivery system is effective and feasible for both benign and malignant strictures of the airway with an approximately 2 grade improvement in the degree of stenosis according to the previously described system.

As we continue to expand our knowledge, it is of utmost importance to contribute our experience with this technology to the literature. Despite its many potential advantages, it continues to be an area in need of scientific validation. Such validation may allow it to become more widely available, ultimately leading to improvement in patient quality of life, outcomes and life expectancy. What was once a limiting disease that greatly affected the way of life for those affected can now be treated on an outpatient basis many times over with minimal morbidity and mortality.

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## Footnote

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