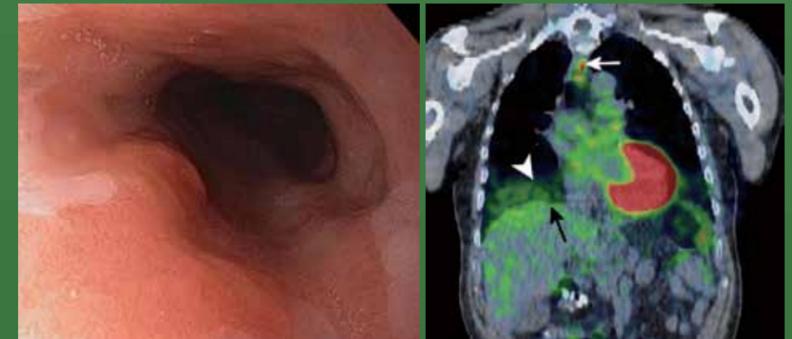


ESOPHAGEAL CANCER

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PREFACE

Esophageal cancer is one of those cancers you never really hear much about in the media. It is an infrequent cancer and unfortunately, it is a cancer that receives very little attention through the media or via national or international funding agencies. Many people are surprised to learn that you can even get cancer of the 'food pipe' and in general there is an enormous lack of education about the risk factors for this cancer in the community. Because esophageal cancer is increasing in the Western world there is an urgent need for substantial improvements in the early diagnosis, treatment and continued management of these patients. It is disturbing to note that over the last sixty years treatments have changed for esophageal cancer, but unfortunately the patient outcomes remain abysmal with 85% to 90% of patients dying within five years. It is imperative that cancer organizations and funding agencies provide funding and resources that will in turn lead to cutting-edge developments in understanding esophageal cancer and decrease the incidence and improve the survival for patients with esophageal cancer.

This first edition book on "*Esophageal Cancer*" which contains a diverse range of articles taken from AME journals and include authors with expertise in molecular biology, diagnosis and treatment, therapeutic endoscopy, surgery, radiotherapy and medical treatment, and prognosis. This book provides a practical collection of articles that will be useful for researchers and clinicians.

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MicroRNAs and esophageal cancer

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Abstract: Cancer of the esophagus is a highly aggressive disease associated with an overall poor prognosis. There is an insistent need for improving our understanding of the molecular basis of this disease. The recent emergence of observations on the role of microRNAs in cancer and their potential as biomarkers has prompted many investigations to examine their relevance to esophageal cancer. This article provides an introduction to microRNA biology and the techniques involved in studying them, and summates what is now known about their role and utility in regard to neoplastic esophageal diseases.

Keywords: Barrett's esophagus, epigenetic mechanism, esophageal cancer, gene expression, microRNA

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Introduction

Esophageal cancer is the eighth most incident and the sixth most fatal cancer worldwide (1). Histologically, in approximately 95% of cases, the disease occurs as esophageal squamous cell carcinoma (ESCC) or esophageal adenocarcinoma (EAC), with the latter being about 50% more prevalent in the United States but at least 20-times less common in Asian countries (1,2). The two forms are associated with different etiology, epidemiology, clinical course, and responsiveness to treatment. Among Caucasian men in the United States, while the annual incidence rate of ESCC has been slowly declining, that of EAC increased four- to six-fold to 3.2-4.0/100,000 during the last two decades of the 20th century, presumably due to increased prevalence of gastro-esophageal reflux disease resulting from obesity (3). The overall outcome of patients with esophageal cancer is dismal, with a five-year survival rate of 8%-30% following treatment with only surgery, and with no clearly significant benefit from adjuvant therapies (4). The disease also poses challenges in early diagnosis, staging, prognosis, and selection and delivery of the optimal therapy. Another challenge is that of screening and follow-up of patients with gastro-esophageal reflux disease with or without Barrett's esophagus (BE), a small

proportion of whom develop EAC, and for whom the only reliable method of follow-up requires endoscopy. There is clearly a need for better understanding of the molecular characteristics of the disease for the development of clinically useful biomarkers and treatment modalities. Biomarkers based on changes in genomic DNA, and in expression of specific mRNA or protein molecules, or of metabolites have been explored for many years now (5). MicroRNAs have emerged as a new class of biomolecules with important roles in cellular functions in both health and disease, and have considerable potential as biomarkers. These epigenetic players are ultrashort non-protein-coding RNA molecules which regulate the expression of a large number proteins by interacting with the coding mRNAs. This review introduces their biology and common approaches to their study, and summarizes the current state of knowledge on their involvement in esophageal cancer.

Biogenesis and mechanism of action of microRNAs

The synthesis, processing and action of microRNAs is simplistically depicted in *Figure 1*. Functionally active microRNAs, or mature microRNAs, are 18-22 nucleotidelong, single-stranded RNA molecules with

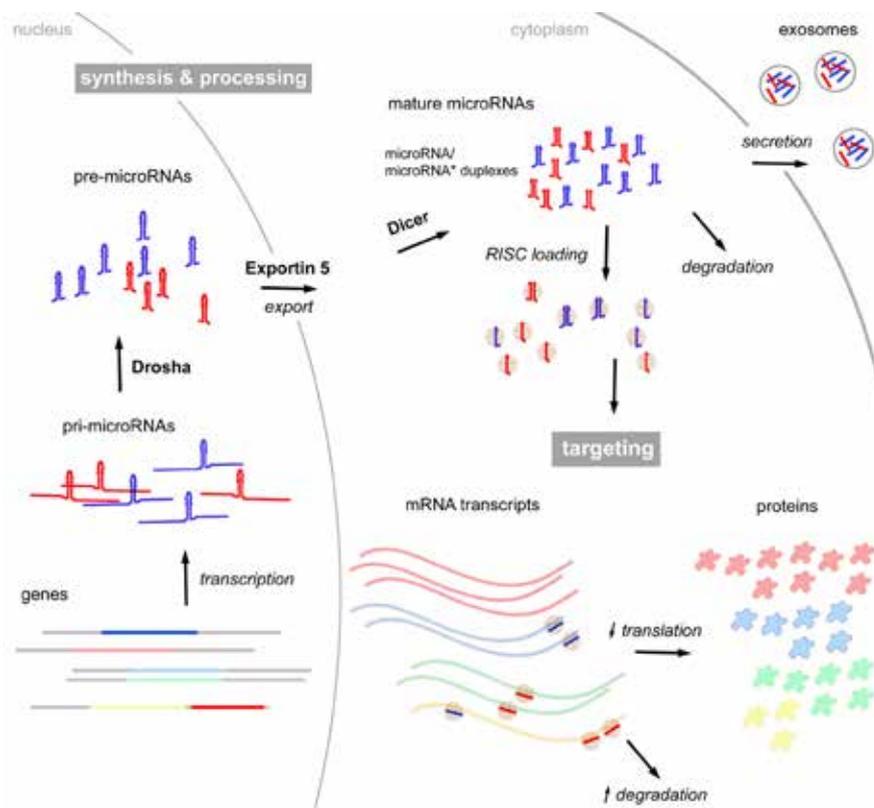


Figure 1 Synthesis and action of microRNAs. Mature microRNAs are generated as a pair of partially complementary RNA molecules, microRNA/microRNA* duplexes, from precursor molecules called pre-microRNAs by the endoribonuclease activity of Dicer in the cytoplasm. Pre-microRNAs are single-stranded RNA molecules with double-stranded secondary structures containing the mature microRNA sequences. They are produced in the nucleus by the action of another ribonuclease, Drosha, on primary microRNA transcripts, and are exported to the cytoplasm by the Exportin 5 transporter. The targeting of protein-encoding mRNA transcripts by microRNAs requires their loading on to multi-protein RISC complexes. After RISC loading, one of the two RNA strands of the microRNA/microRNA* duplex is degraded, and the remaining one guides RISC for mRNA targeting. A single microRNA can target different mRNAs, and a single mRNA can bear one or more targeting sites for multiple microRNAs.

5' phosphate and 3' hydroxyl groups. A nascent mature microRNA, however, arises in pair as a double-stranded RNA molecule known as a microRNA/microRNA-star (*) duplex from a single precursor RNA (pre-microRNA). Pre-microRNAs are ~60-80 nucleotide-long with a hairpin-like stemloop secondary structure. Endoribonuclease activity of a cytoplasmic RNase III enzyme, Dicer, causes the release of the microRNA/microRNA* duplex-bearing stems from the stem-loop structures of pre-microRNAs. Pre-microRNAs themselves are generated in the nucleus by the action of another RNase III endoribonuclease, Drosha, on much longer, primary RNA molecules (pri-microRNAs) that are transcribed by RNA polymerases II and III from microRNA encoding genes (6,7). Two nucleotide-long 3' overhangs on pre-microRNAs are recognized by the

Exportin 5 transporter protein which shuttles them into the cytoplasm (8). Many other proteins are involved in this pathway for microRNA genesis. They include the Ran guanosine triphosphatase, which participates in the nuclear export of pre-microRNAs, and the double-stranded RNA-binding proteins DGCR8 (DiGeorge critical region 8) and TRBP (transactivating response RNA binding protein), which work alongside Drosha and Dicer, respectively. Though most microRNAs arise in this framework, exceptions have been observed. For instance, maturation of microRNA *miR-451* does not require the Dicer-mediated cleavage (9), and the precursor of microRNA *miR-1234* is actually an intron (a 'mirtron') that is spliced out of the mRNA of a protein-coding gene (10). The sequences of mature microRNAs can get modified through 3' uridylation

or adenylation, or nucleotide substitution, with possible effects on their turnover as well as function (11).

Mature microRNAs actuate their function through the multi-protein RNA-induced silencing complex (RISC) that is also responsible for the phenomenon of RNA interference caused by small interfering RNAs (siRNAs). MicroRNAs are loaded as microRNA/microRNA* duplexes on RISC complexes where they are unwound into two single-stranded, mature microRNAs (Figure 1). One of the strands becomes the 'guide' strand and is retained, whereas the other, the 'passenger' strand, is degraded. The selection of the guide strand is not random and is biased by lowered thermodynamic stability at the 5' end and other sequence-specific features of the strands (12,13). The Argonaute family of proteins (Ago 1-4 in humans), key components of the RISC complex, participate in this strand-selection process. RISC complexes are guided to target mRNA molecules by the mature microRNA that is retained as the guide strand to degrade them or to inhibit their translation through mechanisms such as endonucleolytic cleavage and premature dissociation of ribosomes (14). It should be noted that mature microRNAs can be detected within the nucleus as well (15), and their specific roles in directly, and either positively or negatively affecting gene transcription have been documented (16,17).

The targeting of mRNAs by microRNAs requires only partial sequence complementarity between the microRNA and the apposite microRNA-target site in the mRNA, which can be in either the coding or the untranslated region of the mRNA. A mature microRNA can thus target hundreds of different mRNAs, and the same mRNA can be targeted by scores of different microRNAs. A majority of microRNA target sites show perfect sequence complementarity with the 'seed' sequence (nucleotide positions 2-7) of the mature microRNAs targeting them (18). Imperfect complementarity for the seed sequence can, however, be compensated by enhanced base-pairing at the 3' end of the microRNA (19). Target sites lacking both perfect seed pairing and 3' compensatory pairing but depending on Watson-Crick basepairing with the central 11-12 nucleotides of microRNAs have also been identified (20). Bioinformatic algorithms such as miRanda and PicTar that consider such factors to predict mRNA targets of individual microRNAs exist, though their accuracies are not high (21). Biochemical techniques relying on co-immunoprecipitation of target RNA with proteins associated with the RISC complex have been developed to identify microRNA-targeted mRNAs (22,23). Experimental verification of

individual microRNA targets typically involves correlating changes in mRNA and protein levels with changes in the level of the targeting microRNA. Reporter mRNAs, such as those encoding for fluorescent or luminescent proteins, engineered to bear microRNA-target sites are also often used in such studies. Biologically, the degree to which mRNA transcripts are targeted by microRNAs, and the effect of such targeting depends on factors like the amounts of the microRNAs and the mRNAs (24), and the number of microRNA-target sites on the mRNAs. As has been shown for the *PTEN* and *KRAS* genes (25), the targeting by microRNAs can also be diluted by mRNAs which bear target-sites for the same microRNAs and thus act as decoys. Sequence polymorphisms or mutations in microRNAs or microRNA target sites can enhance or diminish mRNA targeting (26). Epidemiological studies have shown correlations between such polymorphisms and the nature of various diseases in human populations (27,28).

Nomenclature, isolation, and detection of microRNAs

As of July 2010, 940 mature microRNAs in humans, and more than 14,000 mature microRNAs in 132 other organisms, including viruses, protozoa, flies, and plants, had been identified. Novel microRNAs are generally discovered through high-throughput, direct sequencing of RNA molecules isolated from biological specimens, through cloning them for sequencing, or through bioinformatic prediction following analyses of genomic sequences (29,30). The miRBase microRNA registry is responsible for assigning names to microRNAs (31). MicroRNA names have a numerical component, and a prefix indicating the taxonomic species of origin is often added to them. Thus, *hsamiR-16*, *mmu-miR-16* and *bla-miR-16*, respectively, refer to the mature human, murine and bovine miR-16 microRNA orthologs. Mature microRNAs with identical or very similar sequences, and therefore considered members of the same microRNA family, but which are products of different genes are distinguished by suffixes. Examples are *miR-16-1* and *miR-16-2*, and *miR-200a* and *miR-200b*. Because the same pre-microRNA can generate two different mature microRNAs, microRNA names are also often qualified by appending '3p' or '5p' to indicate the strand of the hairpin stem from which they arise. Sometimes an asterisk (*) is appended to indicate that that microRNA usually becomes the passenger strand and is thus less abundant than the sister mature microRNA. Thus,

miR-200b-3p may also be referred to *miR-200b**. Because of historical reasons, most family members of the orthologs of the *let-7* microRNA of the nematode worm *Caenorhabditis elegans*, such as *bsa-let-7b* and *mmu-let-7e*, do not contain 'miR' in their designations.

In mammals, microRNA loci are present on all but the Y chromosome (e.g., 32). A significant number of microRNA loci occur in clusters, with consistent expression observable among the members for a majority of the clusters (33). Though microRNAs are ubiquitously expressed in cells, the amounts of individual microRNAs can be cell-type-specific, and can vary temporally or as per physiological or disease state. Some microRNAs, like *let-7a*, *miR-16* and *miR-21*, appear to be extremely abundant in most mammalian cells, while some like *miR-302a* and *miR-122* have expressions that are highly restricted to specific tissues (e.g., 29, 34). In terms of weight, microRNAs are believed to constitute less than 0.05% of cellular RNA, but because of their small size, they form a sizable molar fraction. Extracellular microRNAs, most of which appear to be secreted within microvesicles from cells (exosomes, *Figure 1*), are found in bodily fluids such as urine, milk, serum and sputum. The microRNAs are protected from the strong ribonuclease activity present in such fluids because of their encapsulation within the vesicles (e.g., 35, 36) and possibly because of protection by specific proteins that bind them (37). Total RNA extraction methods, such as those using organic solvents or spin-columns with RNA-binding matrices, are used for the extraction of microRNAs. Techniques to enrich the microRNA-containing small RNA fraction of total RNA preparations are also available. Perhaps because of their small size, microRNAs appear to be preserved very well in formalin-fixed and paraffin-embedded (FFPE) tissues (e.g., 38) as well as in degraded total RNA preparations (39). Extracellular microRNAs have been found to be preserved well in desiccated bodily fluids even without refrigeration (40, 41).

RNA quantification techniques like Northern blotting, reverse transcription-PCR (RT-PCR), in situ nucleic acid hybridization, and microarrays are used for detecting microRNAs. Novel methods that rely on principles such as surface-enhanced Raman spectroscopy (42) and nanomechanical sensing (43) have also been developed. The sensitivity, specificity and cost associated with the different microRNA detection technologies vary, though many of them offer unique advantages (44). For instance, in situ hybridization provides additional information on the spatial distribution of microRNAs, and Northern blots can be used

to simultaneously quantify pre-microRNA levels.

Our knowledge of the functions and mRNA targets of specific microRNAs is currently limited, and studies of microRNA functions often start by first identifying microRNAs whose levels are significantly affected in a disease state. Unlike for microRNAs, there is a significant body of information associating mRNA expression profiles with esophageal cancer (45). At least some of the biological functions of many genes are known, and compared to microRNA profiling, mRNA profiling can more readily delineate the immediate pathways involved in biological processes. However, unlike the latter, microRNA expression studies do not require fresh or frozen specimens and can use cell-free bodily fluids. Further, probably because microRNAs are 20-30-times less in number than mRNAs, their profiles might be more robustly analyzable, yielding more accurate classifiers (46).

Alterations in microRNA levels, and its engineering

Changes in levels of specific microRNAs in tissues have been associated with diseases such as cancers (47) and diabetes (48), and with particular physiological conditions such as pregnancy (49) and muscle hypertrophy (50). Profiles of microRNAs in bodily fluids such as serum, saliva and urine too have been correlated with conditions such as myocardial injury, Sjögren's syndrome and urinary bladder cancer, respectively (51-53). In general, the exact causes underlying such alterations are not known for most cases, though the molecular bases are known for many. Deletions of the genes for *miR-15* and *miR-16* have been shown to cause down-regulation of levels of those microRNAs in chronic lymphocytic leukemia (54). In many cases of mixed lineage leukemia-rearranged acute leukemias, DNA copy number amplification is known to cause overexpression of microRNAs of the *miR-17-92* cluster (55). The reduced amount of microRNA *let-7* that is seen in many tumors is believed to be because of overexpression of Lin28, an RNA-binding protein that causes polyuridylation and degradation of the *let-7* pre-microRNA (56). Global reduction in microRNA levels in cancer cells have also been noted (46). This has been attributed to causes such as mutations in the Dicer-encoding *DICER1* gene in familial pleuropulmonary blastoma (57), targeting of transcripts for Dicer itself by microRNAs *miR-103* and *miR-107* in metastatic breast cancer (58), and mutations in the gene encoding for TRBP protein in many cases of carcinomas (59).

A global increase in microRNA levels too has been found. In high-risk myelomas, this is believed to be caused by an overexpression of the gene encoding for the Ago 2 protein (60).

In vitro studies using cell-culture models have unveiled many pathways responsible for physiological changes in levels of specific microRNAs. For example, during induction of the contractile phenotype in smooth muscle of the human vasculature, signal transduction through the transforming growth factor β (TGF β) and bone morphogenetic protein (BMP) family of growth factors causes a rapid increase in levels of *miR-21* (61). In human breast cancer cells, activation of the estrogen receptor α (ER α) results in reduced levels of many microRNAs, such as *miR-16* and *miR-145*, by suppressing their maturation (62). Binding of hypoxia-induced factor 1 α (HIF1 α) to a hypoxia-responsive element in the promoter of the *miR-210* gene is responsible for the overexpression of *miR-210* in hypoxic cells (63).

Levels of specific microRNAs can be engineered both *in vivo* and *in vitro* to study their biology as well as potential as therapeutic targets. Transgenic techniques for gene knockout or conditional expression have been used for causing aberrant or conditional up-regulation or down-regulation of microRNAs in animals such as mice and in cultured cells (e.g., 64, 65). Overexpression can also be achieved through traditional molecular biology methods such as transfection of plasmid DNA bearing microRNA genes or of precursor microRNA molecules, and transduction by engineered lentiviruses. Antisense nucleic acid molecules are commonly used to cause a knockdown of microRNA levels (66). Functional knockdown of a microRNA *in vivo* or *in vitro* without an actual reduction in levels of the microRNA has also been accomplished using lentiviruses that express decoy RNA with microRNA-target sites (67). Many studies on the therapeutic potential of such microRNA engineering have shown promising results. For instance, intratumoral as well as systemic delivery of synthetic *let-7* microRNA, whose level is downregulated in lung cancer, was found to cause tumor regression in a mouse model of lung cancer (68), and disease progression in a mouse model of hepatocellular carcinoma was found to be halted by systemic delivery of adeno-associated viruses engineered to express *miR-26a* (69).

MicroRNAs and esophageal carcinoma

Guo and colleagues were the first to report microRNA expression profiles in esophageal cancer, in 2008.

Microarrays were used to profile 435 microRNAs in RNA extracted from fresh-frozen specimens of 31 pairs of ESCC and corresponding adjacent normal esophageal tissues (70). One-hundred-ninety-one microRNAs were considered detectable, and their expression profiles could be used to discern cancerous from normal tissue with >90% accuracy. MicroRNAs *miR-25*, *miR-424* and *miR-151* showed upregulation, and *miR-100*, *miR-99a*, *miR-29c*, and *miR-140** showed reduction in cancerous tissue. Higher expression of *miR-103* and *miR-107*, known to affect metastatic potential of cancers by downregulating Dicer levels (58), was associated with poor prognosis. In a study that was published in the same year, Feber, *et al.*, used RNA from fresh-frozen tissue samples from ten cases each of EAC and ESCC, and five cases of BE, to assay the expression of 328 human microRNAs (71). Compared to normal esophagus, *miR-203* and *miR-205* were expressed two-to-ten-fold less in all three diseases, whereas *miR-21* levels were three-to-five-fold higher. Reduced levels of *miR-203* and *miR-205* were also observed in columnar epithelium compared to normal squamous epithelium in a study that examined 377 microRNAs in 16 individuals using microarrays (72). Levels of *miR-205* were also found to be lower in BE mucosa compared to normal adjacent epithelium as well as to neosquamous epithelium generated following ablation of Barrett's epithelium with Argon plasma coagulation in a study involving nine patients (73). MicroRNA *miR-21* was also identified as overexpressed in a study that used RT-PCR to examine 20 cases of ESCC and seven ESCC cell-lines, and in two other studies, and it has been shown to be an oncogene that promoted cell transformation by targeting transcripts for the Programmed cell death 4 (PDCD4) protein (72,74-76). Though some microRNAs, such as *miR-21*, *miR-100*, *miR-203* and *miR-205*, were identified as being affected in esophageal carcinoma in more than one of the aforementioned studies, many, like *miR-143*, *miR-145* and *miR-215*, whose levels are increased in EAC as well as BE (74), were not. Characteristics of patient populations and RNA quantification technologies, and differences in sample-sizes and data analyses are believed to be responsible for this, a theme that occurs recurrently in such biomarker discovery work.

In a large study with a sample-size of 170 (100 EAC and 70 ESCC cases), in which 329 microRNAs were quantified using microarrays, differences in microRNA expression between the two histological types were clearly identified. Specifically, *miR-194* and *miR-375* were found to be expressed 5-6-times more in EAC compared to

ESCC (74). In EAC patients with Barrett's, but not in those without, low expression of *miR-375* was associated with worse prognosis (hazard ratio [HR]=0.3, 95% confidence interval [CI]=0.2-0.7). Among ESCC patients, increased *miR-146b*, *miR-155* and *miR-188*, and decreased *miR-21* were associated with poor prognosis, with HR values ranging from 2 to 4. MicroRNA expression differences between BE and EAC were also been examined by RT-PCR in a cohort of 32 cases, and expression of *miR-143*, *miR-145* and *miR-215* was higher in the former (72). In a similar study involving 50 and 25 cases of BE and EAC, respectively, expression of *miR-143* and *miR-145*, but not of *miR-215*, was higher in BE than in EAC (77). In the same study, using microarray-based assays for some of the cases, alterations in levels of microRNAs between diseased and adjacent normal tissue were seen for 0, 32 and 39 of 470 quantified microRNAs in BE with low-grade dysplasia (n=5), BE with high-grade dysplasia (n=5), and EAC (n=6), with 14 and ten up- and down-regulated similarly in the last two diseases.

The ability to predict a cancer patient's response to chemotherapy or radiotherapy is a major goal of current translational research. Such predictability can be particularly applicable and relevant in esophageal cancer because of the ease with which pre-treatment cancer tissue can be sampled by endoscopy, and the current norm of administering chemoradiotherapy before surgery, in spite of limited pathologic response to it. MicroRNA profiling of the NCI-60 cell-lines has demonstrated associations between microRNA expression and sensitivity to chemotherapeutic drugs, suggesting that microRNAs might be usable as predictors, and possibly even modulators, of chemosensitivity (e.g., 78,79). Recently, Hong, *et al*, showed that *miR-296*, high levels of which were associated with poor prognosis in ESCC, targets transcripts of the *MDR1* drug-resistance gene and affects sensitivity of many esophageal cancer cell-lines to a variety of anti-cancer drugs (80). Targeting of *MDR1* by another microRNA, *miR-27a*, to alter esophageal cancer cell-line chemosensitivity has also been observed (81).

A few studies have examined the association of esophageal cancer with other molecular determinants of microRNA biology, besides microRNA levels per se. In a study involving 71 cases of esophageal cancer, post-operative survival was negatively associated with increased levels of *RNASEN* mRNA, while levels of transcripts for Dicer and DGCR8 had no correlation (82). The HR was 4.6 (95% CI=1.5-13.8). Further, *RNASEN* knockdown

reduced proliferation of esophageal cancer cell-lines *in vitro*. The *RNASEN* protein interacts with DGCR8 and affects pre-microRNA processing (83). Genetic variations in a number of microRNA-related genes were identified as associated with susceptibility to the disease in a study of 346 Caucasian patients in whom 41 variations in 26 genes, including those encoding Dicer, DGCR8 and Ago 1, were examined (84). Certain polymorphisms in the genes for *miR-196a-2* and *miR-631* were associated with an increased risk for the disease (odds ratio [OR] of 1.7 in both cases), whereas a particular polymorphism in the gene for *miR-423* was associated with a reduced risk (OR=0.6). Polymorphisms in the gene for *miR-196a-2* have also been linked with risks for cancers of the liver, lung, breast, stomach, and head and neck (27, 28, 85-87). In a cohort of 11 patients, *miR-196a* was found to mark the progression of BE to low-grade dysplasia, high-grade dysplasia, and EAC, with rising levels (88). Some of these findings on *miR-196a* might be explained through its targeting of the transcript for Annexin A1, an anti-proliferative and apoptosis-mediating protein (88). The microRNA has also been shown to target transcripts for the S100A9 protein, also referred to as *MRP14* (migration inhibitory factor-related protein 14), reduction of whose product has been associated with poorly differentiated ESCC (89). In a study of 444 sporadic ESCC cases among the Chinese Han, a single nucleotide polymorphism in the gene for *miR-146a* was found to be associated with an increased risk for the disease (OR=2.4, 95% CI=1.4-4.2), with risk being higher for smokers (OR=3.2, 95% CI=1.7-4.5) (90). A separate polymorphism was associated significantly with higher clinical tumor-node-metastasis (TNM) staging (OR=1.6, 95% CI=1.2-2.2).

In vitro studies using esophageal cancer cell-lines have helped identify roles for certain microRNAs in the biology of esophageal carcinoma. For example, *miR-373* has been shown to target transcripts for LATS2 (large tumor suppressor homolog 2) protein, whose gene-locus, a locus for which loss of heterozygosity has been reported for esophageal cancer, to stimulate proliferation of cells (91). MicroRNA *miR-10b* was found to cause increased invasiveness and motility of cells by targeting transcripts for KLF4 (Krueppel-like factor 4) protein (92). Elevated expression of the microRNAs in esophageal cancer tissues was shown in both studies. Similarly, *miR-145*, *miR-133a* and *miR-133b*, all of which are downregulated in ESCC, have been shown to target transcripts for FSCN1 (actin-binding protein, Fascin homolog 1) that is associated with

esophageal squamous cell carcinogenesis (93).

Conclusions

The study of the role of microRNAs in esophageal cancer appears to be emerging from infancy, and one can anticipate more extensive examinations in this area in the near future. Many of them will help elucidate biology of the disease, especially when considered in concert with mRNA and protein expression studies. Some may have an immediate translational value through the development of microRNA biomarkers to improve disease screening and management.

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Current status of novel agents in advanced gastroesophageal adenocarcinoma

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Abstract: Gastroesophageal (GE) adenocarcinomas are highly lethal malignancies and despite multiple chemotherapy options, 5-year survival rates remain dismal. Chemotherapy is the mainstay of treatment but patients are often limited by toxicity and poor performance status. Because of molecular heterogeneity, it is essential to classify tumors based on the underlying oncogenic pathways and develop targeted therapies that act on individual tumors. Trastuzumab, a human epidermal growth factor receptor type 2 (HER2) monoclonal antibody, was the first such agent shown to improve response rate, progression free survival (PFS), and overall survival (OS) when added to cisplatin based chemotherapy in patients with HER2 over-expressing GE junction (GEJ) and gastric adenocarcinomas. However, HER2 over expressing GE tumors are in the minority and the need for additional targeted agents is urgent. Though many agents are in development, incorporating targeted therapy in the treatment of GE cancers comes with a unique set of challenges. In this review, we outline oncogenic pathways relevant to GE adenocarcinomas, including HER2, epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), hepatocyte growth factor (HGF), and c-Met, and discuss recent trials with agents targeting these pathways.

Keywords: Gastric and esophageal adenocarcinoma; targeted therapy

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Introduction

Gastroesophageal (GE) adenocarcinomas are commonly diagnosed at an advanced stage and are extremely lethal, with median survival of less than 1 year for metastatic disease (1,2). Over the last 50 years, survival has improved only modestly despite considerable improvements in diagnosis, surgical techniques, and multidisciplinary approaches to care.

Chemotherapy remains the cornerstone of treatment for GE patients with locally advanced and metastatic disease. Many chemotherapy agents have activity including platinum, irinotecan, fluorouracil, taxanes and anthracyclines. Treatment with a combination of three agents has been shown to lead to modest improvements in survival compared to two agents, but at the expense of significant toxicity (3).

The pathogenesis of GE cancers involves multiple genetic and epigenetic alterations, chromosomal aberrations, gene mutations, and altered molecular pathways. During recent years, the molecular heterogeneity underlying carcinogenesis and metastasis has begun to be elucidated. Some of these molecular abnormalities and signaling pathways are amenable to pharmacological interventions (*Figure 1*). Targeted therapies been evaluated in the pre-clinical setting and are now rapidly moving to clinical trials (*Table 1*). The vascular endothelial growth factor (VEGF) receptor, epidermal growth factor receptor (EGFR), human epidermal growth factor receptor type 2 (HER2), insulin-like growth factor receptor (IGF-R), phosphatidylinositol 3-kinase (PI3k)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) pathway, c-Met, fibroblast growth factor receptor (FGFR), poly [adenosine diphosphate (ADP)]-ribose polymerase (PARP) inhibitors, and immunotherapies

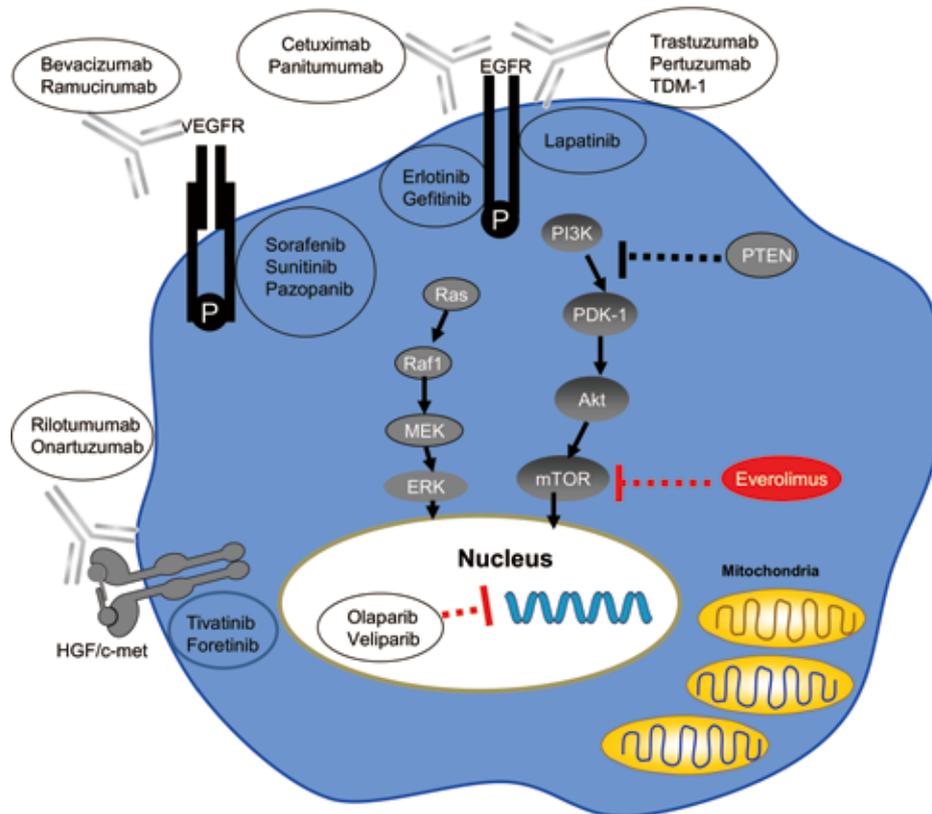


Figure 1 Targeted therapy in gastric cancer and sites of action. VEGFR, vascular endothelial growth factor receptor; EGFR, epidermal growth factor receptor; PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homolog; PDK-1, phosphoinositide-dependent kinase 1; Akt, protein kinase B; mTOR, mammalian target of rapamycin; HGF, hepatocyte growth factor; MEK, mitogen-activated protein/extracellular signal-regulated kinase kinase; ERK, extracellular-regulated kinase.

have been investigated as therapeutics. We will discuss molecular targets and the novel drugs currently approved and in development for patients with GE.

HER2 inhibition

The HER2 receptor is a member of the EGFR/HER family involved with signal transduction, leading to cell growth and differentiation. The HER2 gene is a proto-oncogene, located at the long arm of human chromosome 17 (4), which encodes for a 185 KD transmembrane glycoprotein receptor with intracellular tyrosine kinase activity (5).

HER2 over-expression and amplification in GE ranges from 7-34% of patients, depending on the population studied. The primary tumor site appears to have higher concordance of HER2 amplification by immunohistochemistry (IHC) and fluorescence *in situ* hybridization (FISH) than regional lymph node or distant

metastases (6-8). By consensus, HER2 is considered to be negative if IHC is 0 or 1+. HER2 is positive if IHC 3+. IHC of 2+ is considered equivocal and merits confirmatory testing with FISH (9).

Preclinical studies have shown that anti-HER2 therapies have significant activity for both *in vitro* and *in vivo* gastric cancer models (10,11). The most common approaches to targeting HER2 are through inhibition by monoclonal antibodies (trastuzumab and pertuzumab) or tyrosine kinase inhibitors (TKIs) (lapatinib). Both types of blockade have been examined in clinical trials of patients with GE cancers.

Trastuzumab, pertuzumab, and trastuzumab emtansine (TDM-1)

Trastuzumab is a humanized monoclonal antibody that has been approved by the US Food and Drug Administration (FDA) since 1998 for the treatment of breast cancer.

Table 1 Targeted agents and clinical trials for gastric and gastroesophageal cancers

Class	Agent	Clinical trials
VEGFR inhibitors		
Monoclonal antibody	Bevacizumab	Phase III
	Ramucirumab	Phase III
Receptor tyrosine kinase	Sunitinib	Phase II
	Sorafenib	Phase I/II
	Pazopanib	Phase II
	Vandetanib	Phase I/II
	Telatinib	Phase II
EGFR inhibitors		
Monoclonal antibody	Cetuximab	Phase III
	Panitumumab	Phase III
Receptor tyrosine kinase	Gefitinib	Phase III
	Erlotinib	Phase II
HER2 inhibitors		
Monoclonal antibody	Trastuzumab	Phase III
	Pertuzumab	Phase III
	TDM-1	Phase II/III
Receptor tyrosine kinase	Lapatinib	Phase III
c-Met inhibitors		
Receptor tyrosine kinase	Foretinib	Phase II
Monoclonal antibody	Rilotumumab	Phase II/III
	Onartuzumab	Phase II/III
PARP inhibitors		
	Olaparib	Phase II/III
	Veliparib	Phase I

VEGFR, vascular endothelial growth factor receptor; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor type 2; PARP, poly-adenosine diphosphate ribose polymerase.

Trastuzumab targets the extracellular binding domain of the HER2 receptor and has been combined with cytotoxic chemotherapy in patients with gastric and GE junction (GEJ) tumors in several trials. The trastuzumab for gastric cancer (ToGA) study was an international, open-label phase III trial that randomized patients with treatment naive metastatic or locally advanced unresectable gastric or GEJ adenocarcinoma with over-expressed HER2 to chemotherapy with trastuzumab versus chemotherapy alone. HER2 overexpression was defined as staining 3+ by IHC or by FISH positivity (12).

Patients received cisplatin plus fluoropyrimidine every 3 weeks for six cycles, with or without intravenous trastuzumab at 6 mg/kg after a one time loading dose of 8 mg/kg.

A 2.7-month improvement in median overall survival (OS) for patients who received trastuzumab was demonstrated (median OS 13.8 months compared with 11.1 months). Response rate, time to progression, and duration of response were significantly higher in the trastuzumab plus chemotherapy group as well. Of note, the median survival in the chemotherapy only arm was higher than expected in this study, potentially related to the high proportion of Asian patients in the study (55%). The combination was generally well tolerated with only a slightly increased risk of asymptomatic left ventricular dysfunction and transfusion reaction. This study led to the first FDA approval for targeted therapy for gastric and GEJ adenocarcinoma in 2010 (13).

Based on these encouraging results, several other studies with trastuzumab are being conducted. The HELOISE trial (a study of herceptin in combination with cisplatin/capecitabine chemotherapy in patients with HER2-positive metastatic gastric or GEJ cancer) is currently recruiting patients to evaluate the optimal dose of trastuzumab in advanced gastric and GEJ tumors (14). In the non-metastatic setting, NCT01130337 is a phase II study which treats patients with trastuzumab, capecitabine, and oxaliplatin for three cycles prior to surgery. If an R0 or R1 resection is achieved, patients receive an additional three cycles of treatment. Trastuzumab will be continued for a total of 1-year (15). Similarly, the TOXAG study (a study of the combination of oxaliplatin, capecitabine, and herceptin and chemoradiotherapy in the adjuvant setting in operated patients with HER2+ gastric or GEJ cancer) is ongoing (16). The HER-FLOT study (Herceptin in combination with FLOT as perioperative treatment for patients with HER2-positive locally advanced esophagogastric adenocarcinoma) gives trastuzumab with FLOT (5FU, leucovorin, docetaxol, and oxaliplatin) for four cycles prior to surgical resection. Patients then receive an additional four cycles of chemotherapy with trastuzumab and nine additional cycles of trastuzumab alone (17). For locally advanced esophageal or GEJ adenocarcinoma, RTOG 1010 is a phase III trial which randomizes patients to weekly paclitaxel, carboplatin, and radiation with or without trastuzumab prior to surgery (18). The results of these studies could change the treatment paradigm for HER2 overexpressing GE cancers.

As resistance to HER2 therapy has begun to arise, there has been interest in the second generation HER2 targeting agent pertuzumab, which binds to a distinct site on the

HER2 (and potentially HER3) receptor and leads to the disruption of dimerization and blockade of downstream signaling. Based on pre-clinical work in GEJ, as well as the efficacy of the combination of trastuzumab and pertuzumab in breast cancer (19), the JACOB phase III study (a study of perjeta in combination with herceptin and chemotherapy in patients with HER2-positive metastatic GEJ or gastric cancer) randomizes patients with metastatic or locally advanced unresectable disease to first line cisplatin, fluoropyrimidine, and trastuzumab with or without pertuzumab (20).

TDM-1 is an antibody-drug conjugate which utilizes HER2 overexpression to deliver a cytotoxic agent directly to cancer cells is being evaluated in GEJ patients expressing HER2; a second line phase II/III trial of TDM-1 in advanced gastric cancer is currently recruiting; the study has three arms; TDM-1 at 3.6 mg/kg every 3 weeks, TDM-1 at 2.4 mg/kg every week, or physician's choice of single agent paclitaxel or docetaxel (14).

Lapatinib

Lapatinib is an oral small molecule dual TKI of EGFR and HER2. It has been approved for the treatment of HER2-positive advanced breast cancer previously treated with trastuzumab and in conjunction with hormonal therapy for triple positive metastatic breast cancer (21-23).

Lapatinib has been evaluated in combination with standard chemotherapy in patients with gastric and GEJ adenocarcinomas. In the phase III LOGIC study (lapatinib optimization study in HER2-positive gastric cancer), patients with HER2 over-expressed advanced gastric and GEJ adenocarcinomas were randomized to chemotherapy (capecitabine and oxaliplatin) plus lapatinib versus placebo (24). This study did not meet its primary endpoint of improvement in OS, though certain subgroups (the Asian population and patients under age 60 years) were shown to have a benefit.

The second line phase III TyTAN trial (a phase III Asian study of tykerb in combination with paclitaxel as second-line therapy in gastric cancer) compared weekly paclitaxel with or without lapatinib in second line patients with HER2-positive advanced disease. Again, there was no OS or progression free survival (PFS) benefit for the lapatinib group, though there was a statistically significant increased response rate (25). At present, lapatinib is not ready for widespread implementation in GEJ but ongoing studies might better define its role in combination with other targeted agents.

Of the monoclonal antibodies, only trastuzumab is

approved for locally advanced unresectable and metastatic GEJ and gastric cancers. However, with the results of adjuvant trastuzumab trials as well as the pertuzumab and TDM-1 studies, the role for monoclonal antibodies in GE cancers will likely expand significantly.

EGFR inhibition

The EGFR is a trans-membrane glycoprotein receptor for the EGF family of extracellular protein ligands (26) and is overexpressed in several gastrointestinal (GI) malignancies. Ligand binding to the extracellular domain leads to EGFR activation and phosphorylation of the intracellular tyrosine kinase, which then directs activation of Ras/Raf/mitogen activated protein kinase (MAPK) or the Akt/mTOR pathway (27). EGFR overexpression occurs in 30-50% of GE. It is associated with older age, more aggressive histology, and advanced stage (28-30).

The most common approaches to inhibit the EGFR are by inhibition of the EGFR via monoclonal antibodies (i.e., cetuximab and panitumumab) or TKIs (i.e., gefitinib, erlotinib). Both methods have been studied in patients with GE.

Cetuximab

Cetuximab is an immunoglobulin G 1 (IgG1) type chimeric monoclonal antibody that binds to the extracellular domain of the human EGFR and competitively inhibits the binding of EGF and other ligands, as well as ligand-induced tyrosine kinase auto-phosphorylation. This antibody-receptor interaction prevents receptor dimerization and thereby blocks ligand-induced EGFR tyrosine kinase activation. Cetuximab also induces EGFR internalization, down-regulation, and degradation (31). It is currently approved for the treatment of advanced KRAS wild type colorectal cancer as well as squamous cell head and neck cancers (32,33).

Based on promising phase II data, the phase III trial EXPAND (erbitux in combination with xeloda and cisplatin in advanced GE) randomized 904 patients to cisplatin with capecitabine with or without cetuximab. However, no PFS or OS benefit for the cetuximab group was found (34). RTOG 0436 was a phase III trial which randomized patients with locally advanced esophageal cancer to weekly concurrent cisplatin (50 mg/m²), paclitaxel (25 mg/m²) for 6 weeks and daily radiation 50.4 Gy/1.8 Gy fractions ± weekly cetuximab (400 mg/m² day 1 then weekly 250 mg/m²) for 6 weeks (35). No OS benefit to cetuximab was found.

Unlike in colorectal cancer, KRAS mutations have

not been shown to be a negative predictive biomarker for response to cetuximab in GE (36). Though other biomarkers including EGFR expression, copy number, and phosphorylation have been evaluated, the sample sizes and retrospective nature of these analyses have precluded meaningful conclusions (37-40).

Panitumumab

Panitumumab is the first fully human IgG2 monoclonal antibody targeting EGFR. In gastric cancer, the REAL-3 study [a randomised open-labelled multicentre trial of the efficacy of epirubicin, oxaliplatin, and capecitabine (EOX) with or without panitumumab in previously untreated advanced oesophago-gastric cancer] did not show any benefit at preplanned interim analysis and was stopped early (41). However, these negative results may have been partly due to decreased doses of chemotherapy in the combination arm (42). In the single arm phase II ACOSOG Z4051 trial, patients with potentially resectable disease were given neoadjuvant docetaxel, cisplatin, and panitumumab as well as radiation (43). Some disease activity was found but at the expense of significant toxicity.

Gefitinib

Gefitinib is an oral EGFR TKI with promising activity against several types of malignancy in early phase trials. Based on phase II data (44), a phase III trial (NCT01243398) randomized patients with advanced GE to gefitinib versus placebo after progression on chemotherapy. The study is complete and the pending results will help better delineate the activity of gefitinib in GE (45).

Erlotinib

Erlotinib is another oral EGFR TKI, which has been approved in the US for the treatment of lung and pancreatic cancer. In a phase II analysis, erlotinib was found to be active in patients with GEJ cancer with a response rate of 9%, but with no responses in gastric cancer (46).

Vascular endothelial growth factor receptor (VEGFR) inhibition

Angiogenesis is an important aspect of tumorigenesis and is critical for tumor growth and survival. The VEGF plays a pivotal role in the control of angiogenesis, tumor growth,

and metastasis in many human cancers (47) including GE, which makes it an attractive target for treatment. VEGF-A is an essential mediator of physiologic and pathologic angiogenesis (48), and its activities are mediated by two tyrosine kinase receptors, VEGFR-1 and VEGFR-2. Serum VEGF concentration has been related to metastasis and worse outcome in GE (49,50). Multiple agents have been developed to target the VEGF pathway, including monoclonal antibodies and TKIs.

Bevacizumab

Bevacizumab is a recombinant humanized IgG1 monoclonal antibody against VEGF, which has been shown to have efficacy in colorectal, lung, ovarian, and renal cell cancers (13,51-54). Side effects including thromboembolic events, gastrointestinal perforation, and hypertension have been demonstrated.

Promising phase II trial results in GE cancers led to AVAGAST (avastin in gastric cancer), a phase III multinational, randomized, placebo-controlled trial to evaluate the efficacy of adding bevacizumab to cisplatin based chemotherapy in the first-line treatment of advanced gastric cancer (55). Seven hundred and seventy-four patients from 17 countries were enrolled. Approximately 50% of patients were from Asia. Median OS was 12.1 months in the bevacizumab plus chemotherapy arm compared to 10.1 months with placebo plus chemotherapy arm [hazard ratio (HR) 0.87; 95% confidence interval (CI), 0.73 to 1.03; P=0.1002]. Though the trial did not meet its primary objective of OS, both median PFS and overall response rate (ORR) were significantly improved in the bevacizumab group. No bevacizumab-related safety signals were identified. The genetic heterogeneity of gastric cancer might explain the discordant results between the phase II and III trials. In addition, the patients with GEJ tumors on the AVAGAST study treated with bevacizumab arm had an exceptionally high response rate of 85% and improved OS. Asian patients showed better OS and PFS regardless of the treatment received when compared to European and Americans. Selection bias, sample size, and study design might have limited the conclusions of single-arm phase II studies.

In order to better select patients who might benefit from anti-VEGF therapy, a panel of tumor angiogenic factors was evaluated in the AVAGAST study, including EGFR, VEGF-A, VEGFR-1, VEGFR-2 and neuropilin (56). Low tumor neuropilin expression was associated with shorter

Table 2 Phase II/III trials targeting VEGFR in gastroesophageal cancers

Study	Phase	Setting	Treatment	Patients	PFS	OS
Shah <i>et al.</i> (61)	II	First line	Irinotecan, Cisplatin, and Bevacizumab	47	ORR: 6.5 mo	12.3 mo
Ohtsu <i>et al.</i> /AVAGAST (55)	III	First line	Cisplatin/5FU ± Bevacizumab	774	38.0 vs. 29.5 mo, P=0.0121	12.1 vs. 10.1 mo, P=1.002
Fuchs <i>et al.</i> /REGARD (57)	III	Second line	Ramucirumab vs. BSC	355	2.1 vs. 1.3 mo, P<0.0001	5.2 vs. 3.8 mo, P=0.047
Wilke <i>et al.</i> /RAINBOW (59)	III	Second line	Paclitaxel ± Ramucirumab	665	4.4 vs. 2.9 mo, P<0.0001	9.6 vs. 7.4 mo, P=0.017
Yoon <i>et al.</i> (60)	II	First line	FOLFOX ± Ramucirumab	168	6.4 vs. 6.7 mo, P=0.89	11.7 vs. 11.5 mo, P not available, HR 1.08, 95% CI, 0.73-1.58

VEGFR, vascular endothelial growth factor receptor; PFS, progression free survival; OS, overall survival; ORR, overall response rate; mo, months; 5FU, 5-fluorouracil; BSC, best supportive care; FOLFOX, 5-fluorouracil, leucovorin, oxaliplatin; HR, hazard ratio; CI, confidence interval.

OS in the placebo group. Adding bevacizumab seemed to correct this effect as patients with low tumor neuropilin had an OS treatment HR numerically better than those with high neuropilin in the bevacizumab group. Neuropilin thus appeared to be a promising prognostic biomarker candidate, with potential predictive properties for bevacizumab as well. In addition, lower baseline plasma VEGF-A correlated with longer OS. Further evaluation of these biomarkers is ongoing.

Bevacizumab is being evaluated in the neoadjuvant setting in the United Kingdom. The MAGIC-B study (medical research council adjuvant gastric infusional chemotherapy) is assessing the role of bevacizumab for peri-operative chemotherapy in operable adenocarcinoma of the stomach and GEJ.

Ramucirumab

Ramucirumab is a fully human IgG1 monoclonal antibody that specifically and potently inhibits VEGFR-2. Ramucirumab has demonstrated efficacy and tolerability in several studies. The phase III REGARD study (ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma) randomized second line gastric or GEJ adenocarcinoma patients to single agent ramucirumab or best supportive care (BSC). They found a median OS of 5.2 months in the treatment arm compared to 3.8 months, with a P value of 0.042 (57). Based on this study, the FDA approved ramucirumab in 2014 for use as a single agent in gastric and GEJ cancer after

progression on a platinum or fluoropyrimidine containing regimen (58). This is the first approval of a biologic agent in an unselected GEJ population. Biomarker studies to better delineate the population most likely to benefit are ongoing.

The phase III RAINBOW study (a global, phase III, randomized, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in the treatment of metastatic GEJ and gastric adenocarcinoma following disease progression on first-line platinum- and fluoropyrimidine-containing combination therapy rainbow) randomized 665 second line advanced gastric or GEJ adenocarcinoma patients to paclitaxel with or without ramucirumab. Median OS was 9.6 months in the combination arm versus 7.4 months for paclitaxel alone. Patients in the combination arm had more neutropenia and hypertension (59). These findings will likely lead to approval of ramucirumab in combination with paclitaxel by the FDA later this year. However, a front line phase II study of ramucirumab with or without FOLFOX did not show an improvement in the primary endpoint of PFS (60). The results of the major trials involving bevacizumab and ramucirumab are described in *Table 2*.

Another approach to targeting the VEGF pathway is through so-called dirty kinase inhibitors, which inhibit the VEGF receptor as well as FLT-3, c-kit, and RET. Several TKIs are currently being evaluated and are described below.

Sunitinib

Sunitinib is an oral multi-targeted TKI of VEGFR, platelet-

derived growth factor receptors (PDGFRs), c-kit, RET, and FLT3 that has been approved for the treatment of advanced renal cell carcinoma and imatinib resistant or intolerant gastrointestinal stromal tumors.

Several trials have evaluated single agent sunitinib in the treatment of GEJ. In a phase II second line trial of single agent sunitinib in 78 patients with advanced gastric and GEJ cancer, two patients had partial response and 25 patients had stable disease for ≥ 6 weeks. Median PFS was 2.3 months and median OS was 6.8 months (95% CI, 4.4-9.6 months) (62). Sunitinib has also been evaluated in combination with chemotherapy. A second line phase II trial randomized 107 patients to docetaxel with or without sunitinib. The time to progression was not significantly different (3.9 months in the sunitinib arm versus 2.6 months), but there was an increased response rate of 41.4% compared to 14.3% (63).

Similar to other TKIs, sunitinib has multiple drug interactions and can lead to QTc prolongation and changes in the metabolism of CYP3A4 substrates. Common toxicities include hypertension, hand-foot syndrome, and liver dysfunction.

Sorafenib

Sorafenib is a potent inhibitor of the Raf tyrosine kinase and several other receptor tyrosine kinases, including VEGFR-2, VEGFR-3, and PDGFR- β . Sorafenib has been approved for the treatment of both renal cell carcinoma and hepatocellular carcinoma based on the results of phase III trials (64,65). In tumor xenograft models, sorafenib effectively inhibited tumor growth and angiogenesis in gastric tumors (66).

Sorafenib has been evaluated for the treatment of advanced GEJ in several studies, both in combination with chemotherapy and as a single agent. Though one phase II study of 44 second line gastric cancer patients which combined sorafenib with docetaxel and cisplatin showed an impressive median PFS of 5.8 months and median OS of 13.6 months (67), other studies have not found these results and have been terminated early because of low response rates (68,69).

Pazopanib

Pazopanib is an oral agent which inhibits angiogenesis through multiple pathways, including the VEGFR, the PDGFR, as well as c-kit. It has been approved by the FDA for use in the treatment of metastatic renal cell carcinoma as well as metastatic soft tissue sarcoma based on the results

of phase III trials (70,71). Pazopanib has also been shown to have activity in metastatic thyroid cancer (72).

Pazopanib is currently being evaluated with chemotherapy in two GEJ trials. The phase II PaFLO trial (FLO \pm pazopanib as first-line treatment in advanced gastric cancer) randomized first line advanced gastric cancer patients to 5-fluorouracil, leucovorin, and oxaliplatin with or without pazopanib and is currently accruing patients (73). Another first line phase II trial adds pazopanib to capecitabine and oxaliplatin in advanced gastric cancer patients and is also recruiting (74). The results of these studies will help determine if pazopanib has a role in the treatment of advanced GE cancer.

IGF-1 inhibition

The IGF-1 receptor belongs to the insulin receptor family. IGF-1R is expressed on the cell surface and phosphorylation of intracellular substrates leads to activation of the MAPK and PI3K/Akt pathways which promotes tumor growth, progression and invasion in several cancers, including GE (75).

In GE, IGF-1R expression in resected tumors correlates with poorer clinical outcomes (76). IGF-1R signaling has been associated with resistance to cytotoxic therapy and inhibition of IGF-1R enhances tumor cell apoptosis in numerous models (77). The IGF-1R pathway can be targeted through monoclonal antibodies, IGF-1R antisense/small interfering ribonucleic acid (siRNA), and receptor tyrosine kinases.

In a study of 86 patients with resected gastric tumors, patients with low expression of both IGF-1R and EGFR had significantly longer OS compared to those who lack the low co-expression (76). A phase I trial of docetaxel combined with CP-751,871, an IGF-1R antibody, has demonstrated promising results and warrants further investigation (78).

Fibroblast growth factor (FGF) TKIs

FGF and its signaling receptors have multiple biological properties including cell proliferation, differentiation, motility, and transformation (79,80). FGFR2 is amplified in poorly differentiated gastric cancer (scirrhous cancer) with malignant phenotypes (81), which makes it a potential molecular target for treatment.

In preclinical models, AZD2171, a highly potent oral VEGF, FGFR1, PDGFRB, and VEGFR-2 TKIs, led to tumor inhibition in gastric cancer xenografts in a dose-dependent fashion. The most potent antitumor activity was

seen in xenografts over-expressing FGFR2. These results suggest that AZD2171 might be clinically beneficial in patients with FGFR2 expressing gastric tumors (82).

Ki23057, a broad-range TKI of FGFR2, also inhibits FGFR1, FGFR2, and VEGF2 tyrosine kinases. It inhibits the proliferation of gastric scirrhus cancer cells with FGFR2 gene amplification only. Oral administration of Ki23057 inhibits the growth and peritoneal dissemination of gastric cancer cells through FGFR2-RAS/extracellular-regulated kinase (ERK) inhibition, rather than through FGFR2-PI3k-AKT signaling inhibition (83). To our knowledge, no clinical trials are currently available for this compound in GE.

c-Met TKIs

C-Met is a receptor tyrosine kinase that is expressed in epithelial and endothelial cells. Overexpression of c-Met and activating c-Met mutations have been widely documented in many tumor types including GE and have been correlated with poorer outcomes (84,85). Hepatocyte growth factor (HGF), its ligand, is expressed by cells of the mesenchymal lineage.

A phase II study examined the safety and efficacy of two dosing schedules of foretonib (GSK1363089), an oral small-molecule inhibitor of c-Met and VEGFR-2, as a single agent in patients with metastatic gastric adenocarcinoma. Foretonib was well tolerated but demonstrated minimal antitumor activity in a c-Met unselected population (86).

A phase II study of rilotumumab (a human monoclonal antibody directed against HGF) showed more efficacy in a subset of patients with increased MET expression by IHC (87). Based on this data, the phase III RILOMET-1 trial [an international phase III multicenter, randomized, double-blind, placebo-controlled trial of rilotumumab plus epirubicin, cisplatin, and capecitabine (ECX) as first-line therapy in patients with advanced MET-positive gastric or GEJ adenocarcinoma] is currently recruiting (88). However, a double blind randomized first line phase II study of this combination (ECX with or without rilotumumab) was recently found to be negative for improved PFS (89).

Onartuzumab (a humanized monovalent antibody directed against MET) is also being evaluated in a first line, randomized phase III trial in MET-positive, HER2-negative GE patients in combination with FOLFOX. This study is ongoing and should be complete in 2015 (90).

PI3 kinase pathway inhibition

The PI3K enzymes are involved in the phosphorylation of membrane inositol lipids (91). The activation of PI3K generates the second messenger phosphatidylinositol 3,4,5-trisphosphate (PIP3) from phosphatidylinositol 4,5-bisphosphate (PIP2). This recruits proteins to the cell membrane, including the Akt/PKB kinases, resulting in their phosphorylation by phosphoinositide-dependent kinase 1 (PDK1) and by PDK2 (92,93).

Dysregulation of the PIP3/Akt/mTOR pathway can occur secondary to oncogenic mutations of PIK3CA (94), loss of phosphatase and tensin homolog (PTEN) function (95,96), mutation of Akt/PKB isoforms (97), or upstream activation through other pathways like IGF-1R. Abnormal expression of the PTEN protein in gastric cancer is found in 11% of tumors and is related to the tumor differentiation, advanced staging, and chemoresistance (98). Upregulation of the PI3k/Akt/mTOR downstream pathway correlates with a worse prognosis and may contribute to the resistance to chemotherapy (99).

Everolimus is an oral mTOR inhibitor that has shown anticancer activity both in phase I and II studies (100,101). The phase III GRANITE-1 trial (safety and efficacy of everolimus monotherapy plus BSC in patients with advanced gastric cancer) was performed for further evaluation. Six hundred and fifty-six second or third line advanced gastric cancer patients were randomized to everolimus as monotherapy or placebo with BSC. The median OS was not significantly different, at 5.39 months in the everolimus group compared to 4.34 months in the placebo group (102).

PARP Inhibitors

The function of PARP is to repair single stranded breaks (SSBs). If these SSBs are not repaired, they become double stranded breaks (DSBs) at the next fork replication, which leads to cell death. As cancer therapeutics, the PARP inhibitors prevent the cancer cell's SSB repair mechanism and ultimately allow tumor cell death to occur (103). These agents have shown activity in ovarian and breast cancer, particularly in patients with BRCA1 or BRCA2 gene mutation.

The PARP inhibitor olaparib was studied in a second line phase II trial for metastatic or recurrent GE. Patients received paclitaxel with or without olaparib (104). Though PFS was not significantly different, OS was improved in the

olaparib group. Because preclinical data had shown more olaparib sensitivity in patients with low ataxia telangiectasia mutated (ATM) protein (105), this study performed a subset analysis in which low ATM patients were found to have improved OS with olaparib. Based on these results, an ongoing phase III study of second line GE randomizes patients to paclitaxel with or without olaparib (106). A phase I study of another PARP inhibitor veliparib with FOLFIRI is also currently recruiting (107).

Immunotherapy

Cancer evades host immune recognition through multiple mechanisms acquired during tumor evolution (108). By blocking negative immune regulatory pathways and thereby allowing increased immune activity, cancer immunotherapy is a novel way to attack tumor cells. With the approval of therapies like ipilimumab for melanoma, there has been increased interest in immunotherapy for other diseases. Ipilimumab releases negative immune regulatory pathway by blocking cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), an inhibitory receptor.

The immunotherapy agent nivolumab has also been recently evaluated in cancer. This drug function by blocking binding of receptor inhibitor programmed cell death 1 (PD-1) that is expressed on T-cells to programmed cell death ligand 1 (PDL-1) which prevents T cell death. A phase I trial of nivolumab included patients with gastric adenocarcinoma. Unfortunately, these patients were not included in the efficacy analysis (109).

Pembrolizumab is another agent that blocks the binding of PD-1 and PDL-1 (as well as PDL-2). A phase IB study of pembrolizumab in recurrent and metastatic gastric and GEJ adenocarcinoma patients with PD-L1 tumor positivity by IHC was presented at ESMO 2014 (110). Tolerability as well as anti-tumor activity was demonstrated. Another anti-PDL-1 agent, MEDI4736, has shown activity in gastric cancer (111).

The combination of CTLA-4 and PDL-1 blocking agents has also been investigated. In melanoma, this grouping has been shown to improve response rate and survival in melanoma compared to each drug alone, suggesting synergistic activity of these agents (112). Based on promising pre-clinical data, the combination of MEDI4736 and tremilumumab (an anti-CTLA-4 agent) is being investigated in patients with advanced solid tumors, including gastric cancer (113). Immunotherapy could provide an unmet clinical need to patients with advanced

GE cancers who might not benefit or be able to tolerate further traditional chemotherapy.

Guanylyl cyclase C (GCC) inhibitor

GCC, a trans-membrane cell surface receptor, is expressed on normal intestinal tissue but also expressed on the tumor cells of patients with gastrointestinal malignancies. Expression has been shown to be a good prognostic marker (39). Based on preclinical data that GCC on tumor cells has alterations in epithelial junctions, an antibody-drug conjugate MLN0264 was developed to preferentially target tumor cells. Based on promising phase I results (114), a phase II study of MLN 0264 in previously treated patients with gastric and GEJ cancers whose tumors express GCC by IHC is currently recruiting patients (115).

Conclusions

Together, GE cancers are among the most common malignancies worldwide (116). At diagnosis, approximately 50 percent of patients have disease that extends beyond locoregional confines. Cytotoxic agents have been the mainstay of systemic treatment for decades but carry significant toxicity.

During recent years, several molecular abnormalities underlying GE carcinogenesis have been identified. This has stimulated the search for targeted therapeutic approaches, and many studies are incorporating these agents with chemotherapy as described in this review.

The highly complex nature of the underlying molecular abnormalities and concurrent aberrations in multiple signaling pathways in GE cancers has been established (117). Because of the inherent redundancies in tumor molecular pathways, targeted agents used as monotherapy or even added to a chemotherapy backbone are unlikely to result in dramatic improvements in efficacy. However, pursuing multiple targets simultaneously might be logistically difficult given the current limited understanding of how to combine targeted agents, the issue of designing multi-sponsor trials, as well as the potential for additional toxicities. In the future, molecular profiling will play a role in identifying the specific patient who might benefit from targeted therapy, validate whether the drug inhibits the target, and determine if the tumor having the target is of functional importance.

To better achieve this goal of personalized cancer care, biomarkers should be utilized to predict the efficacy and toxicity of anticancer agents, as with HER2 overexpression

prior to trastuzumab use. However, though selecting patients based on predictive factors is ideal, the lack of validated biomarkers in GE and the diversity of molecular alterations acquired during malignant transformation, recurrence or metastasis makes biomarker incorporation into clinical trials difficult.

Finally, the failure of phase III trials to demonstrate survival benefit despite promising results from phase II studies indicates the need to change the current evaluation system. Targeted agents often result in stable disease rather than disease response, which make assessment more challenging. OS should remain the primary end point of clinical trials because of the short survival in GE cancers.

Apart from the molecular targeted therapies described in this article, many other agents are currently being evaluated in GE cancers. Adequately powered, randomized trials are necessary to define the role of targeted therapies in advanced GE. Further work is needed to determine the optimal use of targeted therapy, validate biomarkers, and bring personalized medicine to GE adenocarcinomas.

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Esophageal cancer: staging system and guidelines for staging and treatment

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Abstract: Survival of esophageal cancer is improving but remains poor. Esophageal cancer stage is based on depth of tumor invasion, involvement of regional lymph nodes, and the presence or absence of metastatic disease. Appropriate work-up is critical to identify accurate pre-treatment staging so that both under-treatment and unnecessary treatment is avoided. Treatment strategy should follow guideline recommendations, and generally should be developed after multidisciplinary evaluation.

Keywords: Esophageal neoplasms; neoplasm staging; esophagectomy

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Introduction

The incidence of esophageal cancer is increasing, with an estimated 17,460 new cases in the United States in 2012 (1-5). More than 90% of esophageal cancers in the United States are either adenocarcinomas (57%) or squamous cell carcinomas (37%) (1-3,6). The distribution of tumor types varies according to race: 64% of cases in whites are adenocarcinomas, while 82% are of squamous cell origin among the black population (6). Interestingly, the incidence among white males has almost doubled while the incidence among blacks has decreased by almost 50% (6). Tobacco use and a history of mediastinal radiation are risk factors for both tumor types (2). Other risk factors for adenocarcinoma include gastroesophageal reflux disease (GERD), obesity, and Barrett's esophagus (2). Barrett's esophagus with high-grade dysplasia is considered a premalignant condition as 50% are found to harbor occult malignant disease at time of biopsy (7). Additional risk factors for squamous cell carcinoma are conditions that cause chronic esophageal irritation and inflammation such as alcohol abuse, achalasia, esophageal diverticuli, and frequent consumption of extremely hot beverages (2). Approximately three quarters of all adenocarcinomas are found in the distal esophagus whereas squamous-cell carcinomas are more evenly

distributed throughout the distal two thirds (2).

Obtaining accurate pre-treatment staging and then subsequently providing stage-appropriate treatment is crucial in optimizing esophageal cancer outcomes. Overall 5-year survival for patients with esophageal cancer remains poor, although some improvement has been achieved with an increase from 5% to 17-19% over the past four decades (4-6). These survival improvements have likely resulted from earlier detection in the setting of Barrett's esophagus, improvements in perioperative care, and the use of adjuvant and induction chemotherapy and radiation. However esophageal cancer treatment and particularly esophagectomy is also associated with significant morbidity. Accurate staging and appropriate treatment can avoid both inadequate and unnecessary treatment to balance the potential benefits of improving prognosis with risks of treatment-related morbidity.

Staging system and guidelines

Staging definitions

Esophageal cancer staging is defined by the American Joint Committee on Cancer (AJCC) Staging System that establishes tumor-node-metastasis (TNM)

Table 1 T, N, and M status and histologic grade definitions for esophagus and esophagogastric junction cancer in the 7th edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual

T status	
T _{is}	High-grade dysplasia
T1	Invasion into the lamina propria, muscularis mucosae, or submucosa
T2	Invasion into muscularis propria
T3	Invasion into adventitia
T4a	Invades resectable adjacent structures (pleura, pericardium, diaphragm)
T4b	Invades unresectable adjacent structures (aorta, vertebral body, trachea)
N status	
N0	No regional lymph node metastases
N1	1 to 2 positive regional lymph nodes
N2	3 to 6 positive regional lymph nodes
N3	7 or more positive regional lymph nodes
M status	
M0	No distant metastases
M1	Distant metastases
Histologic grade	
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

sub-classifications based on the depth of invasion of the primary tumor (T), lymph node involvement (N), and extent of metastatic disease (M). The most recent, 7th edition of the AJCC Cancer Staging Manual for esophagus and esophagogastric junction cancers was developed based on a database of 4,627 esophagectomy patients who were not treated with induction or adjuvant therapy (8). This data from 13 institutions in five countries and three continents was collected by the Worldwide Esophageal Cancer Collaboration (WECC) (9). *Table 1* shows the specific 7th edition TNM definitions. The 7th edition differed from the 6th edition in several respects (10,11). The T status classification was changed to define T_{is} as high-grade dysplasia and all non-invasive neoplastic epithelium. Tumors with T4 status due to invasion of local structures

were subdivided into tumors that involved resectable local structures such as pleura and diaphragm (T4a) and unresectable local structures such as aorta and vertebral bodies (T4b).

Regional lymph nodes were also redefined as any paraesophageal lymph node, including cervical or celiac nodes. The N status had been categorized simply as node-negative or node-positive in the 6th edition and was redefined in the 7th edition to N0-N3 based on the number of lymph nodes. The M1a and M1b subclassifications from the 6th edition were redefined to M1. The 7th edition stage groupings were also defined to consider the importance of histopathologic cell type, tumor grade, and tumor location. *Table 2* shows stage grouping for adenocarcinoma and squamous cell carcinoma, which are no longer equivalent in the 7th edition.

Diagnostic and staging work-up

The Society of Thoracic Surgeons has published guidelines on the diagnosis and staging of patients with esophageal cancer (12). The work-up for esophageal cancer often starts when patients present with symptoms such as dysphagia and weight loss in the setting of an unremarkable physical exam (2,13). Therefore, the most common tests used to initially identify and diagnosis esophageal cancer are upper gastrointestinal (GI) tract contrast studies and upper endoscopy with biopsy. An upper GI contrast study typically shows a stricture or ulceration when malignancy is present. Upper GI endoscopy identifies tumor location and length and allows biopsy for pathologic examination. After a histologic cancer diagnosis has been obtained, subsequent studies are performed to determine clinical stage as accurately as possible before treatment is initiated.

Obtaining a computed tomographic (CT) scan of the chest and abdomen with both oral and intravenous contrast should be the first staging study when esophageal cancer is diagnosed histologically. The CT scan is somewhat limited in defining the local extent and nodal involvement of esophageal cancer but is most useful in identifying the presence of distant disease such as liver or lung metastases. Further studies that evaluate T and N status would not typically impact treatment and therefore are generally unnecessary if distant disease is identified and subsequently confirmed by biopsy. Positron-emission tomography (PET) scans improve staging by detecting previously unsuspected metastatic disease in up to 15-20% of patients and should be considered in place of CT scans or as an additional study

Table 2 AJCC 7th edition stage groupings

Stage	Adenocarcinoma				Squamous cell carcinoma				
	T	N	M	Grade	T	N	M	G	Location
0	is	0	0	1	is	0	0	1	Any
IA	1	0	0	1-2	1	0	0	1	Any
IB	1	0	0	3	1	0	0	2-3	Any
	2	0	0	1-2	2-3	0	0	1	Lower
IIA	2	0	0	3	2-3	0	0	1	Upper, middle
					2-3	0	0	2-3	Lower
IIB	3	0	0	Any	2-3	0	0	2-3	Upper, middle
	1-2	1	0	Any	1-2	1	0	Any	Any
IIIA	1-2	2	0	Any	1-2	2	0	Any	Any
	3	1	0	Any	3	1	0	Any	Any
	4a	0	0	Any	4a	0	0	Any	Any
IIIB	3	2	0	Any	3	2	0	Any	Any
IIIC	4a	1-2	0	Any	4a	1-2	0	Any	Any
	4b	Any	0	Any	4b	Any	0	Any	Any
	Any	3	0	Any	Any	3	0	Any	Any
IV	Any	Any	1	Any	Any	Any	1	Any	Any

Cancer location definitions: upper thoracic, 20-25 cm from incisors; middle thoracic, 25-30 cm from incisors; lower thoracic, 30-40 cm from incisors.

when the CT scan does not show metastatic disease (14,15).

If CT and PET do not demonstrate distant disease, endoscopic ultrasound (EUS) should be performed to establish the extent of locoregional disease (2). EUS provides more accurate evaluation of the depth of tumor invasion (T status) and the extent of lymph-node involvement (N status) than both PET and CT (16,17). However, EUS is less accurate for early-stage lesions such as T1 or T2 compared to more advanced tumors (18-21). Most incidences of understaging are due to missing nodal disease. The specificity and the sensitivity for identifying lymph node disease are better when EUS is combined with fine-needle aspiration (FNA) compared to EUS alone (22).

Performance of the above staging modalities establishes the pre-treatment clinical stage which can be used to guide subsequent treatment, as will be discussed in the following sections. However, occasionally additional studies may be worthwhile before initiation of treatment. First, bronchoscopy should be considered for tumors in the upper and middle esophagus to rule out airway invasion. CT scan and EUS can be suggestive of airway involvement but are not as accurate as direct visualization of the airway. In addition, distant metastases are unfortunately missed even with completion of the staging evaluation described above.

Small liver or lung metastases can be missed by both PET and CT scans, and patients can also have undetected pleural or peritoneal disease (23). Staging via minimally invasive surgical techniques of thoracoscopy and laparoscopy improves the accuracy of the above non-invasive testing (23-25). Use of these invasive techniques is relatively uncommon but should be considered in select patients, such as those who may be considered to have a high risk of treatment-related complications. Staging laparoscopy in particular may have a role for patients with adenocarcinoma of the esophagus or esophagogastric junction (26).

Treatment guidelines

The National Comprehensive Cancer Network (NCCN) provides guidelines for the treatment of esophageal cancer (27). Treatment options include local mucosal resection or ablation therapies, esophagectomy, chemotherapy, and radiation therapy. Recommended treatment is primarily dictated by stage, tumor location, and patients' medical fitness for receiving a particular therapeutic modality. However, definitive data from randomized trials to guide the treatment of esophageal cancer is lacking for many clinical situations. Outcomes also generally are relatively poor with

many treatment strategies, so establishing optimal treatment for different clinical situations remains an area of active research (28). The NCCN guidelines reflect the lack of definitive evidence and often allow a spectrum of potential treatments for many clinical situations. Given both the generally poor overall prognosis and the potential morbidity associated with therapy, multidisciplinary evaluation by surgery, medical oncology, and radiation oncology should be considered for all patients before a treatment strategy is initiated. Treatment that does not follow guidelines should probably only be used in the context of clinical trials.

The stage groupings described above are very useful for both providing prognosis and guiding treatment. However, patients can be categorized even more simply when considering treatment. When considering treatment for esophageal cancer patients, the approach is initially dictated by whether the patients have been determined to have early stage superficial cancers, cancers that are locally advanced with locoregional disease but no distant metastases, and cancers with distant disease. The general treatment guidelines for each of these categories will be discussed in the following sections.

Superficial cancers

Patients with T1-2N0 esophageal cancer typically are recommended to undergo surgery without induction treatment (27). The prognosis for patients treated for intra- and submucosal (T1) esophageal cancers is significantly better than the prognosis for all other patients found to have esophageal cancer, even those also found in other relatively early-stage disease (8). Esophagectomy is effective oncologically for these cancers, but is associated with considerable morbidity and mortality despite improvements over time and the development of minimally invasive techniques (29-35). Although recent data from high-volume centers have shown low mortality rates of 1% to 3.5%, studies involving population-based databases or multicenter trials show that esophageal resection continues to have relatively high perioperative mortality rates of 8.8% to 14% (30,32,35-37). Local treatments with modalities such as endoscopic mucosal resection, radiofrequency ablation, cryotherapy, and photodynamic therapy can provide effective cancer treatment for superficial cancers with much less treatment-related morbidity (38-50). These local treatments are good treatment options for patients with superficial tumors that involve only the mucosa (T1a), but close endoscopic surveillance should be planned post-

treatment. However, local mucosal therapies at the present time are generally not considered appropriate for superficial tumors that involve the submucosa (T1b), as these lesions have occulted lymph node involvement in as many as 50% of patients (51,52). Therefore esophagectomy without induction therapy is recommended for superficial tumors that involve the submucosa (T1b),

The optimal management of esophageal cancer clinically staged as T2N0M0 is somewhat more controversial (53). Clinical staging modalities for this subset are somewhat unreliable, with significant percentages of patients being both under and over staged (18,54-57). Perhaps because clinical staging inaccuracies lead to a relatively high incidence of patients actually having nodal disease present at the time of surgical resection, induction therapy use in this setting has been increasing and was shown recently to exceed 50% for cases that were reported to the Society of Thoracic Surgeons General Thoracic Database in 2011 (54). However, data that proves a survival benefit to induction therapy over surgery alone is still lacking (58). Consistent with the uncertainty of optimal treatment, the NCCN guidelines for medically fit patients allow a wide spectrum of treatment possibilities that include definitive chemoradiation and esophagectomy with or without induction or adjuvant therapy (27).

Locoregional or locally advanced disease

Approximately 32% of esophageal cancer patients have regional disease at the time of diagnosis, with a 5-year survival of only 10-30% (1,2,8). The treatment for locally advanced esophageal cancer that does not have distant metastases and is potentially resectable (T3-4aN0, T1-4aN1M0) is highly variable in practice (59). The NCCN guidelines reflect a lack of available definitive data on the optimal treatment and essentially consider any combination of esophagectomy and chemoradiation or even definitive chemoradiation as acceptable therapy (27).

Many studies involving various combinations of surgery, chemotherapy, and radiation to treat locally advanced esophageal cancer have been conducted and showed conflicting results (28,37,60-66). However, recent evidence suggests that induction chemoradiation followed by surgical resection is the optimal treatment for patients with T3-4a tumors or nodal disease. Several recent trials, retrospective studies, and meta-analyses all showed a survival benefit to both combined and induction therapy (67-72). Most importantly, a recently published randomized trial

demonstrated a survival benefit to induction chemoradiation followed by surgery compared to surgery alone for esophageal or esophagogastric junction cancer (73).

Radiation alone followed by surgery does not improve survival compared with surgery alone and therefore induction radiation alone is not recommended (27,65). Induction chemotherapy without radiation has variably shown to be beneficial but is used by some high-volume centers, and is recommended as a potential treatment by the NCCN for patients with adenocarcinoma (27,37,64). Definitive chemoradiation is the preferred treatment for patients with T4b (unresectable) tumors and occasionally can facilitate surgical resection in selected cases.

Metastatic or unresectable disease

Approximately 50% of patients have evidence of distant metastatic disease at the time of diagnosis (2,6). Palliative therapy is recommended for these patients, and can include chemotherapy, clinical trial enrollment if available, or best supportive care. Best supportive care is often the most appropriate treatment option. Patients' performance status should determine whether chemotherapy is added to best supportive care. Specific symptoms that often need palliation include dysphagia, pain, and nausea. Oncologists often are hesitant to pursue feeding tubes in patients with stage IV cancer, but feeding tubes may be reasonable options in some select patients. Radiation or endoscopic management techniques such as dilation and stenting can be used to palliate dysphagia or cases of bleeding from esophageal tumors. Palliative esophagectomy for patients with metastatic disease may have a role in very few cases, but should be considered only in very select cases given the morbidity of surgery and the poor prognosis with or without surgery.

Other considerations

Role of esophagectomy for esophageal cancer

Concurrent chemoradiation is an effective treatment option for patients with squamous cell carcinoma of the cervical esophageal cancer (74-77). The NCCN guidelines recommend definitive chemoradiation for these patients (27). Surgery is recommended as possible treatment for most other cases of esophageal cancer that do not have invasion of unresectable structures or distant metastatic disease. Esophageal resection can be performed via several different

techniques, with the most appropriate technique for any specific individual patient being dependent on both patient and surgeon factors. Several studies have suggested that complete surgical resection provides the best chance for cure in patients who do not have distant disease (64,78,79). For patients with stage I-III disease who receive surgical treatment, 5-year survival is 28%, compared to 10% for those treated medically (78). However, surgery for locoregional esophageal cancer is utilized in only 30-40% of resectable cases, perhaps because esophagectomy is historically associated with significant morbidity and mortality and disappointing long-term results (78,80). Minimizing perioperative morbidity in any manner possible is critical to increase the use of surgical resection so that primary nonsurgical treatment is reserved for those who refuse surgery, have unresectable cancers, or are not thought to be surgical candidates for other reasons.

Squamous cell carcinoma versus adenocarcinoma

Squamous cell carcinoma was previously the most common histology but now accounts for 37% of esophageal cancers (1,3). Adenocarcinoma is now the most common esophageal cancer. Patients with adenocarcinoma and squamous cell carcinoma have been observed to have similar long-term survival across major treatment modalities, suggesting that both histologies respond similarly to treatment and may share significant physiologic and cellular features (81). Accordingly, staging and treatment guidelines for adenocarcinoma and squamous cell carcinoma were previously essentially equivalent. However, recognition of prognosis and response to treatment between the two subtypes led to separate stage groupings and treatment algorithms in the latest, revised staging system and in the NCCN guidelines (8,27).

Esophageal cancer treatment guidelines are still generally similar to both adenocarcinoma and squamous cell carcinoma (27). However, the benefit of surgical resection in improving survival compared to definitive chemoradiation for esophageal squamous cell carcinoma has been questioned (82). In particular, several randomized trials have suggested that definitive chemoradiation could offer equivalent survival to treatment that involves surgery for locally advanced, non-metastatic esophageal SCC (83-85). Currently for medically fit patients with resectable disease, the NCCN treatment guidelines only recommend definitive chemoradiation for patients who decline surgery (27). However, some centers advocate treatment with chemoradiation for esophageal squamous cell carcinoma, with surgery subsequently used

only when there is persistent or recurrent local disease (86).

Adjuvant therapy

Adjuvant therapy after resection may have a role for some esophageal cancer patients. Postoperative radiation may reduce the incidence of local recurrence in those patients who have residual tumor after resection but is not beneficial in the absence of residual disease (2,87,88). Postoperative chemotherapy has not been definitively shown to have an additive effect on survival compared with surgery alone although additional therapy may be warranted in patients who have a high likelihood of metastatic disease based on a large number of tumor positive nodes (89). The NCCN does not recommend adjuvant therapy if patients have had a complete R0 resection for squamous cell carcinoma, but does recommend consideration of adjuvant chemoradiation, or only adjuvant chemotherapy if induction radiation was administered, for patients who have had resection of adenocarcinoma with either node-positive disease or T2-T4a tumors (27). The guidelines also recommend consideration of adjuvant therapy in the setting of microscopic or macroscopic residual disease after resection.

Conclusions

Survival of esophageal cancer is improving but remains poor. Esophageal cancer stage is based on depth of tumor invasion, involvement of regional lymph nodes, and the presence of metastatic disease. Most patients present with either locally advanced or metastatic disease. Appropriate work-up is critical to identify accurate pre-treatment staging so that both under-treatment and unnecessary treatment is avoided. Staging evaluation should start with CT or PET scan, and patients who do not have metastatic disease should have EUS to determine the locoregional extent of disease. Treatment strategy should follow guideline recommendations, and generally should be developed after multidisciplinary evaluation. Surgery or local mucosal treatments should be considered for superficial cancers. Multimodality therapy that includes surgery is generally considered the best treatment for locally advanced cancers, while patients that have metastatic disease should be considered for chemotherapy along with best supportive care.

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State-of-the-art molecular imaging in esophageal cancer management: implications for diagnosis, prognosis, and treatment

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Abstract: Molecular imaging techniques are increasingly being used in addition to standard imaging methods such as endoscopic ultrasound (EUS) and computed tomography (CT) for many cancers including those of the esophagus. In this review, we will discuss the utility of the most widely used molecular imaging technique, ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography (PET). ¹⁸F-FDG PET has a variety of potential applications ranging from improving staging accuracy at the time of initial diagnosis to assisting in radiation target volume delineation. Furthermore, ¹⁸F-FDG PET can be used to evaluate treatment response after completion of neoadjuvant therapy or potentially during neoadjuvant therapy. Finally, we will also discuss other novel molecular imaging techniques that have potential to further improve cancer care.

Keywords: Positron emission tomography (PET); esophageal cancer; molecular imaging; neoadjuvant therapy

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Introduction

An estimated 18,170 new cases of esophageal cancer will be diagnosed in 2014 and approximately 15,450 of these patients will die from the disease (1). Although outcomes are improved with the addition of neoadjuvant chemotherapy or neoadjuvant chemoradiation (CRT) to surgery alone, outcomes for locally advanced esophageal cancer remain poor (2). Local failure rates even with the addition of CRT exceed 50% (3,4) in locally advanced patients.

The era of personalized medicine has brought increasing awareness that variations in tumor biology drive tumor genesis, response to treatment, and long-term prognosis. The advent of molecular imaging techniques has resulted in improvements in esophageal cancer staging and treatment. Although ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography (PET) is the most commonly studied and clinically used approach, early results using other molecular imaging techniques suggest that further improvements in esophageal cancer care are possible.

Molecular imaging agents

¹⁸F-FDG is the most commonly used agent for PET imaging. However, its sensitivity for very small tumors is low, and uptake is dependent on oxygen supply and glycolysis (5). Choline-derivatives, such as ¹¹C-choline, ¹⁸F-fluoroethylcholine, and ¹⁸F-fluorocholine have been investigated because of their more selective uptake in the mediastinum (6,7). Choline is a precursor in the biosynthesis of phosphatidylcholine, which is a major phospholipid constituent of the cell membrane; consequently, choline uptake is proportional to the rate of cell division. One advantage is that normal tissues, such as brain, lung, heart, bone, and skeletal muscle, have very low uptake of positron-labeled cholines. The more pronounced uptake in malignant mediastinal adenopathy is more striking when compared against low uptake in the lung, heart, and mediastinum. Another benefit of choline-derivatives is the rapid clearance of radiolabeled-choline from the blood after intravenous administration, allowing

for quick initiation of PET imaging, as soon as 2-3 min after radiotracer injection (6). Tian *et al.* compared ^{11}C -choline PET with ^{18}F -FDG PET in 38 patients with various tumors and found a high correlation in differentiation between malignant and benign lesion uptake (8). These researchers also observed differences in imaging acquisition timing, with PET performed 5 min after injection of ^{11}C -choline and 40 min after injection of ^{18}F -FDG. One important logistic limitation of ^{11}C -choline is a short half-life (20 min), which limits its use to facilities with an onsite cyclotron (8). ^{18}F -fluorocholine has a longer lived isotope, with a half-life of 110 min and has shown encouraging results with high tumor-to-background contrast within minutes of injection (9). The relatively low uptake of choline in normal brain tissue allows for good delineation of disease in the brain, and patients can be scanned within 20 min after intravenous injection. However, normal uptake of choline in the liver may potentially obscure identification of metastatic disease below the diaphragm (9).

L-[3- ^{18}F]- α -methyltyrosine (^{18}F -FAMT) is an amino acid tracer developed for PET imaging. ^{18}F -FAMT is accumulated in tumor cells via an amino acid transport system, LAT-1, which plays an important role in cellular proliferation and is widely expressed in cancers, particularly in squamous cell carcinoma (SCC) (10). In oral SCC, uptake of ^{18}F -FAMT has been significantly correlated with LAT-1 expression, cell proliferation, maximal tumor size, and disease stage and is more specific for malignancy than ^{18}F -FDG (10). In a study of 21 patients with esophageal SCC, ^{18}F -FAMT demonstrated lower sensitivity for lymph node staging than ^{18}F -FDG (40% and 47%, respectively) but significantly higher specificity (100% and 50%, respectively) (11). ^{18}F -FAMT may also allow for better delineation of malignancy near the heart, because it does not show the intense cardiac physiologic uptake of ^{18}F -FDG. Use of ^{18}F -FAMT in conjunction with ^{18}F -FDG in PET may help reduce false positives resulting from inflammation. Further studies are needed to establish the relationship between intensity of uptake and patient prognosis with ^{18}F -FAMT.

^{18}F -fluorothymidine (^{18}F -FLT) is a pyrimidine analog that is phosphorylated by thymidine kinase 1, an enzyme within the salvage DNA synthesis pathway. The activity of thymidine kinase 1 and therefore uptake of ^{18}F -FLT reflects cellular proliferation and is more specific than ^{18}F -FDG for differentiating neoplasms from inflammation (12). In a study of 22 patients, both uptake and sensitivity for detection of lymph node metastatic disease were lower with

^{18}F -FLT than ^{18}F -FDG (75% and 83%, respectively), but specificity was higher (99% and 96%, respectively) (13). ^{18}F -FLT has also shown promise in monitoring disease response to treatment (12). The major disadvantage of ^{18}F -FLT is increased risk of false negative results when used alone. ^{18}F -FDG remains the most widely used radiolabeled agent for staging and evaluating treatment response, but other molecular agents continue to be developed and assessed in clinical trials.

Diagnosis of premalignant esophageal lesions

The rate of esophageal cancer diagnosis, particularly in the lower esophagus and gastroesophageal junction (GEJ), has increased dramatically in recent years. One driver of this increase is the rising incidence of chronic gastroesophageal reflux disease (GERD), which leads to Barrett esophagus (BE). In BE, the normal stratified squamous epithelium of the esophagus is replaced by simple columnar epithelium with goblet cells. BE is associated with an increased risk of esophageal adenocarcinoma and is therefore considered a premalignant disease. Endoscopic surveillance is recommended for patients with BE in order to detect neoplastic changes at an early stage. Early detection of progression to malignancy can allow for more limited treatment and result in improved long-term outcomes.

Endoscopy alone for BE surveillance is not ideal because it cannot reliably detect regions of dysplasia. The flat appearance of dysplasia makes it difficult to visualize, despite the advantages accrued with narrow-band imaging, high-yield white-light endoscopy, and chromoendoscopy (14). Only a limited amount of tissue is evaluated with standard random biopsies in BE, allowing areas of dysplasia or invasive carcinoma to remain undetected (15).

Several molecular imaging techniques have been developed in an attempt to increase detection of subtle dysplastic changes within BE. Sturm *et al.* developed a peptide that binds to regions of esophageal high-grade dysplasia as well as adenocarcinoma (16). First-in-human results demonstrated that the peptide was not only safe but also appeared to effectively enhance identification of esophageal neoplasia. Confocal endomicroscopy in 25 patients was performed after topical administration of the peptide, resulting in a 3.8-fold higher fluorescence intensity in regions of high grade dysplasia and esophageal adenocarcinoma than in BE and normal squamous epithelium. This peptide may therefore allow for more directed and higher yield biopsies. Another technique,

probe-based confocal microscopy, uses biophotonics to visualize cellular details during endoscopy (17). Its capabilities for real-time assessment could save significant time and cost associated with biopsy analysis. Other promising molecular imaging strategies include gene expression analysis of stem cell clones from BE biopsy specimens (18,19), targeted proteomics (20-22), and mass spectrometry (23,24).

Esophageal cancer staging

Before routine clinical use of ^{18}F -FDG PET, computed tomography (CT) and endoscopic ultrasound (EUS) were the primary imaging modalities for esophageal cancer staging. These techniques have proven to be complementary; in many patients, CT is better able to determine tumor length and exclude invasion of adjacent structures whereas EUS can better determine the depth of invasion of the primary tumor and identify locoregional lymph node metastasis (25,26). A meta-analysis by Rösch *et al.* reported that the accuracy of EUS for staging the extent of primary tumor involvement was 89% (27).

In contrast to EUS, ^{18}F -FDG PET is less successful in accurately determining the depth of invasion of the primary lesion (26). ^{18}F -FDG PET does not clearly offer a significant benefit in nodal staging over EUS and CT (28). Significant ^{18}F -FDG uptake in the primary lesion may obscure increased uptake in locoregional nodes (29). However, ^{18}F -FDG PET is particularly useful as a complementary imaging tool for detecting distant metastases, which are quite common in patients with esophageal cancer (25,30-32). A study by Lowe *et al.* in 75 newly diagnosed esophageal cancer patients reported the respective sensitivity and specificity for distant metastases to be 81% and 91% for PET, 81% and 82% for CT, and 73% and 86% for EUS (26). A meta-analysis showed that the sensitivity and specificity for detecting distant metastases were 71% and 93%, respectively, for ^{18}F -FDG PET and 52% and 91%, respectively, for CT (25). The superior ability of ^{18}F -FDG PET in detection of occult distant metastasis during the initial staging process may provide sufficient evidence to avoid unnecessary surgery in up to 20% of patients (32,33). A multicenter prospective cohort study of 491 patients showed that PET/CT led to clinically significant changes in stage for 24% of patients (34). The American College of Surgeons Oncology Group Z0060 trial prospectively evaluated the utility of ^{18}F -FDG PET after standard staging workup by randomizing 262 potentially resectable

esophageal cancer patients after CT to either ^{18}F -FDG PET or no PET imaging (35). ^{18}F -FDG PET identified biopsy-proven distant metastasis not detected by CT in 4.8% of patients who proceeded to surgery. An additional 9.5% of patients had PET-detected metastases that were not biopsy-proven. Of note, PET/CT coregistration was not performed in this trial.

Integrated PET/CT has higher sensitivity and specificity for tumor staging than ^{18}F -FDG PET alone (36). In fused scans, the CT has two main purposes. The first is to serve as an attenuation map to correct for the fact that photons originating from deeper structures are more highly attenuated than those originating closer to the skin surface. This correction is essential not only to improve image quality but to allow for accurate quantitative measurements of metabolic activity performed using the standardized uptake value (SUV). The SUV is the ratio of metabolic activity (Bq/mL) in the region of interest to the decay-corrected activity of injected ^{18}F -FDG (Bq/g). The second purpose is to provide anatomic and structural reference data that complements the metabolic findings on PET imaging, fusing form (anatomic) and function (metabolic) information.

^{18}F -FLT may offer significant imaging advantages over ^{18}F -FDG for esophageal cancer staging with PET. One of the primary disadvantages of ^{18}F -FDG is its nonspecific uptake within benign lesions, which may result in inappropriate upstaging of patients (37). ^{18}F -FLT has higher uptake in proliferating tumors and better discrimination between malignant and benign lesions, as shown in both *in vitro* and *in vivo* studies (38). Han *et al.* compared the abilities of ^{18}F -FLT and ^{18}F -FDG PET in detection of regional lymph node metastasis in 22 patients with SCC of the esophagus using pathologic findings (13). Only three false-positive nodes were found using ^{18}F -FLT, whereas ^{18}F -FDG PET identified 14. The sensitivity and specificity of ^{18}F -FLT PET were 74% and 99%, respectively, and of ^{18}F -FDG PET were 83% and 96%, respectively. However, ^{18}F -FLT may result in a higher rate of false-negative results, as suggested by van Westreenen *et al.* (39). Additional work is needed to evaluate the benefits of ^{18}F -FLT in esophageal cancer staging, and ^{18}F -FDG remains the current agent of choice.

Pretreatment ^{18}F -FDG PET and prognosis

^{18}F -FDG PET is not only useful for staging but may be effective in determining prognosis prior to treatment. The

first report of ^{18}F -FDG PET in prognosis for esophageal cancer was in 1998, when Fukunaga *et al.* reported that patients with tumor SUV >7 had poorer outcomes (40). This correlation between higher maximum SUV (SUV_{max}) and worse overall and disease-free survival (OS and DFS, respectively) has since been supported by numerous studies (41-46). A literature review by Omloo *et al.* reported that 12 of 15 studies included in their analysis showed that pretreatment SUV is a predictor for survival in univariate analysis (46). However, only 2 studies showed that this significance persisted in multivariate analysis. Furthermore, it is unclear whether SUV_{max} is an independent prognostic factor when compared with tumor stage (46,47). Although pretreatment SUV may be prognostic, a wide range of SUV_{max} thresholds have been reported as being significant. For example, significant survival differences were shown by Rizk *et al.* (41), who used a SUV_{max} threshold of 4.5, whereas Cerfolio and Bryant suggested 6.6 as an ideal threshold (42). Better characterization of SUV_{max} thresholds in this disease setting is needed to better evaluate and apply the prognostic utility of this PET parameter.

The majority of ^{18}F -FDG PET studies define therapeutic response by quantifying the SUV_{max} of the tumor (Table 1). However, this metric does not account for the significant heterogeneity of ^{18}F -FDG tumor uptake or account for the fact that many tumors have both malignant and nonmalignant components. Spatial ^{18}F -FDG PET features such as tumor volume (57), tumor shape (58), and texture features (59) have been suggested to be more informative than SUV_{max} . Investigators also have evaluated metabolic tumor volume (MTV), or the volume of tumor with increased glycolytic activity above a specified SUV threshold, because it includes both anatomic tumor burden and metabolic information. Just as no standardized thresholds are agreed upon for SUV_{max} , various MTV definitions have been used; thus, it is difficult to compare studies and evaluate the usefulness of MTV. Emerging data suggest that MTV may be a significant predictor for survival, and perhaps may be more powerful than SUV_{max} . In 2010, Hyun *et al.* were the first to report the use of MTV in 151 esophageal cancer patients, most with SCC (60). Although SUV_{max} and MTV were each significant predictors of survival in univariate analysis, only MTV was significant in multivariate analysis, along with T and M stage. Chen *et al.* recently studied 90 patients with locally advanced SCC of the esophagus who received definitive CRT and underwent a pretreatment ^{18}F -FDG PET scan (61). These researchers reported that MTV 20% (tumor volume

with at least 20% of $\text{SUV}_{\text{max}} > 40$ mL) was the only significant predictor of survival in multivariate analysis. They also evaluated MTV2.5 (tumor volume with $\text{SUV}_{\text{max}} \geq 2.5$), which was not significant. Another ^{18}F -FDG PET parameter is total lesion glycolysis (TLG), defined as the MTV multiplied by the mean SUV (SUV_{mean}). Larger TLG values are believed to reflect increased amounts of hypoxia resulting from larger amounts of tumor being in glycolysis. Although data are limited with respect to TLG and esophageal cancer, a recent report by Li *et al.* suggests that TLG may be a useful prognostic factor (62).

Current literature suggests that these pretreatment ^{18}F -FDG PET parameters are promising prognostic factors, but further validation is warranted. If these parameters are to become widely used in the clinic, standardization is critical (63).

^{18}F -FDG PET for radiation treatment planning

Gross disease must be accurately delineated in esophageal cancer patients who receive radiation therapy. This is particularly important when highly conformal radiation delivery techniques, such as intensity-modulated radiation therapy (IMRT), are used. Clearly distinguishing primary tumor from normal esophagus is challenging with CT alone. Using the assumption that the primary esophageal tumor volume identified by EUS was accurate, CT was found to routinely underestimate or overestimate the proximal and/or distal extent of the tumor by several centimeters (64). Thus, investigators have looked to ^{18}F -FDG PET to aid in more accurately defining the gross tumor volume (GTV) for esophageal cancer patients. Incorporation of ^{18}F -FDG PET has proven useful in radiation planning for other disease sites, such as lung (65,66), lymphoma (67), and head and neck (68).

The impact of ^{18}F -FDG PET on radiation treatment planning for esophageal cancer has been evaluated retrospectively and prospectively (69-71). Leong *et al.* studied 21 esophageal cancer patients scheduled to receive definitive CRT (69). Two GTVs were contoured, one using CT alone (GTV-CT) and another using both PET and CT. When the contours were compared, a portion of PET-avid disease was excluded in 69% of the GTV-CTs, which would have led to a "geographic miss" in 31% of patients. As expected, the proximal and distal extents differed in the majority of patients. However, the radiographic tumor extent was not confirmed pathologically. Moureau-Zabotto *et al.* also prospectively evaluated the use of ^{18}F -FDG PET

Table 1 Prospective studies evaluating metabolic response during or after neoadjuvant treatment in esophageal cancer patients

Study	No.	Tumor histology	Timing of 2nd PET	Chemotherapy	Mean RT dose	Definition of metabolic response	% of metabolic responders with major histological response vs. nonresponders	P value	Survival of metabolic responders vs. nonresponders	P value
Wieder <i>et al.</i> , 2004 (48)	38	SCC	14 d	5FU	40 Gy	Decrease in SUV uptake $\geq 30\%$ vs. $< 30\%$	SUV dec $> 30\%$: 100% R0 resection vs. 63% in SUV dec $< 30\%$	0.03	Median survival: 38 vs. 18 mo; 2-y OS: 79% vs. 38%	0.011
Song <i>et al.</i> , 2005 (49)	32	SCC	Week 8 (3-4 wk post CRT)	cis/5FU until 2002, then switched to 5FU and capecitabine induction + cis/capecitabine with RT	45.6 Gy in 1.2 Gy bid (n=7), later modified to 46 Gy in 2 Gy daily (n=25)	Initial SUV > 4.0	pCR in 66% total group mCR: 71% vs. 25% in metabolic partial response	NR	NR	NR
Ott <i>et al.</i> , 2006 (43)	65	AC	14 d	cis/5FU x2 cycles, AEG I tumors received paclitaxel	None	Decrease in SUV uptake $\geq 35\%$	44% vs. 5%	0.001	3-y survival: 70% vs. 35%. Median OS: not reached vs. 18 mo. Patients with mCR: > 50 vs. 24 mo in metabolic nonresponders	0.01
Lordick <i>et al.</i> /MUNICON, 2007 (50)	110	AC	14 d	Induction platinum + 5FU chemo	None	Decrease in SUV uptake $\geq 35\%$	49% vs. 0%	0.015	Median OS: not reached vs. 25.8 mo	0.015
Higuchi <i>et al.</i> , 2008 (51)	50	SCC	2-4 wk post chemo or CRT	Chemo (cis + doxorubicin + 5FU) or CRT (cis + 5FU)	40 Gy	SUV _{max} < 2.5	87.5% of SUV _{max} < 2.5 achieved good response vs. 6.9% of SUV _{max} ≥ 2.5 achieved good response	< 0.0001	Median CSS in PET-neg group: 84.2 vs. 18.2 mo in PET + group. 5-y CSS 67.7% vs. 36.5%	0.0042; HR post tx SUV ≥ 2.5 , 3.628, 0.0071
Javeri <i>et al.</i> , 2009 (52)	151	AC	5-6.5 wk post CRT	5FU with RT + either platinum or taxane, some received all 3	Either 45 or 50.4 Gy	$> 52\%$ SUV _{max} decrease vs. $\leq 52\%$ SUV _{max} decrease	21% with pCR, 63% had some degree of response to CRT (1% to $\leq 50\%$ residual carcinoma in resected specimen)	NR	3-y OS: 72% vs. 43% in $\leq 52\%$. Median survival: not reached for responders vs. 2.49 y	0.02

Table 1 (continued)

Table 1 (continued)

Study	No.	Tumor histology	Timing of 2nd PET	Chemotherapy	Mean RT dose	Definition of metabolic response	% of metabolic responders with major histological response vs. nonresponders	P value	Survival of metabolic responders vs. nonresponders	P value
Roedl et al., 2009 (53)	49	SCC	Avg 13.1 d post CRT (SD =6.5 d)	Cis +5 FU	50.4 Gy	Diameter-SUV index >55%	Diameter-SUV index >55% associated with 91% sensitivity and 93% specificity in predicting histopathologic response	AUC =0.931 optimal cutoff value of 55%	Mean DFS 32 vs. 16 mo	<0.001
Vallböhmer et al., 2009 (54)	119	53 AC, 66 SCC	2-3 wk post CRT	Neoadj CRT with cis and 5FU	36 Gy	No specific cutoff values	Major histopathologic response seen in 39.5% in entire group	NR	5-y survival for major pathologic responders: 34% vs. 14% for minor responders, HR 2.2	0.005
zum Büschenfelde, et al./MUNICON II, 2011 (55)	56	AC	14 d	Induction platinum + 5FU chemo. If responder: continue 2 cycles of neoadj chemo. If nonresponder: 2 cycles cis or 5FU + RT	32 in 1.6 Gy bid only in metabolic nonresponders. No RT for metabolic responders	Decrease in SUV uptake $\geq 35\%$	36% vs. 26%	0.561, NS	Median survival: not reached vs. 18.3 mo; 2-y OS estimate 71% \pm 8%, 42% \pm 11%	NR; NS
van Heijl et al., 2011 (56)	100	82 AC, 18 SCC	14 d	Paclitaxel + carboplatin	41.4 Gy	Any SUV decrease (0% cutoff value)	90.6% pathCR vs. 9.4%	NR	NR	NR

Abbreviations: AC, adenocarcinoma; SCC, squamous cell carcinoma; 5-FU, 5-fluorouracil; cis, cisplatin; RT, radiation therapy; CRT, chemoradiation therapy; SD, standard deviation; SUV, standard uptake value; OS, overall survival; NR, not reported; CSS, cancer-specific survival; pCR, pathologic complete response; DFS, disease-free survival; NS, not significant; mCR, metabolic complete response; HR, hazard ratio; AEG, adenocarcinoma of esophagogastric junction.

in radiation treatment planning in 34 esophageal cancer patients (70). Compared to CT alone, the addition of PET resulted in a GTV decrease in 35% of patients and a GTV increase in 21%. Changes to GTV also influenced dose-volume histograms of neighboring organs. The total lung volume receiving at least 20 Gy changed in nearly 75% of patients, including 12 with dose reductions and 13 with dose increases. The total volume of heart receiving at least 36 Gy increased in 11 patients and decreased in 12 patients. This trial did not correlate pathologic tumor extent with radiographic tumor extent.

Although limited information is available about the use of ^{18}F -FLT PET for esophageal radiation planning, a study by Han *et al.* suggests that ^{18}F -FLT PET can be used to accurately define the GTV and may allow for decreased dose to normal organs (13). A particular strength of this study is that GTV delineation using ^{18}F -FLT and ^{18}F -FDG PET was validated against pathologic findings. Various normal tissue parameters, such as mean lung dose and mean heart dose, were improved using ^{18}F -FLT PET. The authors noted that ^{18}F -FLT PET should be used cautiously for esophageal radiation planning until these findings have been validated.

^{18}F -FDG PET for treatment response assessment

Treatment for esophageal cancer, similar to that for other solid malignancies of the thorax, depends on the stage of the malignancy at the time of diagnosis. Although patients with stage IV disease do not benefit from surgical resection, studies have shown that most patients with stages 0-III esophageal cancer will benefit from surgical intervention. The timing of surgical intervention and schedule of associated chemotherapy and radiation will vary depending on the stage of disease. For example, those with stage 0 esophageal cancer or stage I esophageal cancer with a T1 lesion (no invasion of muscularis propria) often undergo surgery as a first-line treatment. However, a survival benefit and lower recurrence rates have been shown in those with more locally advanced disease who respond to concurrent chemotherapy and radiation therapy prior to surgical resection (72-75). Local failure rates after CRT can exceed 50% (3,4). Nonresponders are exposed to the toxic side effects of CRT therapy while appropriate surgical therapy is delayed (76-78). Therefore, it is important to be able to differentiate responders from nonresponders early during treatment so that future management can be optimal for each patient.

Invasive, minimally invasive, and noninvasive methods are available to assess treatment response. Endoscopic biopsy is limited in this effort, because it samples only the most superficial layers of mucosa; thus, biopsy may miss superficial in situ tumor as a result of sampling error, and cannot accurately determine the presence of residual nodal disease. In one large study of 118 patients with negative endoscopic biopsy after neoadjuvant therapy, only 37 patients (31.4%) demonstrated a complete pathologic response after esophagectomy (79). Similar findings were seen in a smaller study with 52 patients with negative endoscopic biopsies, 40 of whom (77%) had residual disease at resection (80). Given these limitations of biopsy, noninvasive methods have been used to help assess for residual disease after neoadjuvant therapy.

Multiple noninvasive or minimally invasive imaging procedures are used to evaluate treatment response after neoadjuvant therapy and include CT, EUS, and ^{18}F -FDG PET. Although CT is an important tool in evaluating treatment response in many thoracic malignancies, its sensitivity (33-55%) and specificity (50-71%) in esophageal cancer after treatment are relatively poor (81). This is likely the result of the infiltrative growth pattern of esophageal cancers, which makes accurate measurements difficult, especially when tumors are small or extend into the stomach. This can limit the ability to assess response using the Response Evaluation Criteria in Solid Tumors criteria (82). Assessing treatment response can become even more challenging in the setting of radiation therapy, where inflammation, edema, and scarring can be difficult to differentiate from residual esophageal disease (*Figure 1*) (83). In addition, because many newer cancer therapies are cytostatic instead of cytotoxic, good tumor response may occur without a major reduction in tumor size (84).

By providing information on the metabolic activity of tumor cells, ^{18}F -FDG PET has become a powerful tool in assessment of treatment response in malignancies throughout the body. In one large meta-analysis assessing the performance of ^{18}F -FDG PET after CRT in patients with esophageal cancer, sensitivities and specificities of PET ranged from 71% to 100% and 55% to 100%, respectively (81).

Given that the metabolic change on PET imaging is an important indicator of tumor response, new criteria were created to refine and validate quantitative approaches to monitoring PET tumor response (84). PET Response Criteria in Solid Tumors (PERCIST) is used to evaluate tumor response through quantitative assessment of changes in metabolic activity. The primary measurement of

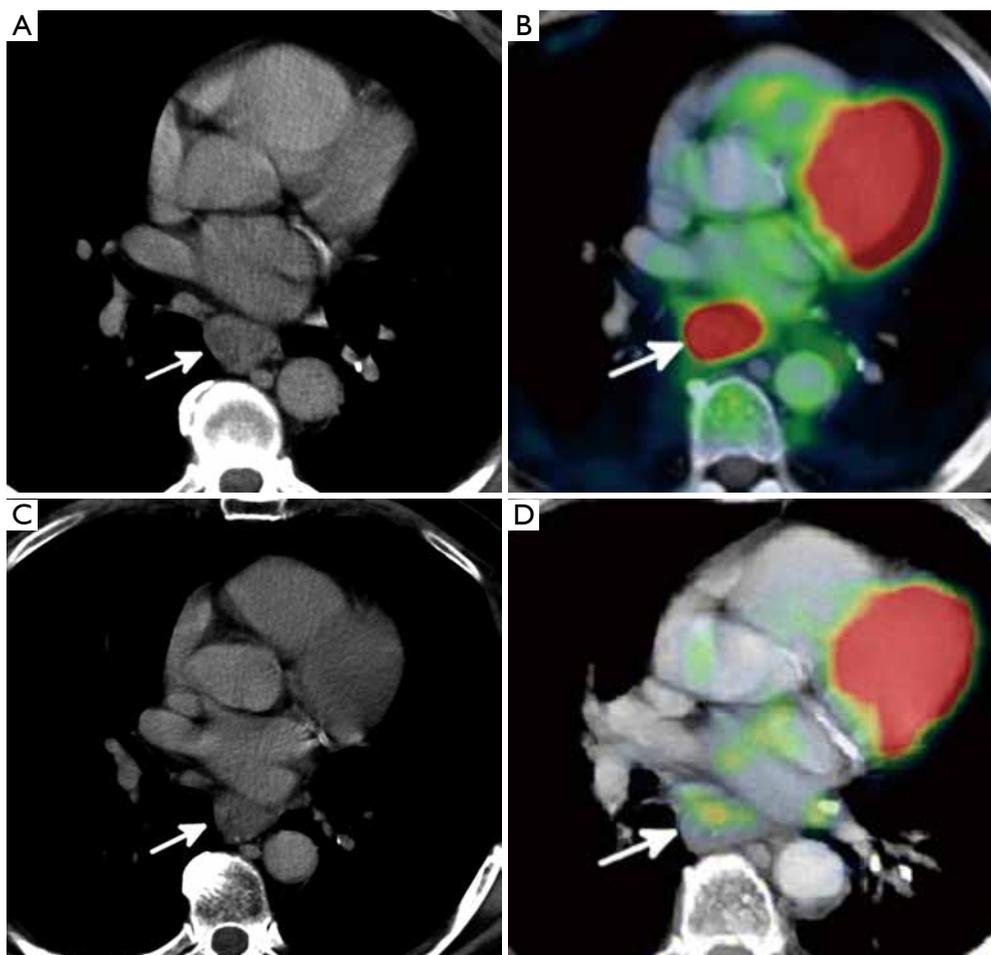


Figure 1 Pretreatment and posttreatment imaging in a 61-year-old man with stage II esophageal cancer. (A) Pretreatment CT showing focal circumferential thickening of the midesophagus (arrow); (B) PET/CT acquired on the same day showing intense uptake in the area of thickening (arrow) secondary to tumor; (C) posttreatment CT scan after concurrent chemotherapy and radiation therapy prior to esophagectomy showing persistent thickening of the midesophagus (arrow), nearly identical to the pretreatment scan; (D) PET/CT acquired on the same day showing near-complete absence of metabolic uptake in the area of residual thickening (arrow). Histopathologic analysis after esophagectomy found no viable tumor in the specimen (complete pathologic response), although areas of radiation-induced inflammation were noted, accounting for increased uptake on posttreatment PET/CT. PET, positron emission tomography; CT, computed tomography.

metabolic activity is the SUV, which is calculated by dividing metabolic activity by the injected dose and body weight. For PERCIST criteria, the SUV is corrected for lean body mass (SUL), because this metric is less susceptible to variations in the patient's body weight (85). Metabolic response using PERCIST criteria is determined by assessing changes in the peak SUL, measured by drawing a spherical region of interest 1.2 cm in diameter (which correlates to a voxel size of 1 cc) over the area of greatest uptake in the tumor. It is important to note that the peak SUL measurement on repeat imaging may be placed on a different area within

a tumor or in a different lesion altogether when assessing tumor response (57).

Based on changes in peak SUL, PERCIST defines four categories of treatment response. In complete metabolic response, the metabolic uptake in all lesions is less than the average SUL of liver and equal to normal surrounding tissue SUL (Figure 2). Partial metabolic response is defined as a >30% decrease in peak SUL (Figures 1 and 2). Progressive metabolic disease is defined as is >30% increase in the peak SUL. Stable metabolic disease occurs when PET findings do not meet any of these criteria. Recent studies have

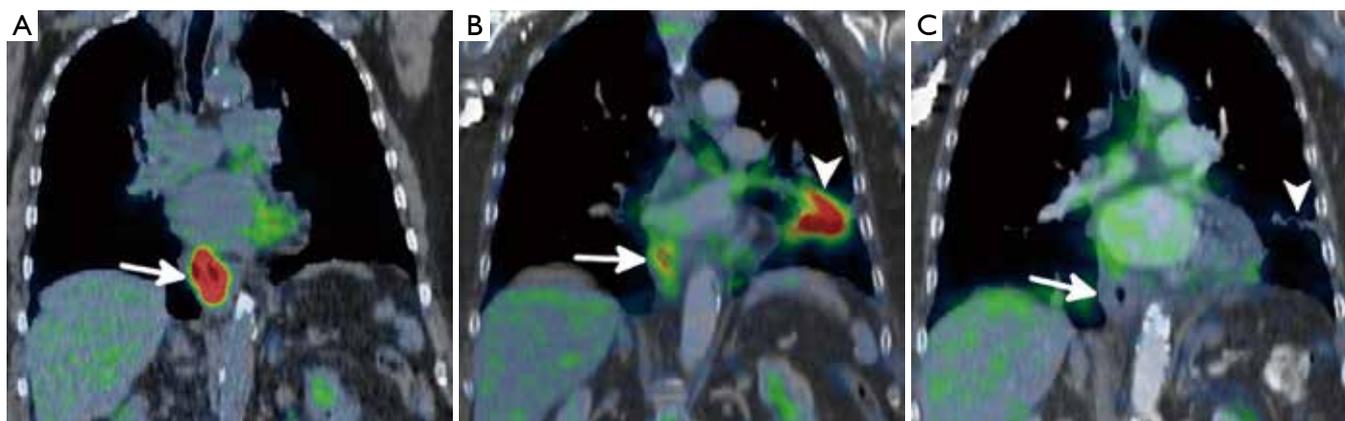


Figure 2 Progression of metabolic response on PET/CT during course of chemotherapy and radiation therapy in a 77-year-old man with a distal esophageal cancer. (A) Pretreatment PET/CT showing distal circumferential thickening of the esophagus with avid FDG uptake (arrow) and an $SUV_{max}=14.8$; (B) posttreatment PET/CT obtained 4 weeks after initiation of concurrent chemotherapy and radiation therapy (CRT) demonstrating a significant decrease in thickness of the distal esophagus as well as a marked reduction in FDG uptake (arrow), with an $SUV_{max}=4.6$, consistent with a partial metabolic response. The area of intense uptake in the left lower lobe (arrowhead) was secondary to a bacterial pneumonia; (C) posttreatment PET/CT scan acquired 12 weeks after initiation of CRT, demonstrating mild persistent thickening of the distal esophagus with complete absence of FDG uptake (arrow), consistent with a complete metabolic response. The left lower lobe pneumonia has also resolved, although a small amount of residual scarring (arrowhead) is visible. Histopathologic examination after esophagectomy showed no residual tumor. PET, positron emission tomography; CT, computed tomography.

shown that PERCIST criteria are an independent predictor of survival in those with advanced esophageal cancer (82).

Although PET imaging is a strong noninvasive tool for assessment of treatment response in patients with esophageal cancer, it is by no means infallible. Increased ^{18}F -FDG uptake can be seen in any process that leads to an increased metabolic rate, such as infection or inflammation (Figure 2). Because radiation therapy leads to direct esophageal injury, subsequent inflammation and ulceration will often demonstrate increased uptake on PET imaging and can be mistaken for residual tumor (Figure 1) (86,87). Because radiation esophagitis usually begins 2 weeks after initiation of therapy and is more common with higher radiation doses, evaluating treatment response within the first 2 weeks of treatment, before esophagitis has had time to develop, may be more accurate and less prone to false-positive findings (88).

The accuracy of PET imaging can be limited by respiratory motion artifact, which is greatest at the level of the diaphragm (Figure 3), and has been reported to occur in up to 84% of patients undergoing PET/CT (89,90) This can lead to quantitative inaccuracies in the calculation of SUV_{max} by up to 50%, which can lead to misalignment of 2-4.5 cm between the CT and PET (91). These artifacts can be counterbalanced by incorporating respiratory-gated

CT imaging or volume-average CT imaging (88,89,91,92).

PET is also limited because metabolic response is determined by assessing only a small focal area with the most intense tracer uptake. However, this fails to evaluate the entire tumor; recent studies have emerged suggesting that spatial PET/CT features, including tumor volume, tumor shape, total glycolytic volume, and spatial patterns, are more informative than the traditional response measure of SUV_{max} in various tumors (41,93).

^{18}F -FDG PET and response during treatment

Many patients with locally advanced esophageal cancer are referred to neoadjuvant therapy with either chemotherapy alone or CRT because of the potential OS benefit (2). However, it is well recognized that individual patient response to neoadjuvant therapy is variable, and it has been suggested that only 40-50% of patients will have a significant response to neoadjuvant therapy (94). Therefore, some patients may experience treatment-related toxicity without any significant benefit. Individualizing treatment to maximize treatment effect and minimize toxicity using noninvasive parameters would be ideal, and attempts have been made to correlate findings on ^{18}F -FDG PET with clinical and pathologic outcomes.

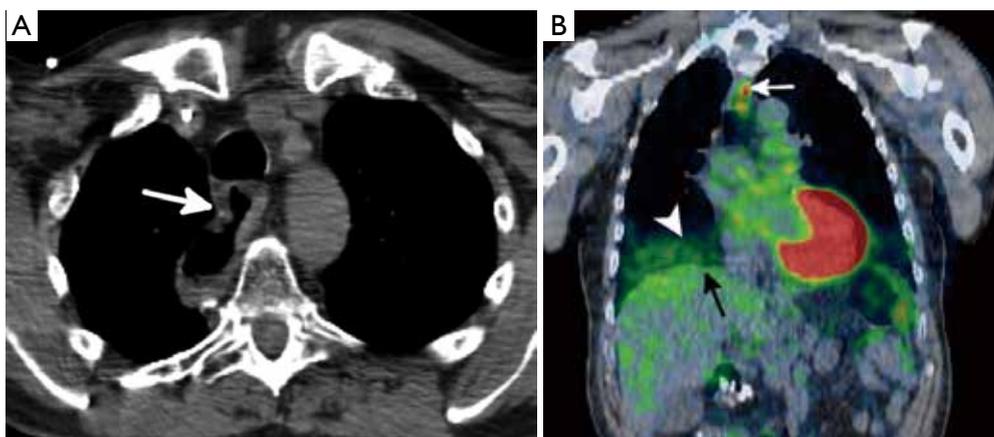


Figure 3 Local recurrence of esophageal cancer after esophagectomy. (A) Axial CT image from a PET/CT scan, showing minimal thickening of the esophagus at the anastomotic site (arrow) that was not prospectively detected; (B) fused coronal PET/CT showing uptake in the thickened portion of the esophagus at the anastomotic site (white arrow). Biopsy confirmed recurrent adenocarcinoma in this 55-year-old man. Misregistration is apparent between the physiologic liver uptake on the PET image (arrowhead) and the anatomic location of the liver (black arrow) on the study. PET, positron emission tomography; CT, computed tomography.

Weber *et al.* published data in 2001 suggesting that locally advanced esophageal cancer patients receiving neoadjuvant chemotherapy could be stratified into metabolic responders and nonresponders based on ^{18}F -FDG PET response and that this differentiation was directly correlated to disease control and survival (95). Patients underwent ^{18}F -FDG PET imaging prior to treatment and 14 days after starting cisplatin-based chemotherapy. A dramatic difference in tracer uptake was seen in responders (54%) and nonresponders (15%), and the authors proposed an optimal cutoff value to be 35% reduction in initial ^{18}F -FDG uptake. This cutoff was later prospectively validated by Ott *et al.* (43). Significantly more resected patients who were metabolic responders had either histopathologically complete or subtotal tumor regression than those who were not responders (53% and 5%, respectively). Metabolic response also predicted for longer time to disease progression ($P=0.01$) and longer overall survival ($P=0.04$).

Wieder *et al.* performed a similar assessment in 27 patients with esophageal SCC who underwent ^{18}F -FDG PET imaging at baseline and 14 days after initiation of neoadjuvant therapy (48). Unlike the study by Weber *et al.*, patients in this study received neoadjuvant radiation therapy in addition to chemotherapy, and the definition of metabolic response was slightly different ($\geq 30\%$ decrease in SUV uptake). Similar to the results of the study by Weber *et al.*, early metabolic responders had improved survival ($P=0.011$) and significant histopathologic response was

more common than in nonresponders (44% and 21%, respectively; $P=0.0055$). It is important to be aware that radiation therapy can induce inflammation that may cause false overestimation of true uptake in actual tumor during treatment (96). Preclinical data suggest that ^{18}F -FLT PET may allow for better differentiation between inflammation and residual tumor during neoadjuvant therapy (97,98).

The phase II MUNICON (metabolic response evaluation for individualisation of neoadjuvant chemotherapy in esophageal and esophagogastric adenocarcinoma) trial evaluated the feasibility of using early ^{18}F -FDG PET response to guide therapy (50). Patients classified as metabolic responders, defined by a $\geq 35\%$ reduction in metabolic activity between pretreatment imaging and imaging performed 14 days after initiation of therapy, continued with neoadjuvant therapy prior to surgery. However, metabolic nonresponders proceeded directly to surgery in an attempt to spare these patients from chemotherapy-related toxicity. After a median follow-up of 2.3 years, median event-free survival (EFS) and OS in the nonresponders were 14.1 and 25.8 months, respectively. For metabolic responders, median event-free survival was 29.7 months and median OS was not reached, both of which were significantly higher than for metabolic nonresponders. Significant pathologic treatment effect ($<10\%$ residual tumor) was noted in 58% of responders, whereas no such effect was seen in the nonresponders. Metabolic responders who also achieved a major histologic response had significantly higher EFS

[hazards ratio (HR) 3.03 (1.28-7.16); $P=0.006$] and OS [HR 4.55 (1.37-15.04); $P=0.004$] than the 21 metabolic responders who did not achieve a significant histologic response.

The MUNICON II trial was devised to determine whether metabolic nonresponders would have improved outcomes with the addition of salvage neoadjuvant CRT when $<35\%$ decrease in SUV uptake was identified on an ^{18}F -FDG PET scan obtained at day 14 (55). Metabolic nonresponders switched from neoadjuvant chemotherapy to concurrent cisplatin and 5-fluorouracil and radiation therapy (32 Gy in 1.6-Gy fractions given twice a day). Metabolic responders continued to receive neoadjuvant chemotherapy for 3 months prior to surgical resection and did not receive radiation therapy. The primary endpoint was to increase the margin negative resection (R0) rate for metabolic nonresponders from 74% to 94%. Although R0 resections were obtained in 82% of the metabolic responders and 70% of the metabolic nonresponders, the primary endpoint was not met. One-year progression-free survival was higher among responders than nonresponders (74% and 57%, respectively; $P=0.035$). Median OS was lower in the nonresponders than in the whole group (18.3 and 38.3 months, respectively), and the median OS had not been reached for responders. The authors noted that although the radiation dose of 32 Gy was relatively low, a major histopathologic response was observed in 26% of the metabolic nonresponders who underwent CRT. As mentioned previously, none of the metabolic nonresponders in the first MUNICON trial had a major histopathologic response after chemotherapy alone, raising the possibility of cell killing as a factor in a subset of patients who received CRT. The authors concluded that salvage neoadjuvant CRT led to local remissions in a select group of patients; however, systemic disease continued to influence clinical outcomes and survival.

A recent Cancer and Leukemia Group B 80302 phase II trial (NCT00316862) is looking at whether giving induction chemotherapy of cisplatin and irinotecan followed by CRT therapy will have any influence on pathologic complete response rate at time of surgery. One of the secondary objectives is to evaluate for potential response or progression of disease during induction chemotherapy with ^{18}F -FDG PET. Thus, patients will receive ^{18}F -FDG PET imaging at baseline, 15-19 days after the start of induction chemotherapy, and within 7 days before beginning chemoradiotherapy. The results of this study are not yet available, but could potentially provide additional

information about treatment response related to pathologic response.

^{18}F -FDG PET and response after treatment

Although assessment of response during treatment is promising, the utility of posttreatment ^{18}F -FDG PET imaging has been more thoroughly studied. Most of these studies are single-institution retrospective reports with fairly small patient numbers, but they collectively suggest that uptake on ^{18}F -FDG PET after neoadjuvant treatment is associated with long-term outcomes and histopathologic outcomes (99-102) (Table 2). A recently published systematic review of 26 studies including 1,544 esophageal and GEJ cancer patients who received neoadjuvant therapy suggested that posttreatment ^{18}F -FDG PET can effectively predict long-term outcomes (63). In fact, the pooled HR for complete metabolic response compared to no response was 0.51 for OS (95% CI, 0.4-0.64; $P<0.0001$) and 0.47 for DFS (95% CI, 0.38-0.57; $P<0.0001$).

As previously discussed, investigators have questioned whether ^{18}F -FDG PET metrics other than SUV_{max} are more useful for evaluating treatment response after neoadjuvant therapy. A recent study from the University of Maryland extracted comprehensive spatial-temporal ^{18}F -FDG PET features from pre- and post-CRT PET scans in an attempt to predict pathologic tumor response in 20 esophageal patients (4). An area under receiver operating characteristic curve (AUC) value was used to quantify the ability of each feature to predict pathologic tumor response. In addition to SUV_{max} decline, two PET intensity features (mean SUV decline and skewness) and three PET texture features (inertia, correlation, and cluster prominence) were significant predictors of pathologic response. These novel PET features either had the same or higher AUCs than SUV_{max} . Recent data published by the same group using a support vector machine and logistic regression models suggest that these spatial-temporal ^{18}F -FDG PET features may more accurately predict pathologic tumor response when combined with conventional PET/CT measures and clinical parameters (93).

When a patient undergoes esophagectomy, PET/CT is often used to monitor for recurrent or metastatic disease. Local disease recurrence most commonly occurs near the anastomotic site and may be a subtle finding on CT alone (Figure 3). In addition, PET can often detect distant metastatic disease, which can occur in 8-17% of patients on restaging imaging, before disease becomes apparent

Table 2 Retrospective studies evaluating metabolic response during or after neoadjuvant treatment in esophageal cancer patients

Study	No.	Tumor histology	Timing of 2nd PET	Chemo	Mean RT dose	Definition of metabolic response	% of metabolic responders with major histological response vs. nonresponders	P value	Survival of metabolic responders vs. nonresponders	P value
Swisher et al., 2004 (103)	103	90 AC, 13 SCC	3-5 wk post CRT	CRT or induction [irinotecan + taxotere + 5FU] then CRT	50.4 Gy	Post-CRT SUV <4	SUV ≥ 4 had highest accuracy for predicting pathologic nonresponse: 76%	NR	18-mo survival: 77% vs. 34%	0.01
Konski et al., 2007 (71)	81	18 AC, 7 SCC	4-6 wk post CRT	At discretion of medical oncologist	Preop: median 45 Gy, (7.2-50.4 Gy); Definitive: median 50.4 Gy (7.2-62.08 Gy)	Percent SUV change >32.3%	25% with pCR for total group	NS	Median OS for trimodality therapy: 16.7 mo vs. definitive CRT: 5.2 mo	NR
Mamede et al., 2007 (104)	25	22 AC, 3 SCC	22.3 \pm 14.5 d	Depended on clinical trial (cis + irinotecan, cis + irinotecan + cetuximab, cis + others)	50.4 Gy	Average percent SUV change >32.3%	Sensitivity of pathologic response 75% and specificity 62.5%	AUC 0.64	PostCRT SUV _{max} ≤ 4.35	0.0196
Monjabez et al., 2010 (105)	163: 88 trimodality therapy, 75 definitive CRT	122 AC, 42 SCC	Post CRT but exact time NR	Varied: 5FU + platinum, carboplatin/taxol, FU alone, capecitabine	Median: 50.4 Gy	Post CRT SUV ≤ 3	53% vs. 33%	NS	Median OS: 29.7 mo vs. 15.9 mo	0.01
Sharma et al., 2011 (106)	40	26 AC, 14 SCC	4-6 wk post CRT	At discretion of medical oncologist	Median: 50.4 Gy	Decrease in postCRT SUV	NR	NR	DFS: HR 1.3, 95% CO =1.03-1.6	0.03
Jayachandran et al., 2012 (107)	37	27 AC, 10 SCC	Median 32 d after completing CRT (range 2-58 d)	At discretion of medical oncologist	Median: 50.4 Gy	MTV _{2,5Post} ≤ 7.6 vs. >7.6 cm ³ rMTV ₂ ≤ 0.39 vs. >0.39	71% pCR for total group of resected patients: 67% pCR in SCC, 39% pCR in AC	MTV _{2,5Post} P=0.01; TGA _{2,5Post} P=0.025	2-y OS MTV _{2,5Post} ≤ 7.6 cm ³ 84% vs. 29% >7.6 cm ³ ; rMTV ₂ ≤ 0.39 vs. >0.39 for rMTV ₂ >0.39, P=0.04	MTV _{2,5Post} P=0.007; rMTV ₂ ≤ 0.39 P=0.04

Abbreviations: AC, adenocarcinoma; SCC, squamous cell carcinoma; 5FU, 5-fluorouracil; cis, cisplatin; RT, radiation therapy; CRT, chemoradiation therapy; SUV, standard uptake value; OS, overall survival; NR, not reported; CSS, cancer-specific survival; pCR, pathologic complete response; DFS, disease-free survival; NS, not significant; mCR, metabolic complete response; HR, hazard ratio; AUC, area under curve; MTV, metabolic tumor volume; rMTV, ratio of MTV_{PostCRT}/MTV_{PreCRT}; TGA, total glycolytic activity.

on standard anatomic imaging (83,88). Although disease recurrence after esophagectomy has a poor prognosis, therapy can be tailored toward palliation to improve patient symptoms and quality of life. Those who develop local or distal disease may be candidates for palliative therapy, including CRT, if adjuvant therapy has not been previously administered.

Conclusions

Advances in molecular imaging have led to dramatic improvements in care for esophageal cancer patients, ranging from diagnosis at an earlier and more manageable stage to altering treatment based on the degree of treatment response. Although ^{18}F -FDG PET is the most widely used molecular imaging technique, its optimal utilization in esophageal cancer management is still unclear. The Cancer and Leukemia Group B 80302 trial may provide additional information about how to best incorporate ^{18}F -FDG PET at various time points in the treatment of esophageal cancer.

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Current management of esophageal cancer

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Abstract: Management of esophageal cancer has evolved since the two last decades. Esophagectomy remains the primary treatment for early stage esophageal cancer although its specific role in superficial cancers is still under debate since the development of endoscopic mucosal treatment. To date, there is strong evidence to consider that locally advanced cancers should be recommended for a multimodal treatment with a neoadjuvant chemotherapy or a combined chemoradiotherapy (CRT) followed by surgery. For locally advanced squamous cell carcinoma or for a part of adenocarcinoma, some centers have proposed treating with definitive CRT to avoid related-mortality of surgery. In case of persistent or recurrent disease, a salvage esophagectomy remains a possible option but this procedure is associated with higher levels of perioperative morbidity and mortality. Despite the debate over what constitutes the best surgical approach (transthoracic versus transhiatal), the current question is if a minimally procedure could reduce the perioperative morbidity and mortality without jeopardizing the oncological results of surgery. Since the last decade, minimally invasive esophagectomy (MIE) or hybrid operations are being done in up to 30% of procedures internationally. There are some consistent data that MIE could decrease the incidence of the respiratory complications and decrease the length of hospital-stay. Nowadays, oncologic outcomes appear equivalent between open and minimally invasive procedures but numerous phase III trials are ongoing.

Keywords: Esophagectomy; esophageal cancer; minimally invasive esophagectomy (MIE); neoadjuvant therapy; mucosectomy

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Introduction

The epidemiology of esophageal cancer has radically changed in the last fifty-years in the Western world. Changes in the predominant type of squamous cell carcinoma (SCC) to adenocarcinoma, disparities between different ethnicities, and the exponential increase in incidence rates of adenocarcinoma have established esophageal cancer as a major public health problem requiring urgent attention specifically in North America (1). It ranks sixth among all cancers in mortality (2) and it is one of the least studied and deadliest cancers worldwide because of its extremely aggressive nature and poor survival rate. The overall 5-year relative survival is 17% (1). Reason to explain this poor outcome stands on the fact that esophageal cancer is diagnosed at rather late stage. Overall at the time

of presentation, more than 50% of patients have metastatic disease, near 30% have a locally advanced stage and less 20% have a localized stage that can be cured (1-3).

Management of non metastatic esophageal cancer has evolved since the two last decades. With the advanced of CT-scan, development of the endoscopic ultrasound (EUS) and the emergence of FDG-PET, the assessment of the disease has refined year after year. To date, the staging of the disease is of paramount importance and every treatment decisions should routinely be based on multidisciplinary discussion in the tumor board.

Esophagectomy remains the primary treatment for early stage esophageal cancer although its specific role in superficial (T1A) cancers is still under debate since the development of endoscopic mucosal treatment. There is strong evidence to consider that locally advanced cancers

should be recommended for a multimodal treatment with a neoadjuvant chemotherapy or a combined chemoradiotherapy (CRT) followed by surgery (4,5). However, there are differences in the perceived role of surgery in achieving local control between Western and Eastern surgeons, leading to the considerable differences in the use of multidisciplinary therapy. For locally advanced SCC or for a part of adenocarcinoma, some oncologists have proposed treating with definitive CRT to avoid the mortality of surgery. In case of persistent or recurrent disease, a salvage esophagectomy is a possible option but this procedure remains associated with higher levels of perioperative morbidity and mortality.

There is a global agreement over the oncological principles of surgery (6). Surgical resection must consist in a radical, complete, R0, en-bloc esophagectomy associated to an extended two-field lymphadenectomy (7-10). Patients requiring surgical treatment of esophageal cancer should be referred to high-volume centers, especially those with established care pathways or enhanced recovery programs to improve outcomes including morbidity, mortality, survival, and quality of life. Despite the debate over what constitutes the best surgical approach (transthoracic versus transhiatal) (10), the current question is if a minimally procedure could reduce the perioperative morbidity and mortality without jeopardizing the oncological results of surgery. Since the 1990', minimally invasive esophagectomy (MIE) or hybrid operations are being done in up to 30% of procedures internationally. There are consistent data that minimally invasive procedures could decrease the incidence of respiratory complications and decrease length of hospital-stay. At this point, oncologic outcomes appear equivalent between open and minimally invasive procedures, however numerous clinical phase III are ongoing.

Staging and preoperative assessment

Current management of esophageal cancer is mainly based on exhaustive preoperative assessment. The accuracy of the preoperative staging is essential as the decisions of the tumor board regarding the application of multimodal treatment will be directed according to the accuracy and the specifics of the clinical staging assessment. Standardized assessment of a patient being considered for a curative treatment for early or for advanced esophageal cancer includes upper endoscopy, high-resolution contrast CT scan, FDG-PET scan and EUS (6).

CT scan provides useful information regarding

longitudinal extension of the tumor especially with the trachea and the aorta (T4B disease). Suspicions of direct invasion of the thoracic aorta or the tracheobronchial tree should be confirmed with MRI scanning and bronchoscopy respectively. FDG-PET scan provides the most accurate information regarding potential metastatic disease. As a result, FDG-PET scan increases the accuracy for occult metastasis as much as 20% over CT scanning alone (11). Moreover FDG-PET is considered as a reliable technique for post-treatment reassessment and to appreciate the response to neoadjuvant therapy (12). However, its specific role in this situation has to be confirmed (13). EUS provides excellent information with respect to depth of invasion (T status), but its ability to discriminate subtle differences in T1 disease, i.e., T1a versus T1b, is less exact (14). The meta-analysis from Young *et al.* comparing EUS and endoscopic mucosal resection (EMR) staging demonstrated that EUS predicted accurate depth of tumor invasion in only 56% of patients (14). Therefore, especially if endoscopic treatment is contemplated, staging should include EMR, and any indication of submucosal invasion should lead to recommendation for surgical resection in appropriate candidates. Another limit of the EUS is its ability to provide accurate staging after neoadjuvant therapy. In this context EUS is strongly limited due to post-treatment adherence and fibrosis (15). EUS remains the best modality for assessing locoregional lymph node (LN) involvement especially when fine needle aspiration biopsy of suspicious nodes can be selectively applied to provide specific pathologic information and staging (16).

Early stage cancer

Incidence and definitions

Esophageal adenocarcinoma has seen a dramatic increase in Europe and in the United States over the last 20 years, whereas the rates of SCC of the esophagus has remained relatively stable or decreasing in Western countries (1-3). This epidemiologic change is mainly due to the increase of the Barrett's Esophagus (BE) in the general population. It is currently estimated that 10% of patients with chronic reflux have BE (1-3). Today, incidence of BE in the USA population may be as high as 5.6% (17,18). In cases of patients with high-grade dysplasia (HGD), up to 30% will develop EAC within five years. Endoscopic surveillance of patient with chronic reflux or known to have BE would explain that 20% of all EAC are detected as an early stage

(T1) with disease confined to the mucosa or submucosa (17,18). For SCC, clinical stage I disease accounts for only about 20% of all detected esophageal cancers in Japan (19).

Early stage cancer includes T1a and T1b according to the 7th edition of the AJCC (20). The T1a includes HGD and intramucosal cancer limited to the muscularis mucosa. T1b includes cancer invading muscularis mucosa and extending to the submucosa. A more comprehensive subclassification of early esophageal cancer has been proposed with mucosal disease and submucosal disease divided into three categories respectively (m1-3, and sm1-3) based on depth of invasion (21-23).

HGD and intramucosal tumor

In HGD or in T1a cancer (including m1-3 tumor), the risk of LN disease correlates to the depth of involvement of the cancer and to the histological type. For HGD or for intramucosal cancer, a systematic review of the surgical literature, has reported the rates of occult invasive cancer in patients who were undergoing esophagectomy for prophylactic treatment of HGD. The pooled average was 12.7% in the 441 patients who underwent esophagectomy for HGD among 23 studies (24). The rate of LN involvement for HGD and for intramucosal cancer is estimated between 0 to 2%. A large retrospective review of 126 T1 adenocarcinomas, of which 75 were T1a and 51 T1b, revealed N+ disease of 1.3% and 22% respectively (22). Data on superficial SCC have shown that m3 cancer, or disease extending to the muscularis propria has upwards of 6% risk of LN metastasis (21). Additional characteristics which impact the risk of LN involvement include vascular invasion, tumor size, and the degree of tumor differentiation.

Given the low risk of LN involvement in mucosal disease, there is a general agreement of the reliability and of the efficiency of the endoscopic management of early stage esophageal cancer confined to the mucosa (T1a). Endoscopic resection is, therefore, a potentially curative treatment for such lesions. Initially, options included argon beam coagulation, laser, and photodynamic therapy. More recently, EMR, endoscopic submucosal dissection (ESD), radiofrequency ablation (RFA), cryotherapy, and free-hand mucosal resection have been increasingly applied (25). Because current data on what constitutes the best treatment are limited, it seems not possible at the present time to favor a technique compared to another (26). However, there is global agreement that all visible lesions have to be removed by EMR for definitive histopathological staging and to

ensure adequacy of resection margins. This agreement stands on the poor accuracy of EUS to discriminate between T1a and T1b. EMR remains the sole technique able to stage the degree of invasion into the esophageal wall. For intramucosal cancer associated to BE, eradication of the metaplastic mucosa must occur to protect against potential lesion development. For BE segments that measure ≤ 5 cm and harbor HGD or intramucosal cancer, an EMR approach is used. For patients with BE segments > 5 cm, all focal lesions have to be resected with EMR or ESD and the remaining flat BE is ablated using RFA to decrease the rate of stricture formation (25).

Submucosal and T2 tumor

In contrast to T1a tumor where LN invasion is uncommon, invasive cancers (T1b and T2) which penetrate into the submucosa, have a high risk of LN involvement. The invasion of the muscularis mucosa seems to be of paramount importance for the dissemination to the submucosal lymphatic network. There is debate over what constitutes the limit of endoscopic resection. Lesions extending into only the most superficial submucosal layer staged sm1 seem to be critical in this context. A clinical series reported by Manner *et al.* demonstrated that EMR could be used to treat "low-risk" submucosal sm1 tumors with low-grade tumor differentiation (27). With a mean follow-up of five years, there were no tumor-related deaths. However, two series reported high rate of nodes positive in sm1 tumor: 16.5% for Leers and 21% for Sepesi (22,28). For tumor invading beyond sm1, existing literature demonstrates that the incidence of LN involvement in patients with T1b cancer ranges between 21% and 50% (22,28-30). For T2 lesion, a review of the outcomes of this subcategory demonstrated that the current approaches to clinical staging resulted in accurate pathologic stage in only 13% of cases. Of the patients inaccurately staged, 63% were overstaged and 37% were understaged. Subsequent recommendations for treatment of cT2N0M0 patients involved proceeding directly to surgery as this would currently be considered a definitive treatment in patients who are accurately staged or overstaged. Patients who are discovered to be understaged can be considered for adjuvant therapy (31).

There is a global agreement for T1b and for T2 cancer to proceed to surgical resection without neoadjuvant therapy that would have a negative effect on survival in this context (32). Indications for esophagectomy in early stage include all incomplete EMR and all failure of endoscopic

Table 1 High-risk characteristics leading to consider esophagectomy for early stage tumor; adapted from Konda *et al.* (24)

Endoscopic characteristics
Long-segment BE
Visible lesions with high risk endoscopic characteristics
Polypoid mass
Excavated lesions or ulcers
Evidence of LN involvement by EUS + FNA
Pathological characteristics
Multifocal HGD
Evidence of submucosal invasion (T1B)
Deeper two thirds of the submucosa carries high risk of LN metastasis
Moderately or poorly differentiated tumor
Evidence of lymphatic channel invasion
Evidence of vascular invasion
Evidence of neural invasion
Treatment characteristics
Failure of ablation of remainder for Barrett's epithelium
Incomplete endoscopic mucosal resection
Piecemeal endoscopic resection (as opposed to <i>en bloc</i> resection)
Longer time to achieve eradication
BE, Barrett's esophagus; EUS, endoscopic ultrasound; FNA, fine needle aspiration; HGD, high grade dysplasia; LN, lymph node.

therapy. Invasion of tumor into the submucosa is still considered a strong indication for esophagectomy, although invasion into the superficial third of the submucosa does not carry the same LN metastasis risk as the deeper two thirds, and potentially could be treated endoscopically (33,34). The risk factors to be considered in the management strategy are listed in *Table 1*. These risk factors need to be weighed with patient characteristics, patient preferences, available surgical expertise, available endoscopic expertise, and surgical approach options to decide if esophagectomy or endoscopic therapy is appropriate for each case. In this context, a vagal-sparing esophagectomy has been advocated as an alternative to standard resection. Vagal-sparing esophagectomy involves removing the esophagus from the mediastinum with a stripping device that leaves the vagal nerves and the LN in place. In appropriate candidates, vagal-sparing esophageal resection has demonstrated advantages over standard approaches including maintaining meal size,

gastric emptying, and BMI (35,36). However, few data are available to promote the technique.

Indication of neoadjuvant therapy in early stage cancer

Esophagectomy remains the standard treatment of early stage cancer. There are very few data on the benefits of a neoadjuvant treatment for very localized esophageal cancer. The Fédération Francophone de la Cancérologie Digestive (FFCD) 9901 assessed whether preoperative CRT improves outcomes for patients with localized (stages I or II) esophageal cancer (32). From 2000 to 2009, 195 patients were randomized in 30 French centers: 98 were assigned to surgery alone and 97 to neoadjuvant CRT group. Postoperative morbidity rates were 49.5% in surgery group *vs.* 43.9% in CRT group (P=0.17). The 30 day-mortality rates were 1.1% in surgery group *vs.* 7.3% in CRT group (P=0.054) respectively. After a median follow-up of 5.7 years, the median survivals were 43.8 in surgery group *vs.* 31.8 months in CRT group [HR 0.92; 95% confidence interval (CI), 0.63-1.34; P=0.66]. The conclusion of this trial was that neoadjuvant CRT with cisplatin and fluorouracil does not improve overall survival but enhances postoperative mortality rate for patients with stage I or II esophageal cancer compared with surgery alone.

Locally advanced esophageal cancer

Resectable locally advanced esophageal cancer refers to T3-T4A or documented LN involvement (N+ disease) according to the 7th edition of the AJCC (20). At the moment of the diagnosis, vast majority of esophageal tumor are found to be locally advanced cancer. Traditionally, locally advanced esophageal SCC and adenocarcinoma have been managed with surgical resection. Indeed, esophagectomy with radical lymphadenectomy seems to be the best treatment in terms of achieving local control. However, survival was poor, and metastatic disease or locoregional recurrence developed in many patients after surgery. Poor outcomes after surgery alone and analyses of disease recurrence patterns have prompted the addition of adjuvant treatment. However, because esophagectomy is a major procedure with a high rate of postoperative morbidity, multimodal strategy has shifted to neoadjuvant treatment. In some cases and especially for SCC, most oncologist advocate a definitive CRT as first line treatment and reserve surgery as a second therapeutic option in case of failure of the definitive CRT. In this case, the surgery

consists in a “salvage esophagectomy”.

Neoadjuvant chemotherapy or CRT

Radiotherapy and chemotherapy could improve survival and disease-free survival before surgery. These improvements can be seen with several aspects. Both treatments are known to improve the control of local or general disease by downstaging cancer and increasing the surgical resectability. Chemotherapy has the potential to eradicate micrometastatic disease by decreasing cancer-cell dissemination. Numerous meta-analyses have been performed to increase the accuracy of comparisons and better estimate potential benefits of neoadjuvant treatment.

Gebski *et al.* have reported a meta-analysis that evaluated pooled data from clinical trials of neoadjuvant chemotherapy and CRT including both adenocarcinoma and SCC (4). This analysis combined the results of 10 randomized trials of neoadjuvant CRT *vs.* surgery alone and 8 randomized trials of neoadjuvant chemotherapy *vs.* surgery alone in patients with locally resectable esophageal carcinoma. The hazard ratio (HR) for all-cause mortality for neoadjuvant chemotherapy was 0.90 (95% CI, 0.81-1.00; $P=0.05$), indicating a 2-year absolute survival benefit of 7%. For patients with SCC, neoadjuvant chemotherapy did not have a survival benefit [HR for mortality 0.88 (0.75-1.03); $P=0.12$]. For the adenocarcinoma group, the survival benefit was significant [HR for mortality 0.78 (0.64-0.95); $P=0.014$]. The HR for all-cause mortality with neoadjuvant CRT *vs.* surgery alone was 0.81 (95% CI, 0.70-0.93; $P=0.002$), corresponding to a 13% absolute difference in survival at two years. Analysis of the neoadjuvant CRT studies that had histology data available found a significant benefit over surgery for both histological tumour types: 0.84 (0.71-0.99; $P=0.04$) for SCC and 0.75 (0.59-0.95; $P=0.02$) for adenocarcinoma.

In 2011, Sjoquist *et al.* have published the latest updated meta-analysis (5). The inter-group analysis clearly demonstrated strong arguments for CRT compared to CT in patients with SCC or adenocarcinoma. The updated analysis contained 4,188 patients whereas the previous publication included 2,933 patients. They included all 17 trials from the previous meta-analysis and seven further studies. This updated meta-analysis contains about 3,500 events compared with about 2,230 in the previous meta-analysis (estimated 57% increase). The HR for all-cause mortality for neoadjuvant chemotherapy was 0.87 (0.79-0.96; $P=0.005$); the HR for SCC only was 0.92 (0.81-1.04; $P=0.18$) and for adenocarcinoma only

was 0.83 (0.71-0.95; $P=0.01$). The HR for all-cause mortality for neoadjuvant CRT was 0.78 (95% CI, 0.70-0.88; $P<0.0001$); the HR for SCC only was 0.80 (0.68-0.93; $P=0.004$) and for adenocarcinoma only was 0.75 (0.59-0.95; $P=0.02$). The HR for the overall indirect comparison of all-cause mortality for neoadjuvant CRT versus neoadjuvant chemotherapy was 0.88 (0.76-1.01; $P=0.07$).

The Sjoquist's meta-analysis did not include the latest published phase III trial. The “CROSS trial” compared the outcome of concurrent CRT (carboplatine,plaxitaxel and 41 Gy) followed by surgery and surgery alone (37). A pathological complete response was achieved in 47 of 161 patients (29%) who underwent resection after CRT. Postoperative complications were similar in the two treatment groups, and in-hospital mortality was 4% in both. Median overall survival was 49.4 months in the CRT surgery group versus 24 months in the surgery group. Overall survival was significantly better in the CRT group [HR 0.657 (0.495-0.871; $P=0.003$)].

To summarize, the optimum neoadjuvant treatment regimen has not been established, because including western and eastern populations, trials used different drugs, doses, and schedules of chemotherapy and radiotherapy. However, there are strong arguments and a global agreement for patients with locally advanced esophageal cancer, that neoadjuvant CRT remains strongly recommended compared to neoadjuvant chemotherapy alone.

CRT: sequential or concomitant?

From the Gebski's meta-analysis, there was no survival benefit of sequential CRT for patients with SCC [HR for mortality 0.9 (0.72-1.03); $P=0.18$] (4). The results of sequential CRT were similar to that for patients with SCC assigned neoadjuvant chemotherapy. Concomitant CRT in patients with SCC had a significant benefit [HR for mortality 0.76 (0.59-0.98); $P=0.04$]. On this basis, the use of concomitant neoadjuvant CRT is strongly recommended compared to sequential CRT.

Neoadjuvant or adjuvant treatment?

The Japan Clinical Oncology Group has conducted randomized, two controlled trials to assess potential benefits of adding adjuvant therapy to surgery in patients with SCC: the JCOG 9204 and the JCOG 9907 (38,39). The JCOG 9204 study assessed the benefit of postoperative adjuvant CT with cisplatin plus 5-FU compared with surgery alone in

patients with resectable stage I or II esophageal cancer (38). Overall survival did not differ significantly between the groups (5-year survival rate 52% *vs.* 61%; $P=0.13$). Disease-free survival was improved significantly in the patients who received postoperative CT and especially in N+ patients. In the JCOG 9907 study, neoadjuvant CT with cisplatin and 5-FU was compared with postoperative CT with cisplatin and 5-FU in patients with clinical stage II or III esophageal cancer (39). Neoadjuvant CT was found to be superior to postoperative CT in overall survival. The 5-year survival rate was 60% in neoadjuvant group *vs.* 38% in adjuvant group ($P=0.013$). On the basis of these results, neoadjuvant chemotherapy followed by radical surgery compared to adjuvant strategy is recommended in case of locally advanced SCC.

Neoadjuvant CRT followed by surgery or definitive CRT?

The concept of a definitive CRT was introduced with the results of the Radiation Therapy Oncology Group (RTOG) 8,501 study (40). This trial compared the effect of RT alone (64 Gy) to a scheme of a concurrent CRT (cisplatin, 5-FU, and radiotherapy 50 Gy). The study included both SCC or adenocarcinoma of the esophagus. This study demonstrated the strong sensitivity of SCC to a concomitant CRT. Concomitant CRT resulted in better overall survival and decrease in local failure than RT alone. These results lead a Japanese phase II to assess the effectiveness of definitive CRT (cisplatin, 5-FU, and classic portal radiation 60 Gy) (41). A complete response (CR) was obtained in 68% with a 3-year survival rate of 46%. These results were not superior to those obtained with conventional surgical resection with or without chemotherapy. Two large randomized trials were conducted to compare definitive CRT with neoadjuvant CRT in esophageal SCC (42,43). In a study performed by the German Esophageal Cancer Study Group, the 2-year overall survival results were similar in the surgery (39.9%) and nonsurgery (35.4%) treatment groups (42). A disadvantage of neoadjuvant therapy group was early postoperative mortality, while the definitive CRT in the nonsurgery group was associated with more local relapses. These results were confirmed in another large randomized study performed by FFCD 9102 study where surgery was proposed in responders to CRT. Once again, surgery improved local control, but did not improve survival, because neoadjuvant therapy was associated with increased early mortality (43). An FFCD trial comparing systematic surgery *vs.* salvage esophagectomy in responders after a

neoadjuvant CRT is ongoing in France and it will provide an answer to this important issue.

On the basis on these results, definitive CRT or neoadjuvant CRT followed by surgery seem to have similar long-term results. Despite flaws in these studies, surgery seems to provide a better local control of the tumor but without benefit on long-term outcome. Moreover, this benefit is possible at the cost of major surgery and to the subsequent postoperative mortality.

The particularity of locally advanced signet ring cell adenocarcinoma

Nowadays, in Western countries and for unclear reasons, we assist to a dramatic increase in the incidence of the diffuse form of esophagogastric adenocarcinoma, particularly signet ring cell (SRC) tumors (44,45). Because of their infiltrating and aggressive characteristics, SRC tumors are often diagnosed at a locally advanced stage, with high propensity for peritoneal metastasis and LN invasion (46,47). The problem related to this specific histological subtype remains its innate chemoresistance suggested in gastric cancer (46). In 2010, the FREGAT (French Eso-Gastric Tumors) Working Group carried out a retrospective multicenter study in France of all consecutive esophagogastric cancer treated in 21 centers between 1997 and 2010. Reporting on more than 1,000 patients, survival was significantly shorter in the perioperative chemotherapy group compared to surgery alone, a variable identified as an independent predictor of poor survival and providing evidence of a potential chemoresistance for SRC (47). An alternative option has been suggested with the use of a neoadjuvant CRT (48). This beneficial advantage of CRT was also found in the Sjoquist's meta-analysis suggesting survival benefit when compared with surgery alone (5). Recently, the FREGAT working group demonstrated in a retrospective study comparing neoadjuvant CRT versus surgery alone in stage III advanced SRC, the benefits of such strategy. There was evidence of significant tumoral, nodal and ypTNM downstaging after neoadjuvant CRT (49). In the neoadjuvant group and in the surgery group, 3-year overall survival was respectively 51% and 21% ($P=0.002$). The disease recurrence rate was 30.4% in the CRT group compared to 59.5% in surgery group ($P=0.015$) respectively. In multivariate analysis the sole independent favorable prognostic factor identified was the administration of neoadjuvant CRT (OR: 0.41, $P=0.020$). Further trials evaluating neoadjuvant therapeutic strategies for

Table 2 Pooled-analysis of salvage esophagectomy versus planned resection; adapted from Markar *et al.* (60)

	Salvage esophagectomy N=242 (%)	Planned esophagectomy N=712 (%)	POR	CI	P
Postoperative mortality	9.5	4.1	3.02	1.64-5.58	<0.001
Anastomotic leakage	24.0	14.5	1.59	1.24-3.22	0.005
Respiratory complications	29.8	17.0	2.12	1.47-3.05	<0.001

POR, pooled odd ratio; CI, confidence interval.

esophagogastric tumors need to include stratification on SRC histology to prospectively confirm the best treatment strategy.

Salvage esophagectomy

In Japan and in Western countries, medical and radiation oncologists have reported satisfactory results with definitive CRT thus blurring the boundaries of traditional treatment strategies. Burned by unsatisfying related-treatment mortality of surgery, definitive CRT is now considered as treatment option in potentially resectable patients. This has been also motivated by the 15-30% of complete response in the resected specimen after neoadjuvant therapy (5). However, local failure after definitive CRT remains problematic. Persistent or recurrent local disease after definitive CRT remains the greatest drawback of this strategy: 11-26% of patients do not exhibit any morphologic tumor response leading to a dismal prognosis with a median survival at nine months (50). For a subset of carefully selected patients, salvage esophagectomy remains the only curative option.

Locoregional recurrence is defined as tumor detected more than three months after CRT. Persistence is defined by tumor detected within three months in the same site (51). Unfortunately, locoregional control is often quite poor with definitive CRT, and 40% to 60% of the patients have persistent or relapsed tumor at the primary site within one year (43). In this way, salvage esophagectomy stands out as the logical answer for selected patient who received up to 50 Gy of radiation and who are physiologically fit for salvage operation. They can be offered a salvage surgery, a procedure intended to rescue them from an isolated local failure after definitive CRT. Local problems can be related to a neoplastic disease but can also be due to a local toxicity or a mechanical complication.

Previous studies have demonstrated the feasibility of the salvage esophagectomy (50-59). These data suggested that despite the increased morbidity and mortality, a

subset of patients were cured after salvage esophagectomy with an acceptable long-term outcome. The decision to proceed with salvage esophagectomy is problematic and each individual case must be considered. Because of the fibrosis due to the high dose of radiotherapy, histological confirmation of the malignancy is difficult to obtain, in less 60% of cases (59). Because the high postoperative mortality, selection of these patients and indications of this salvage procedure must be considered after careful consideration. Initial studies examining the utilization of 'salvage esophagectomy' indicated that these procedures were associated with significant increases in operative mortality, respiratory and anastomotic complications and increased length of ICU and in-hospital stay (50-60). A recent pooled-analysis of more than eight studies comprising 954 patients revealed that salvage esophagectomy resulted in significant higher mortality and morbidity rate (Table 2). Salvage resection was associated with a significantly increased incidence of post-operative mortality, anastomotic leak, pulmonary complications and an increased length of hospital stay (60). Much of this concern originated from a historical impression that surgical resection outside of 4-8 weeks following radiotherapy or CRT was more technically challenging and associated with increased postoperative morbidity and mortality. This opinion has recently been challenged (61) and there are now several publications demonstrating that selected utilization of salvage surgery in patients who have failed definitive CRT for SCC can be done with acceptable levels of both mortality and morbidity (51,54,59). Special attention has to be paid of the volume dose of radiation. Salvage surgery is a highly invasive and morbid operation after a volume dose of radiation exceeding 55 Gy (59). It should be noted, however, that a randomized clinical trial that assessed long-term outcomes indicated that definitive radiation chemotherapy had the potential for producing progressive deterioration in pulmonary function when compared to surgery alone (61).

Table 3 Main results of the first randomized control trial of open esophagectomy versus MIE (67)

	Open esophagectomy N=56	MIE N=59	P
Primary outcomes			
Pulmonary infections within two weeks	16 (29%)	5 (9%)	0.005
Pulmonary infection in-hospital	19 (34%)	7 (12%)	0.005
Secondary outcomes			
Hospital stay days [range]	14 [1-120]	11 [7-80]	0.044
Operative time min [range]	299 [66-570]	329 [90-559]	0.002
Blood loss mL [range]	475 [50-3,000]	200 [20-1,200]	<0.001
VAS (10 days)	3 [2]	2 [2]	0.001
Vocal cord paralysis (%)	8 (14%)	1 (2%)	0.012

MIE, minimally invasive esophagectomy; VAS, visual analogue scale pain score.

Minimally invasive esophagectomy (MIE)

Over the last decades, MIE has expanded worldwide. It is estimated that between 15-30% of all esophagectomies use nowadays such procedures (62,63). MIE includes a huge mix of several techniques including hybrid techniques, full MIE and robotic surgery (64). There are now centers who are publishing consecutive series of over 1,000 minimally invasive procedures (65). The most appropriate approach to the esophagectomy will vary from center to center, and the decision should be based on adapting the surgical approach to individual physiologic and tumor-related issues in each patient and referring to centers who have achieved and documented acceptable baseline outcomes (66). It seems likely that importance of MIE will exceed hybrid techniques that have been probably at the onset of the training and the development of the techniques.

There are currently one prospective controlled trial and numerous uncontrolled retrospective comparisons of open versus minimally invasive operations (67-75). All demonstrate the beneficial advantages of the minimally invasive procedures requiring more operative time but being associated with less blood loss and potentially less respiratory complications with a reduced hospital stay. In the TIME trial (67) (Table 3), 56 patients were assigned to open esophagectomy and 59 to a MIE. Sixteen (29%) patients in the open esophagectomy group had pulmonary infection in the first two weeks compared with five (9%) in the minimally invasive group. Nineteen (34%) patients in the open esophagectomy group had pulmonary infection in-hospital compared with seven (12%) in the minimally invasive group. For in-hospital mortality, one patient in the open esophagectomy group died from anastomotic leakage

and two in the minimally invasive group from aspiration and mediastinitis after anastomotic leakage. Although operating time was significantly longer in the MIE group than in the open esophagectomy group, blood loss was lower for patients undergoing the minimally invasive procedure. Hospital stay in the MIE group was significantly shorter than that in the open group. These data had been confirmed by others meta-analyses of case control studies performed to date (68-72).

If the feasibility of MIE seems to be confirmed, the main drawback of the current knowledge in this context remains that MIE have been poorly investigated in term of standardized oncologic criteria's such as survival, disease-free survival or number of LN retrieved. A recent extensive review of evidence-based surgical treatment of esophageal cancer has highlighted the potential advantages of MIE, but also cautioned that there may be a 'patient selection bias' in that patients with less comorbidities and earlier tumors may be more prevalent in reports of the early experience of MIE. In addition, there could also be a 'publication bias' in that the published results of minimally invasive surgery will be from the most experienced and successful centers, while other centers who have attempted the transition to minimally invasive techniques with poorer outcomes are less likely to publish (72). In contrast, in the same period that has seen the widespread of MIE, there have been significant improvements in anesthesia, in perioperative management and in standardized esophageal clinical pathways, resulting in a more difficult interpretation of these potential benefits of the MIE (73).

The best information available on oncologic outcome after MIE comes from a meta-analysis from Dantoc *et al.* (69,70). This review focused on the oncologic merits of MIE techniques compared with conventional open

techniques. In the analysis of the data procured from 16 separate case control studies, the capability of surgeons to perform an adequate lymphadenectomy using MIE was established. Evidence points to the capacity of MIE techniques for greater LN yield owing to better visualization of the operative field. In addition, the authors found no statistically significant difference in survival rates between open procedures and MIE. In comparing East *vs.* West, Western centers had a statistically better LN yield with open *vs.* MIE, but the difference was not significant in Eastern centers. On survival, Eastern and Western centers showed no statistically significant survival advantage for MIE. Finally, although a lack of standardized and controlled data limits the methods used in this study, the evidence suggests that the use of MIE was no better or worse in achieving similar oncologic outcomes than were open techniques. Further randomized controlled studies are needed to provide credible clinical evidence of the oncologic outcomes of open techniques *vs.* MIE. Thus, two others phase III trials are currently recruiting and are ongoing: the French' MIRO trial (74) and the Netherlands' ROBOT trial (75).

Conclusions

Management of esophageal cancer has been refined since the last decades. What is clear, is surgery continue to play a pivotal role in the treatment of the disease, alone or in combination of multimodal approach. Progress in anesthesia and in surgery has lead to significant decrease of the mortality rate. These improvements in mortality can be seen on national levels in either Western or Eastern countries. Mortality rate of 5% and even under 2% in some experienced centers are increasingly being seen and expected. The progress made in surgery lead surgeons to consider minimal techniques to reduce morbidity and mortality of such high-risk procedures. New techniques of MIE and robotic surgery in a near future will provide opportunity to push the boundary of the indications in very selected group of patients. Based on an commitment of respect the oncological principles including at least a two-stage LN dissection and a specific surgical planning targeted to achieve an R0 resection, these minimal techniques have to provide satisfactory results in term of early and long-term outcome without jeopardizing the disease-free survival. MIE will exceed hybrid techniques and will be compared to robotic esophagectomy. A high-degree of qualification with a high-level of expertise in a high-volume centers seem to be crucial in this context.

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Systemic treatment of gastric and esophageal adenocarcinoma in elderly patients

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Abstract: This article explores the treatment of cancer of the stomach and of the lower esophagus in older individuals. The incidence of both malignancies increases with age and, at present, the biology of the diseases, including sensitivity to chemotherapy, does not seem to change with age. The treatment of these cancers in patients 70 and over includes assessment of life expectancy secondary to physiologic age and evaluation of the individual's tolerance to stress. For this purpose a comprehensive geriatric assessment (CGA) is the best validated instrument. For individuals whose life expectancy without cancer exceeds that with cancer, the estimate of the risk of chemotherapy complications may reveal those patients in need of additional care and those patients in whom the risk of treatment may exceed the potential benefits. All older individuals receiving chemotherapy may need adjustment of the doses to the glomerular filtration rate, support with myelopoietic growth factors, and special care to prevent severe and irreversible neurotoxicity.

Keywords: Gastric and esophageal adenocarcinoma; systemic treatment; elderly patients

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Cancer of the stomach and of the gastro-esophageal junction (GEJ) are diseases of older individuals. The median age for stomach cancer worldwide is 61 (1). While the incidence of cancer of the fundus is declining in the USA, the incidence of cancer of the cardia and of the GEJ is increasing in all age groups and particularly among individuals 65 and older (2).

The treatment of cancer with chemotherapy in the older aged person involves two types of questions: Is the cancer susceptible to the treatment? Is the treatment going to be beneficial? To answer the second question it is necessary to estimate the patient's life-expectancy and the ability to tolerate the treatment, termed functional reserve.

Is the cancer different in older individuals?

At present, there is no conclusive evidence that the biology of stomach and lower esophageal cancer changes with age. This statement is based on review of pathology, molecular markers, and genomic data. In general, younger age may

be associated with more aggressive tumors, with a higher prevalence of linitis plastica and advanced stage (3).

Since 1965 adenocarcinoma of the stomach and of the GEJ has been described as intestinal type or diffuse (4). The diffuse type is an independent poor prognostic factor for survival. Since the original classification, the prevalence of the two types changed with age and the poor prognosis diffuse type became less common with increasing age (4).

It is clear that different molecular steps are involved in the pathogenesis of the two different tumors, but it is not clear which of these steps may be responsible for the difference in aggressiveness (5). Unlike other cancers, it has not been clearly established whether different genomic profiles purport different prognoses in cancer of the gastric cardia (5-7). A recent report from China described the intestinal stem cell marker LGR5, as a poor prognostic factor for stomach cancer and found that the prevalence of this marker increased after age 55 (8).

In the case of adenocarcinoma of the esophagus, a number of biomarkers, including COX2, VEGF, cyclin D and

survival, appear associated with a shorter patient survival (9). It is not clear whether the prevalence of these changes varies with age. Recently, a 3-gene panel was reported to be associated with decreased survival in adenocarcinoma of the esophagus (10), and the prevalence of these genetic changes increased with the age of the patients. Two of the many molecular markers identified in adenocarcinoma of the stomach and of the lower esophagus are targets for therapeutic interventions, HER2 and VEGF (6). It does not appear that the prevalence of these markers changes with age.

In conclusion, the evidence related to the interaction of the biology of adenocarcinoma of the stomach and lower esophagus and age is confusing and somehow contradictory. Though the prevalence of clinically aggressive gastric cancer appears to decrease with age, one cannot find any indication to change the type of systemic treatment, chemotherapy or biological therapy, according to the age of the patients.

Who are the elderly and what are the consequences of age on cancer treatment?

Aging is associated with a progressive reduction in functional reserve and with an increased prevalence of chronic diseases and of debilitating conditions referred to as geriatric syndromes (11). This association leads to increased susceptibility to diseases and to stress, resulting in an increased risk of death. The prevalence of functional disability and functional dependence also increases with age (12). Functional dependence implies that a person is not able anymore to perform by her/himself the basic activities of daily living (ADL) or the instrumental activities of daily living (IADL). This person may need the assistance of a caregiver to survive. The ADLs include continence, transferring, feeding, grooming, dressing, and toileting. The IADLs include use of transportation, ability to go shopping, to providing one's meal, to use the telephone, and to manage one's finances. Loss of functional dependence may have different causes that may include decreased eyesight or hearing, debilitating conditions such as a stroke, and increased prevalence of the so called geriatric syndromes such as dementia, severe depression, delirium following mild infections or medications, dizziness, falls, fractures, incontinence, neglect and abuse, and failure to thrive (13). Functionally dependent individuals may not be able to obtain adequate medical treatment in the absence of a caregiver, and for this reason the evaluation of the socio-economic context is extremely important prior to planning the treatment of cancer in an older aged person. As the

need for home caregivers is increasing with the aging of the population, the pool of potential caregivers is shrinking due reduced birth rate, dissolution of the extended family, and full employment of women (14).

While aging is universal it occurs at different rates in different individuals. The chronologic age of a person does not reflect the physiologic age that is of interest in medical decisions. The assessment of the physiologic age involves the estimate of a person life expectancy and tolerance of the planned treatment (12).

A number of laboratory tests may predict life expectancy. The so called *inflammatory index* (15) has been validated in two large cohort studies of aging individuals: the in *Chianti* and the *Baltimore longitudinal study*. The index is obtained by adding together the log of the circulating concentration of interleukin 6 and two logs of the concentration of the tumor necrosis factor receptor 2. Aging is associated with a progressive and chronic inflammation and the concentration of inflammatory markers predicts the risk of mortality, of cardiovascular diseases, and of geriatric syndromes. The inflammatory index has not been validated yet in cancer patients. Seemingly, the presence of cancer may be responsible of increased concentration of inflammatory markers that may decline once the cancer is in remission. The length of leukocyte telomeres is inversely related to life expectancy and stress tolerance (16). In epidemiological studies, this assay may be very helpful to study the association of age with disease, disability and death. However, the wide inter-individual variation in telomere length may make it unsuitable to estimate individual physiologic age (17). Other markers of aging include the expression of the gate-keeper gene p16 NIK4a in normal tissues (18). This assay is promising but it requires biopsy sampling of normal tissues.

A comprehensive geriatric assessment (CGA), involving function, assessed as ADLs and IADLs, the presence of geriatric syndromes, polymorbidity, polypharmacy, emotional and cognitive disorders, and socioeconomic status (with special emphasis on the presence and the adequacy of the caregiver) is currently the best validated instrument for estimating a person's physiologic age (19). Based on the CGA, one may estimate a person's risk of mortality with and without cancer up to 9 years post diagnosis (20) as well as the risk of chemotherapy induced toxicity (21,22). Based on the geriatric assessment, the risks and benefits of cancer treatment in the individual patients may be estimated and the treatment may be personalized (*Figure 1*).

The figure represents a reasonable suggestion of how

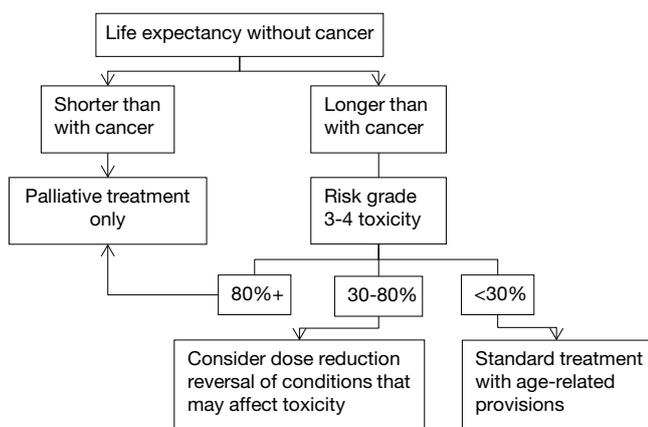


Figure 1 Proposed decision tree for the management of older patients.

to incorporate the principles of geriatric medicine in the treatment of cancer. Of course, every final decision will have to be negotiated with the patient and his caregiver(s). For some individuals, the risk of serious toxicity of 30% may be so high as to preclude acceptance of any treatment able to prolong survival for just a few months, while for others, the same few months of life may be worthwhile to accept a risk of toxicity higher than 80%.

Senior adult oncologists strongly recommend that all patients whose disease is incurable receive a palliative care consult at the beginning of treatment. In patients with metastatic non-small cell lung cancer, this approach has resulted in improved survival and decreased cost due to the reduction in futile and possibly harmful care (23).

Reversible conditions that may increase the risk of toxicity include de-conditioning and malnutrition that are common in older individuals who have been bedridden for a prolonged period of time, acute diseases, poorly controlled chronic illnesses, polypharmacy with a high risk of drug-drug interactions (24), and an absent or inadequate caregiver.

An unsolved question concerns which patients should have a CGA. It is recommended at present that all individuals 70 and older undergo, at the very least, some form of geriatric screening to establish whether they may benefit from the full CGA (19). The age threshold of 70 was selected because it is between age 70 and 75 when the incidence of age-related changes start increasing more steeply. It should be underlined that age 70 does not define older physiologic age. It is simply a threshold beyond which the majority of physiologically old individuals are found.

A number of special precautions are indicated in all older cancer patients receiving chemotherapy (19) irrespective of the patient's functional status. Age is associated with an almost universal drop in glomerular filtration rate and for this reason it is suggested that the first dose of a medication be adjusted according to the estimated creatinine clearance of each patient. Age is also associated with a decline in the hematopoietic reserve and for this reason it is recommended that individuals 65 and older be treated prophylactically with filgrastim or pegfilgrastim when receiving chemotherapy with a risk of myelotoxicity comparable to CHOP.

The management of cancer of the stomach and of the lower esophagus may involve a platinum derivative or a taxane. The neurological condition of these patients should be monitored at each visit as peripheral neuropathy is more common and more debilitating in older individuals and may also be irreversible. Another chemotherapy-related complication whose risk increases with age is cardiotoxicity. Anthracyclines are now seldom used for the management of these cancers, but approximately 25% of patients may be eligible to receive trastuzumab, a monoclonal antibody that may cause a generally reversible decline in ejection fraction.

Conclusions

The incidence and the prevalence of adenocarcinoma of the stomach and of the lower esophagus increase with age. The biology of these diseases may not change with age, but the benefit of chemotherapy may decline due to a reduction in life expectancy and an increased risk of treatment related complications. We recommend that the treatment of individuals 70 and over with these malignancies be personalized based on life expectancy and risk of complications. The CGA is currently the instrument best validated for assessing these parameters.

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T1 esophageal cancer, request an endoscopic mucosal resection (EMR) for in-depth review

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Abstract: Endoscopic management of superficial esophageal adenocarcinoma has gained wider acceptance with the growing literature on its efficacy. Patient selection is critical in deciding who should be a candidate for surgery or endoscopy in the management of T1 esophageal cancer. This article discusses the key role EMR plays in the diagnostic evaluation.

Keywords: Superficial esophageal cancer; endoscopic mucosal resection

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Esophageal adenocarcinoma (EAC) has seen a dramatic increase in Europe, Australia and the United States over the last 30-40 years, whereas the rates of squamous cell cancer of the esophagus has remained relatively stable or decreasing in Western countries (1-3). In 2013, it is estimated that there will be 17,990 new diagnoses of esophageal cancer in the United States, with 15,210 patients who will die from this disease (4). In the United Kingdom and the United States, adenocarcinoma has become the dominant histologic form of cancer in the esophagus (5). Twenty percent of all EAC in the United States is early stage (T1) with disease confined to the mucosa or submucosa (6,7). Traditionally surgery has been the standard of care for early stage EAC. However, there is substantial morbidity (30-50%) associated with esophagectomies (8,9). In addition in-hospital mortality rates can be high as 8% in low-volume hospitals compared to 2-3% in high-volume institutions (10). A less invasive alternative to surgery for early stage EAC is endoscopic resection and ablation.

In early stage EAC the risk of lymph node metastasis correlates to the depth of involvement of the cancer (11). A large retrospective review of 126 T1 EAC, of which 75 were T1a and 51 T1b, revealed lymph node metastasis of 1.3% and 22% respectively (12). A more comprehensive subclassification of early esophageal cancer has been

proposed with mucosal disease and submucosal disease divided into three categories respectively (m1-3, and sm1-3) based on depth of invasion (11,13). Data on superficial squamous cell cancer of the esophagus (SCCA) have shown that m3 cancer, or disease extending to the muscularis propria has upwards of 6% risk of LN metastasis (11). Additional characteristics which impact the risk of lymph node metastasis include lymphovascular invasion, size of the tumor, and the degree of tumor differentiation (11,12,14). Given the low risk of lymph node metastasis in mucosal disease, endoscopic management of early stage EAC is limited to disease confined to the mucosa (T1a).

Data on the efficacy of endoscopic therapy in early EAC is limited to case series with short follow-up duration. At present there is no randomized controlled trial comparing the outcomes between endoscopic therapy and surgery in the management of early stage EAC. Given the inherent challenge in trying to randomize between two radically different treatments, such a study will be difficult to accomplish. Current literature suggests that in appropriately selected patients with early stage EAC, endoscopic management does have comparable outcomes to surgery with fewer complications, but a higher rate of recurrence (15,16). A large retrospective cohort study which evaluated endoscopic resection in combination with photodynamic therapy compared to surgery showed comparable survival

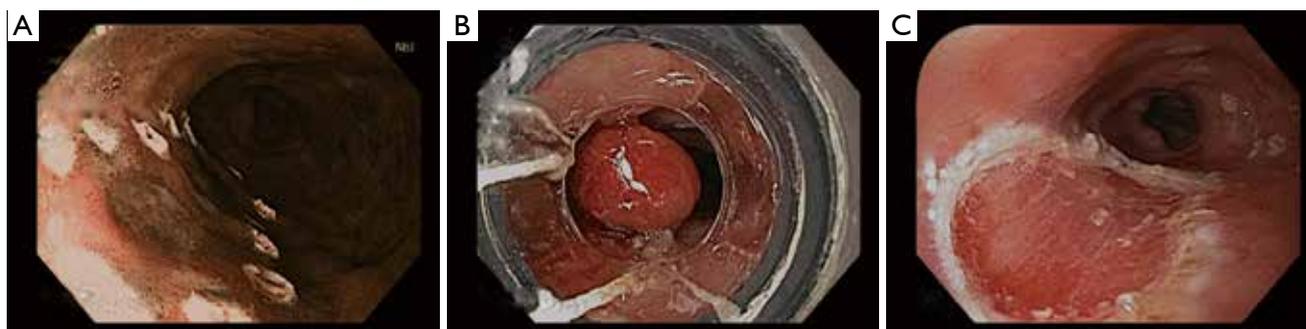


Figure 1. Three pictures of a multiband mucosectomy. A. shows Barrett's esophagus with intramucosal cancer. The lesion was circumferentially outlined by argon plasma coagulation; B. a multiband mucosectomy cap is used to create a pseudopolyp; C. shows complete resection of the lesion.

in patients with T1a EAC in Barrett's esophagus (BE) (15). A second study examining endoscopic resection in combination with argon plasma coagulation of remaining non-dysplastic BE compared to transthoracic resection with 2-field lymphadenectomy in T1a EAC, showed similar rates of complete remission (16). The surgical group did have a higher morbidity and mortality, whereas the endoscopy group had a higher rate of metachronous lesions which were managed by endoscopy (16). There is emerging data showing that pT1b EAC with favorable characteristics (sm1, well-to-moderate tumor differentiation and no lymphovascular invasion) maybe potential candidates for endoscopic therapy for curative intent (17,18). With increasing data on the efficacy of endoluminal therapies, endoscopic resection and ablation have gained wider acceptance as an alternative to surgery in the management of early EAC (19). The key challenge for physicians is determining which patients are appropriate candidates for endoscopic therapy.

Endoscopic ultrasound (EUS) is an integral component in the locoregional staging of esophageal cancer. The overall T-stage accuracy of EUS improves with increase depth of invasion, with the highest accuracy seen in T4 tumors (88-100%) (20), however, there has been controversy surrounding the accuracy of EUS in the evaluation of early EAC. A meta-analysis of 12 studies showed that in comparison with surgical or endoscopic mucosal resection (EMR) pathology, EUS had T-stage concordance of only 65% in early EAC (21). A recent larger meta-analysis encompassing 19 studies with a total of 1,019 patients including EUS with radial probes and higher frequency mini-probes, showed EUS to have overall good accuracy in staging T1a and T1b esophageal cancers with area under the curve ≥ 0.93 (22). Given the variable range on the accuracy of EUS in early EAC, the role of EUS in the clinical decision making in early EAC has been questioned.

A retrospective study of 131 patients evaluated if EUS changed the management approach of patients with early EAC (23). In this study 105 of the 131 patients had an unremarkable EUS. After EMR 17 patients were found to have submucosal invasion, 2 patients with positive deep resection margins and 6 with poorly differentiated cancer and/or lymphovascular invasion. Despite a normal EUS, after EMR, 25 out of the 105 patients had risk factors for lymph node metastasis that would have been missed without the corresponding histology. This study highlights the potential risk of "under-treatment". Conversely in the 26 patients who had an EUS suggestive of submucosal invasion or lymph node metastasis, EMR revealed no risk factors for lymph node metastasis in 10 of these patients. Referral to surgery based on the EUS findings would have subjected these patients to "over-treatment". In this series of patients with early EAC, EUS had no clinical impact on patient management.

EMR has grown in importance in the management of early EAC as both a diagnostic and therapeutic modality (Figure 1). A large single center study examining complete Barrett's eradication EMR (CBE-EMR) for the management of BE with high grade dysplasia (HGD) and intramucosal cancer (IM) for curative intent reinforces the importance of EMR in early EAC (24). In this study a total of 49 patients with biopsy confirmed BE with HGD/IM underwent CBE-EMR for a total of 106 EMR sessions. Overall 32 patients were able to complete CBE-EMR and on surveillance 31 of 32 (96.9%) had normal squamous epithelium. In the pathologic comparison of the pre-EMR biopsy and the CBE-EMR, there was a 45% change in the final pathologic stage. 14% of patients were upstaged and an additional 31% were down staged. The upstaging of disease was likely due to the limited depth of the biopsy specimens whereas the down staging was attributable to the complete removal of

the HGD/IM foci with biopsies. Furthermore, four patients were found to have advanced disease, two with submucosal invasion and two with lymphovascular invasion, requiring a referral to surgery. In this study, EMR provided accurate staging data in addition to providing information which affected patient management.

EMR as an endoscopic technique has been around for more than 20 years. It was initially described by Inoue using a cap technique for resection of early neoplastic lesions (25). A transparent cap with a circumferential rim where a diathermic snare can be loaded is fixed to the tip of the endoscope. After the neoplastic lesion is identified, the border of the lesion is marked with APC probe. Then saline is injected at the base of the lesion, providing a lift. Methylene blue can also be added to the saline solution to help differentiate the submucosa from the muscle layer. Next, the marked lesion is sucked into the distal attachment and the snare is used to grasp and ligate the lesion with electrocautery. En-bloc resection of up to 20 mm can be achieved with the cap technique.

An alternative to the EMR technique is the use of a reusable variceal band ligating device attached to the tip of the endoscope. The neoplastic lesion is sucked into the ligation cap, and then a rubber band is applied creating a pseudopolyp. The endoscope is withdrawn and the band ligating device is disassembled and standard polypectomy is performed on the pseudopolyp. With this technique submucosal injection of saline is not necessary.

A prospective randomized trial examined these two techniques in 72 patients with early EAC who underwent 100 endoscopic resections (26). Fifty endoscopic resections were performed with the cap technique with prior submucosal injection of a dilute saline solution of epinephrine, and 50 resections were performed with a “suck-and-ligate” device without prior submucosal injection. Both techniques were safe with no severe complications and only a minor case of bleeding in each group. With regards to size of the resected specimen, there was no statistically significant difference between the cap group and the ligation group (15.7 mm × 10.7 mm versus 16.4 mm × 11 mm).

Recently, EMR with the band ligating device has been supplanted by multiband mucosectomy (MBM). MBM uses a modified variceal band ligator containing six bands and allows passage of a snare through the biopsy channel of the endoscope. Up to six resections can be performed without the need to remove the endoscope between banding and polypectomy. A prospective study of MBM in 170 patients who underwent a total of 243 MBM procedures, with 1,060 resections demonstrated the safety and efficacy of this technique (27). Complete endoscopic resection was achieved

in 91% of focal lesions. There were no perforations and delayed bleeding occurred in 2% of patients, all of whom were managed by endoscopy. A multicenter randomized control trial comparing endoscopic resection-cap technique and MBM for piecemeal endoscopic resection of early Barrett's neoplasia found procedure time (34 vs. 50 min) and cost was significantly cheaper (euro 240 vs. euro 322) with MBM (28). MBM did result in smaller resection specimens than endoscopic resection-cap technique (18 mm × 13 mm vs. 20 mm × 15 mm), however, this was felt to be clinically insignificant as the depth of resection of both techniques were the same.

As the role of therapeutic endoscopy expands into the realm of early EAC, accurate staging is of utmost importance. Overestimating the T-stage may subject patients to surgery with high morbidity and a considerable mortality rate when it may have been managed by endoscopy. Underestimation of the T-stage may lead to insufficient treatment by endoscopy with potential lymph node metastasis being left untreated. EUS has played a significant role in the staging of EAC, however, EUS cannot definitively discriminate between mucosal and submucosal disease in early EAC. On the other hand, EMR is an established endoscopic technique, with a good safety profile. An EMR can provide clear detail on the depth of invasion in early EAC and further sub classify the disease (m1-3 and sm1-3). In addition, the histologic correlate from the EMR provides valuable information regarding risk factors for lymph node metastasis. For T1 EAC, EMR should be the final diagnostic step in determining whether a patient should undergo surgery or endoscopic therapy.

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Endoscopic options for early stage esophageal cancer

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Abstract: Surgery has traditionally been the preferred treatment for early stage esophageal cancer. Recent advances in endoscopic treatments have been shown to be effective and safe. Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) allow endoscopists to remove small, superficial lesions, providing tumor specimen that can be examined for accurate pathologic tumor staging and assessment of adequacy of resection. Endoscopic ablation procedures, including photodynamic therapy (PDT) and radio frequency ablation (RFA), have also been shown to safely and effectively treat esophageal dysplasia and early stage neoplasia, with excellent long-term disease control. Both approaches are becoming more widely available around the world, and provide an alternative, safe, low risk strategy for treating early stage disease, making combined endoscopic therapy the recommended treatment of choice for early stage esophageal cancers.

Keywords: Esophageal cancer; high grade dysplasia (HGD); endoscopic mucosal resection (EMR); endoscopic submucosal dissection (ESD); radio frequency ablation (RFA)

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Introduction

In 2014–2015, the majority of esophageal cancers diagnosed in the United States will be esophageal adenocarcinoma (EAC); this represents a shift in incidence since the 1960s when 90% of all esophageal cancers were of the squamous cell type (1,2). Worldwide, however, esophageal squamous cell carcinoma (SCC) remains more common than EAC with the highest incidence seen in China (3). Increasing research into the pathogenesis of these two malignancies has revealed different risk factors, pathophysiology, and treatment options. EAC arises most commonly in the distal esophagus and is shown to be associated with gastroesophageal reflux disease (GERD) and obesity (4,5). The increasing incidence of EAC has also led to an increasing recognition of the precursor lesions of this disease including Barrett's esophagus (BE), low-grade dysplasia (LGD), high-grade dysplasia (HGD), and intramucosal adenocarcinoma (ImCa)—defined as carcinoma limited to the mucosal layers of the esophagus. BE is histologically described as specialized intestinal metaplasia (SIM). SCC, however, is more common in

the upper and middle esophagus and is associated with risk factors of smoking and alcohol use (3). SCC arises through a progression of squamous cell dysplasia from low-grade intra-epithelial neoplasia (LGIN) to high-grade intra-epithelial neoplasia (HGIN) to early squamous cell carcinoma (ESCC) or non-invasive SCC (historically referred to as carcinoma *in situ*) to invasive disease. These represent the World Health Organization (WHO) defined categories of disease progression.

With the increasing recognition of the association of GERD and BE, patients with GERD often undergo upper endoscopy (EGD) to screen for BE. National guidelines recommend surveillance EGD once every 3 years in patients with BE (6,7). This has resulted in an increase in diagnosis of early stage esophageal cancer of both EAC and SCC types. The remainder of patients, however, often don't present until symptoms develop, generally representing more advanced disease. Approximately 50% of patients with esophageal cancer present with loco-regional disease and potentially curable disease; the remainder have distant metastatic disease or extra-regional nodal disease at the time of diagnosis (2). Patients with loco-regional disease

are extensively evaluated for combination therapies to attempt to achieve the greatest success of cure with the least co-morbidity of treatment. Treatment options include a combination of endoscopic treatment, chemotherapy, radiation therapy, and surgical resection. The optimal course of therapy is largely defined by the histopathology of disease, the stage of disease at presentation, and patient co-morbidities. Cancer limited to the mucosal layer (AJCC classification T1aN0M0) may be treated with endoscopic methods yielding a greater than 80% cure rate of dysplasia in the adenocarcinoma sequence and a greater than 70% cure rate of all BE (8-10). While the use of endoscopic techniques is newer for treatment of early SCC, case series report similar cure rates for patients with mucosal disease (11-13). This article presents a focal discussion of the role of endoscopic evaluation in diagnosis and treatment of early stage esophageal cancer, of both, adenocarcinoma and squamous cell varieties. Understanding the tools available for diagnosis, patient selection criteria, and endoscopic treatment options for early stage esophageal cancer can improve patient outcomes and reduce patient morbidity and mortality.

Endoscopic techniques for diagnosis

Patients with esophageal cancer are identified on EGD and confirmed by histopathological review of biopsy specimens taken during this evaluation. EGD may be initiated as a result of screening in patients with a long history of GERD or as a diagnostic evaluation tool in patients with symptoms including dysphagia, dyspepsia, or atypical chest pain. Current guidelines recommend screening patients with BE every 3 years with targeted biopsies of any abnormal lesions within the Barrett's mucosa and systemic 4-quadrant biopsies every 2 centimeters within the remaining mucosa to detect dysplastic tissue (6,7). While this technique increases the yield of diagnosis over random biopsies, there remains sampling error. Enhanced endoscopic technologies have significantly improved the ability of the endoscopist to identify subtle variations in the mucosal appearance and recognize lesions that are in the precancerous or early stages of cancer development. Further improvement in technologies to enhance the ability of the endoscopist to identify premalignant lesions and improve the diagnostic yield of endoscopy is ongoing.

High definition white light endoscopy (HDWLE) has increased the ability of the endoscopist to identify and differentiate normal squamous epithelium from abnormal

Table 1 Siewert classification of EGJ tumors

Siewert	Description	Surgical approach
I	Tumor center located between 5 and 1 cm proximal to the anatomical cardia	Approached as esophageal or EGJ cancer
II	Tumor center located between 1 cm proximal and 2 cm distal to the anatomical cardia	Approached as esophageal or EGJ cancer
III	Tumor center located between 2 and 5 cm distal to the anatomical cardia	Approached as gastric cancer

EGJ, esophago-gastric junction. Ref: NCCN guidelines Version 1. 2014.

SIM and dysplastic tissue (14). HDWLE has become the standard used in all modern EGDs. With HDWLE, BE appears as salmon colored mucosa, an alternation from the normal subdued pink mucosa. Within normal mucosa or BE, HDWLE will allow for the inspection and identification of any raised nodules or patches of nodular mucosa, which is one common presentation of dysplasia or ImCa in either the adeno or squamous cell pathways. Obvious masses can be inspected. Using HDWLE, the endoscopist can take targeted biopsies of any abnormal mucosa for further differentiation and identification. EGD should be used to describe the location of any abnormalities, best represented as distance from the incisors. The size and length of any abnormality should be described and the relationship of the abnormality relative to the gastroesophageal junction (GEJ) is described. The percentage of circumference involved or the location on a clock-face can be helpful in further characterizing the lesion (15). The extent of BE should also be characterized using the well described Prague classification system; this uses a "C" distinction to note the level of circumferential BE and an "M" distinction to note the maximal length of esophagus affected with BE (16). Additionally, the gastric cardia should be carefully examined and the degree of extension of esophageal or GEJ tumors into the gastric cardia should be documented using the Siewert classification system (*Table 1*) (17-19). Supplementing the use of HDWLE is the use of narrow band imaging (NBI) or virtual chromoendoscopy, a form of imaging using specific wavelengths of light in the blue and green part of the spectrum which enhances the mucosal and vascular pattern of BE and dysplastic tissue at the time of endoscopy. NBI is available on certain modern endoscopes with the use of a separate switching

button, which turns on the blue-green filter. NBI has been shown to increase the real-time identification of HGD with sensitivity and specificity of greater than 90% by allowing for identification of irregular mucosal pit patterns and irregular microvasculature (20). This can increase the ability of the endoscopist to perform targeted biopsies to confirm the abnormal endoscopic findings and potentially the development of neoplasia (14).

Chromoendoscopy can additionally supplement the endoscopist's ability to recognize subtle lesions. Chromoendoscopy refers to the use of dyes sprayed within the esophagus to detect mucosal variation secondary to dysplasia or early neoplasia. The most commonly used application of chromoendoscopy is the use of Lugol's solution, a combination of potassium iodide and iodine, which has an affinity for glycogen in squamous cells. Lugol's solution is sprayed to coat the squamous mucosa in the esophagus resulting in a brown staining of normal squamous cells; absence of uptake is associated with dysplasia and carcinoma. Lugol's staining has been shown to have a sensitivity of 91-100% and a specificity of 40-95% for the detection of squamous cell neoplasia (21). The adjunct use of Lugol's in patients with squamous cell dysplasia and carcinoma has been shown to increase the yield of diagnosis and to allow for better characterization in terms of size, location, and multi-focality of squamous dysplastic lesions. For detection of dysplasia and neoplasia in BE, dyes available include indigo carmine, methylene blue, crystal violet, and acetic acid (22), though these have been less well characterized than in the SCC pathway. A recent meta-analysis looking at the use of chromoendoscopy and advanced imaging techniques such as NBI for the detection of dysplasia or carcinoma in patients with BE demonstrated improvement in the yield of diagnosis with the use of these supplemental techniques (22).

Confocal laser endomicroscopy (CLE) is an enhanced optical technique designed to further enhance real-time assessment of dysplastic and neoplastic cells of the esophagus. After intravenous injection of fluorescein, a blue laser light probe is passed into the esophagus and used to assess cellular and subcellular structures within the esophagus. CLE allows for *in vivo* assessment of dysplasia and carcinoma. Studies have assessed its efficacy including a recent multicenter study, which suggested improved ability to detect dysplasia and neoplasia above HD-WLE and NBI (23,24); however, CLE requires specific training and expertise and while it is actively used in research studies and shows great promise, this technology is not yet widely

available clinically.

Finally, newer techniques including optical coherence tomography and endocytoscopy have been developed and described as potential probe based enhanced imaging techniques to increase the visualization of the tissue microstructure in the esophagus. These techniques have only begun to be studied *in vivo* and remain experimental technologies that may have a role in real time diagnosis of esophageal cancer precursor lesions in the future.

Histopathology remains the gold standard for diagnosis of esophageal cancer and its precursor lesions. Histopathology should be reviewed by an expert GI pathologist and in cases of initial diagnosis of precursor lesions, should be confirmed by a second GI pathologist. Pathology should describe the presence of SCC or adenocarcinoma. The degree of differentiation, depth of invasion and any lymphovascular invasion should be described, as these factors affect prognosis and treatment plan. In the setting of precancerous lesions, the degree of dysplasia should be characterized and degree of focality should be described (unifocal or multifocal).

Staging

The 2010 American Joint Committee on Cancer (AJCC) has recommended that esophageal cancer be staged based on a T (tumor size), N (nodal involvement), and M (metastatic disease) based system. For patients with localized esophageal cancer, the T and N criteria are imperative to determining the optimal course of treatment. The 5-year survival for T1a adenocarcinoma (tumor invades lamina propria and/or muscularis mucosae) is between 88-90% versus 47-62% for T1b disease (tumor invades submucosa) (25-28). This significant decrease in survival is driven by the increase in lymphovascular invasion and development of lymph node involvement once the tumor has penetrated into the submucosa, but is also affected by the progression of histopathological grade (well/moderate differentiation to poor differentiation). Recent reviews of resected early surgical specimens of both, EAC and SCC, revealed that patients with T1a disease have 0% risk of lymph node involvement with increase to 4-46% of lymph node involvement when the tumor has reached T1b disease. Depth of submucosal (SM) involvement can be further delineated into SM1, SM2 and SM3 involvement with 0-21% nodal involvement seen in SM1 disease (upper 1/3 of SM) to 43-67% in SM3 disease (deepest 1/3 of SM) (29-31).

Accurate preoperative staging of patients with esophageal cancer is imperative to direct treatment and is dependent on a combination of techniques including EGD, endoscopic ultrasound (EUS), computed tomography (CT) scans, and positron emission tomography (PET) scans using fluorodeoxyglucose (FDG) activity. After initial diagnosis of esophageal cancer with EGD and biopsy, all patients should undergo CT scan of the chest and abdomen for evaluation of loco-regional disease and distant metastases. Metastatic disease should be described in terms of distant metastases (unresectable disease) or invasion into adjacent resectable structures (T4a disease) such as pleura, pericardium, and diaphragm, which is identified by loss of fat planes on CT scan. CT is otherwise not useful in distinguishing T stage. For nodal disease, CT has a sensitivity of 47-82% and a specificity of 25-92% (28,32,33). Supplementing CT information is the use of PET with FDG activity, which can identify occult metastatic disease in up to 10-20% of people not identified on standard imaging (34). CT combined with PET is the optimal study to combine these two roles (35).

In patients with no evidence of metastatic disease, further staging is completed with EUS evaluation. EUS allows for completion of staging with information on the T stage and N stage. The overall accuracy of EUS for T staging ranges between 72-76% (28,36-38). EUS is more accurate in staging T3 and T4 disease than in staging T1 disease. Additionally, in T1 disease, EUS using high frequency probes (12-20 MHz) can help distinguish between T1a (mucosal involvement) and T1b disease (SM involvement) and is able to successfully do this in 75-82% of cases (39). Thus, EUS staging for distinction between T1a and T1b disease is often augmented with the use of endoscopic resection of lesions to obtain more accurate staging and possibly curative treatment in the same session.

Endoscopic resection techniques

Endoscopic resection has been described with two approaches, including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), both of which were initially developed in Japan for the treatment of early esophageal and gastric cancer. EMR procedures include strip biopsy using saline injection followed by cautery snare resection, EMR with a cap fitted onto the endoscope (EMRC), and EMR with the use of a band-ligating device (EMRL). ESD is a newer method of endoscopic resection developed to permit a wider, *en bloc* excision of the entire lesion with a surrounding margin, without cutting through the lesion.

Endoscopic mucosal resection (EMR)

One of the earliest descriptions of endoscopic resection of early gastric cancer was published in 1980 (40). Papazian *et al.* also described the technique using an insulated tip cautery knife to endoscopically resect a gastric leiomyoblastoma in the stomach of an elderly patient (41). In 1990, Inoue *et al.* reported successful mucosal resections of early esophageal cancers, with almost no complications, using a clear tube attached to the tip of the endoscope to perform EMR, leaving an intact muscularis propria (42,43). They also demonstrated that this technique can be safely performed in a patient with esophageal varices (44). Since then commercially available kits have been marketed around the world providing access to reliable devices, permitting endoscopists to safely perform the technique.

The two most used devices in the United States include the Olympus EMR kit (Olympus America; Center Valley, USA) and the Cook Medical Duette EMR kit (Cook Medical; Bloomington, Indiana). Both kits include a clear, short plastic tube, which fits onto the tip of a standard gastroscope, and is paired with a special snare to resect the desired lesion. In the case of the Olympus EMR kit, the snare opens inside the cap forming a noose, which will ensnare the desired lesion or mucosa. An injection needle is also provided to allow instillation of either saline or another liquid substance such as Hyaluronic acid into the submucosa, beneath the lesion, separating it from the muscularis propria, for safe resection. Although the original description of this technique included the injection of saline into the submucosa, EMR has also been described to be effective and safe for removing esophageal lesions without the injection (45).

During the procedure, the endoscopist identifies the lesion for resection with careful inspection, and may mark the area for resection by placing cautery marks a few millimeters around the lesion for easy localization during resection and also to ensure complete excision. The endoscopist then brings the lesion close to the edge of the clear cap, applies suction causing the lesion and surrounding mucosa to be pulled into the clear cap. The snare is then closed, cinching the mucosa surrounding the suctioned lesion, and high-frequency electrocautery is applied, cutting through the mucosa at the point it is cinched by the snare, simultaneously cauterizing any superficial blood vessels. The Duette kit provides multiple small rubber bands that are applied to the suctioned lesion, cinching the mucosa at the base of the lesion, forming a pseudo-polyp which

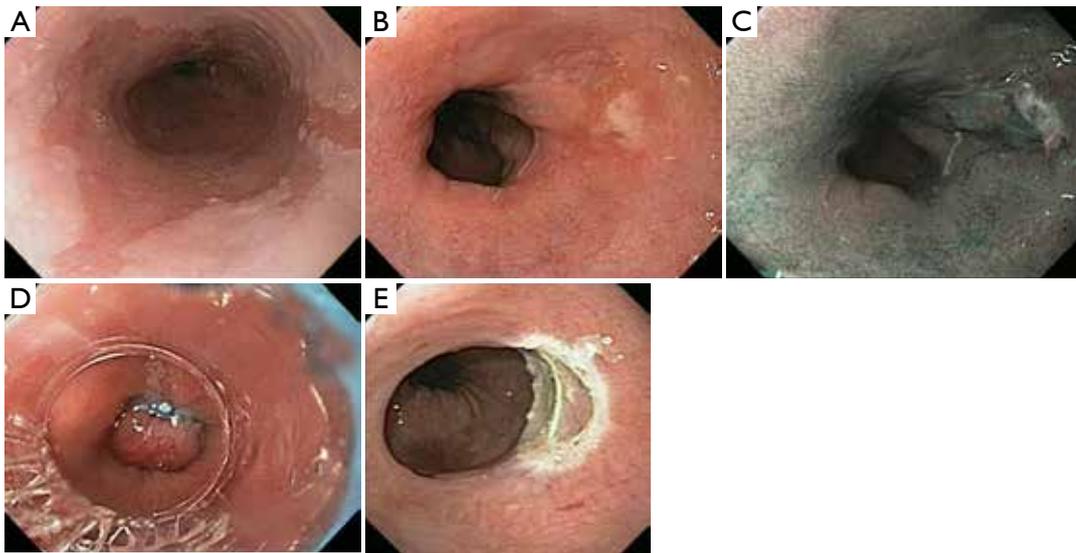


Figure 1 Endoscopic mucosal resection. (A) HDWLE of a patient with long-segment BE; (B) image of a small nodular patch of mucosa at the distal end of the BE; (C) NBI image of the distal area of BE showing the small nodular patch on the right side; (D) EMRL being performed with band applied to the patch of nodular mucosa; (E) image of the site of EMR showing complete resection of the abnormal nodular mucosa, with healthy, non-bleeding submucosal visible. HDWLE, high definition white light endoscopy; BE, Barrett's esophagus; NBI, narrow band imaging; EMR, endoscopic mucosal resection.

can then be snared and resected in standard polypectomy fashion (*Figure 1*). Both devices work well for the resection of small lesions measuring up to 1.5 cm in diameter, but can be repeatedly applied to remove larger lesions in piecemeal fashion. In fact, this approach has also been described to completely remove large areas of BE by repeatedly applying the suction and snaring to neighboring areas of mucosa until the entire field of Barrett's epithelium has been excised (46).

The earliest reports of EMR demonstrated success in small series of excising small superficial squamous cell esophageal cancers (42,43). In 2000, Ell *et al.* reported use of the strip biopsy technique or EMRC in the treatment of patients with HGD or superficial (T1) adenocarcinoma in the setting of BE (45). EMR was successful in achieving complete local resection based on histopathology in 97% of patients with well differentiated, non-ulcerated, mucosal lesions <2 cm in maximal diameter. The success rate was lower in those with more advanced disease, including size >2 cm, ulcerated lesions and higher differentiation grade. Other groups from other parts of the world have published similar results, indicating that EMR is an important tool in the evaluation and management of patients with superficial esophageal neoplasia (13,47-49). An important finding in several of these reports is the change in staging noted in 20-30% of patients, both up-staging and

down-staging, following EMR (47). Also important are the reports of a metachronous rate of cancer as high as 21% (13).

Endoscopic submucosal dissection (ESD)

The technique of ESD was first developed in Japan to permit the *en bloc* resection of large superficial lesions of the GI tract. It is performed by initially marking the periphery of the lesion with cautery markings 5-10 mm around the edge of the lesion, making a circular mucosal incision around the lesion, then careful, meticulous dissection with a cautery device beneath the lesion through the submucosa, slowly separating it from the muscularis propria of the stomach wall, eventually removing the entire lesion with its surrounding margin of normal mucosa. The technique was originally described by Gotoda *et al.* in the treatment of a large flat rectal lesion, and then subsequently adapted to the treatment of early gastric cancers and now esophageal lesions (50-55).

In an initial series, Oyama *et al.* reported treating 102 patients with superficial esophageal squamous cell cancer ranging in size of lateral spread from 4-64 mm, using the hook knife to perform ESD. They achieved successful *en bloc* resection in 95% and had a local recurrence rate of 0% with mean follow-up period of 21 months (range, 3-54 months).

They experienced no major bleeding events or perforations, but had six cases of mediastinal emphysema (6%) that they treated successfully with 2 days of IV antibiotics (54).

In another series, Fujishiro *et al.* (55) reported performing ESD for 58 esophageal squamous cell neoplasms in 43 patients (intraepithelial neoplasm or intramucosal invasive carcinoma). They achieved *en bloc* resection for 100% of the lesions, but had negative margins in only 78%. They experienced no significant bleeding, but had four perforations, which they were able to close endoscopically. Nine patients experienced subsequent esophageal strictures requiring balloon dilation. One patient developed a local recurrence 6 months after ESD, which was treated successfully by a second ESD.

Based on experiences such as these, some have suggested that ESD can be considered for curative treatment of patients with superficial esophageal neoplasia in Japan (56). This technique has been adopted in Korea for treatment of gastric cancer (57), but has very slowly been adopted in the United States and Europe. As the technology to perform the procedure becomes more widely available, greater experience should follow.

Endoscopic ablation techniques

Supplementing the use of endoscopic resection techniques is the use of ablation to eliminate all flat neoplastic or dysplastic disease and all precursor disease such as BE. In patients with early stage EAC treated with EMR or ESD, the remaining BE generally contains residual dysplasia; recurrence of carcinoma can occur in 19% to 30% of cases (58). Thus, the goal in endoscopic management is to eradicate all BE in the treatment process. Ablation techniques have evolved with the further development of technologies.

Laser

Laser therapy has been described and was previously used for ablation of BE. The 1,064-nm neodymium yttrium aluminum garnet (Nd:YAG) laser and 940-nm diode laser have been used for tissue destruction with results in the range of 65-67% complete eradication. Laser therapy has a limited area of treatment and requires numerous sessions to ablate large areas making this less favorable than other ablation techniques. Additionally variable levels of subsquamous BE have been described (59), possibly because of non-uniform application throughout the affected

area. Laser therapy has therefore gone out of favor, and is infrequently used for early esophageal neoplasia.

Photodynamic therapy (PDT)

PDT requires multiple steps to achieve ablation ; the patient is first administered a light-sensitizing drug that accumulates in the BE or neoplastic tissue. A light-diffusing fiber is then placed in the esophagus and monochromatic laser light is applied resulting in free oxygen radical formation and ischemia of the treated tissue with controlled tissue destruction. Porfimer sodium or oral 5-aminolevulinic acid are the most commonly used photosensitizers (60). PDT has been studied for the treatment of LGD, HGD, and ImCa and has yielded successful ablation in 93%, 78%, and 44% respectively. Approximately 5% of patients developed subsquamous or “buried” adenocarcinoma. Complications including strictures have been described in up to 30% of patients with one session of PDT (61). PDT was previously widely used for treatment of BE but has become less common with the advent of safer methods of treatment such as radiofrequency ablation.

Radio frequency ablation (RFA)

RFA is the current standard of care of ablative techniques. RFA uses a bipolar electrode to apply 465 kHz of energy waveform to the affected tissue resulting in cauterization and destruction of the epithelial layer. RFA can be applied to the full circumference of the esophagus (*Figure 2*) using a balloon-based device or can be applied in smaller increments using a cap-based device for focal ablation (HALO360 or HALO90 system; BARRX Medical, Sunnyvale, California) (62). RFA has been evaluated for the treatment of dysplastic precursor stages in both adenocarcinoma and SCC pathways and has been shown to be safe and effective.

In patients with BE and dysplasia, a multicenter randomized control trial of 127 patients randomized to RFA versus sham procedure revealed significantly improved rates of complete eradication of BE, decreased rates of progression, and fewer cancers in patients who underwent RFA (63) with low rates of complication (chest pain, bleeding, esophageal stricture). A meta-analysis of 18 studies involving 3,802 patients who underwent RFA revealed complete eradication of BE in 78% of patients with recurrence of BE in 13% of patients and progression to cancer in 0.7% of patients after complete eradication of BE. Esophageal stricture, the most common complication

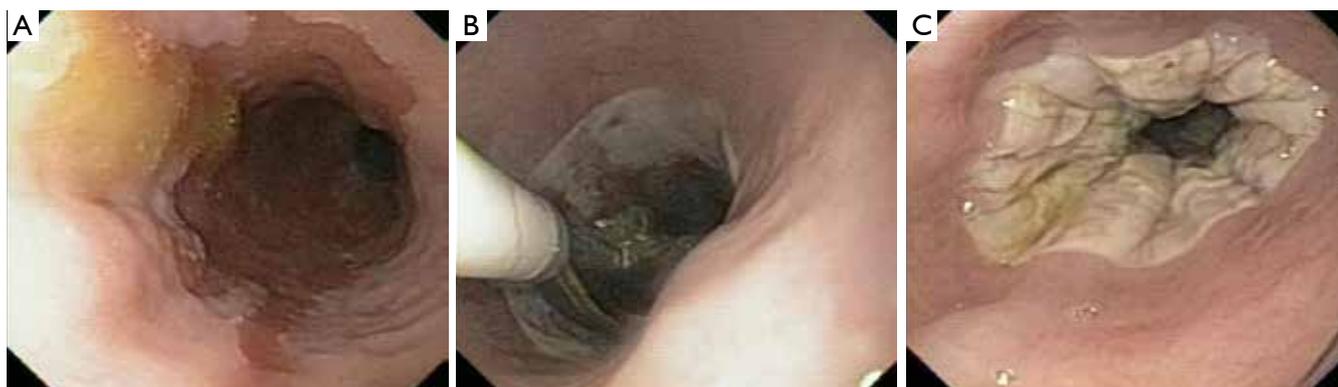


Figure 2 Radiofrequency ablation. (A) HDWLE of a patient with long-segment BE; (B) image of RFA being performed with the use of the Halo 360 catheter; (C) image of successful circumferential ablation of area of BE. HDWLE, high definition white light endoscopy; BE, Barrett's esophagus; RFA, radio frequency ablation.

reported, was noted in 5% of patients (64). Patients with longer segments BE (length >10 cm) and dysplasias have also successfully been treated using EMR and RFA (58).

Patients with squamous cell dysplasia and early flat SCC have been treated with RFA as well, though the literature remains unclear as to its role in this disease. The largest series to date presented a single center study of 29 patients treated with RFA resulting in 97% complete eradication of disease at 12 months (62). A second prospective cohort of patients treated with RFA from the United Kingdom revealed only 50% of patients with complete eradication of disease at 12 months (65). These small series with varying protocols and varying results indicate further research is needed to determine if RFA is effective in the treatment of early SCC.

Argon plasma coagulation (APC)

APC is a widely available, alternative way to ablate dysplastic tissue in the esophagus. APC uses a probe device that has a constant flow of ionized argon gas that transmits high-frequency current to tissue to cause superficial cautery effect and tissue destruction. Efficacy of APC varies in studies with 66% to 100% of complete eradication of BE and relapse rates of 3% to 11% per year (60,66,67). Complications have been reported with APC including strictures, pleural effusions, and perforations. Given this mixed profile, APC for BE is less routinely performed in favor of techniques such as RFA.

Cryoablation

Cryoablation is a form of ablative therapy that involves

spraying liquid nitrogen onto the area of abnormal tissue, resulting in intracellular disruption and ultimate ischemia of the cells. Few studies have looked at outcomes after cryotherapy for ablation of dysplastic BE and further research is needed before this is used widely as a modality for treatment (60).

Endoscopic approach to the patient with early stage esophageal cancer

Patients with early stage esophageal cancer, staged as T1a lesions, are candidates for endoscopic approach for treatment and potential cure of their disease. Patients with T1a lesions have a less than 2% risk of lymph node metastases, making them appropriate candidates for this approach. Patients with T1b may be considered for endoscopic treatment on a case-by-case basis; in a recent study, 28% of patients with T1b disease had lymph node involvement and the rate of lymph node involvement increased with involvement of SM1 to SM3 with 54% of patients with SM3 disease having lymph node metastases. In patients who are surgical candidates, surgery is the recommended approach for definitive treatment; in select patients with multiple co-morbidities or higher surgical mortality risk and with SM1 involvement, endoscopic treatment may be considered for curative intent (68).

Patients who are selected to undergo endoscopic treatment are generally treated with combination treatment with the goal of eradication of all dysplastic tissue in addition to eradication of all precursor abnormalities such as BE. Patients are carefully inspected on initial exam to identify all raised or nodular lesions. These lesions are

treated with either EMR or ESD depending on the depth of disease and size of the lesion. After endoscopic resection of all raised lesions is completed, patients are treated with high dose PPI therapy for 3 months for improved wound healing. Patients return at 3 months intervals for follow up evaluation; ablative therapy is applied to all residual flat disease at the next session with the goal of eradication of all precursor lesions. Patients generally undergo on average 2 to 3 sessions of ablative therapy for successful elimination of all flat dysplasia and BE (9). Patients are recommended to undergo surveillance endoscopy and retreatment every 3 months for the first year.

Several series have reported long-term outcomes after combination endoscopic treatment for HGD or early EAC. The largest published case series to date included long term follow up (mean 56.6±33.4 months) of 1,000 patients who underwent endoscopic treatment of intra-mucosal carcinomas (T1a) by combination therapy of EMR followed by ablative therapy including APC or RFA. In this series, complete remission of carcinoma was achieved in 96.3% of patients. Recurrence of HGD or intramucosal carcinoma occurred in 14.5% of patients and repeat endoscopic treatment was successful in 85% of these patients. Major complications (bleeding, perforation) from endoscopic treatment were seen in 1.5% of patients and minor complications (stricture) were seen in 1.3% of patients (8).

While combination therapy is the most described, some series have looked at patients treated with EMR alone or with ablation alone. A recent study described 107 patients treated with EMR only for complete eradication of all dysplasia and BE; 72% of patients achieved complete remission of HGD/ImCA and all BE with 40% of patients developing strictures that required dilation (69).

There is less reported literature on long-term outcomes after combination endoscopic treatment for squamous cell HGD or intramucosal carcinoma. A recent retrospective study, at a Japanese institution, presented 204 patients with early SCC, defined as histological confirmation of invasion limited to SM1, treated with endoscopic therapy followed by ablation if positive margins remained. In this group, 11% of patients experienced metachronous recurrence and 2% developed local recurrence during a median follow of 36 months. All patients were able to be treated with subsequent endoscopic therapy. Approximately 4% of patients developed complications including one perforation and eight strictures (70). While these results are promising, combined modality endoscopic treatment for early SCC continues to be investigated.

Surveillance after endoscopic treatment is essential to ensure complete eradication of dysplastic tissue and to observe for the possible recurrence of dysplasia in the treated area. Recurrence of “buried” BE or the development of subsquamous BE and cancer is a concern that requires close monitoring. “Buried” BE has been reported in case series in up to 5% of patients treated with endoscopic modalities. Surveillance endoscopy should include a high-resolution exam with diagnostic tools including HDWLE, NBI, or chromoendoscopy as clinically indicated. All surveillance endoscopies should include four quadrant biopsies of the entire length of previous BE or dysplastic tissue to evaluate for recurrence or subsquamous disease. Surveillance intervals are generally recommended to be every 3 months for the first year with lengthening of the interval following this.

Published guidelines

The National Comprehensive Cancer Network (NCCN) guidelines updated in January 2014 describe the addition of endoscopic resection or endoscopic resection followed by ablation as possible alternatives for surgery for patients with Tis or T1a SCC of the esophagus (71). Additionally, endoscopic resection followed by ablation can be considered in medically unfit patients with T1bN0 disease. In patients with Tis, T1a or superficial T1b EAC, endoscopic resection followed by ablation is considered the preferred treatment of choice. Patients are recommended to undergo endoscopic surveillance following endoscopic treatment every 3 months for the first year followed by annual surveillance thereafter.

Summary

Endoscopic treatment should be considered for patients with early esophageal cancer. A combination of modalities including endoscopic resection and ablation is safe and effective to achieve eradication of all dysplastic and neoplastic tissue. As technical skills improve and newer technology becomes available, more options will become available to affected patients. Comparative studies will become necessary to determine the best approach for the treatment of patients with early esophageal cancer. Although wide field resections such as with ESD requires greater technical skill and is associated with greater risk of bleeding and perforation, it is our impression that it provides a greater potential for accurate assessment of

disease and stage, more definitive treatment of the disease, and a resulting greater accuracy in prognostication.

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Peroral endoscopic myotomy for esophageal achalasia

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Abstract: Peroral endoscopic myotomy (POEM) is one of the alternative treatment for achalasia. Due to concept of natural orifice transluminal endoscopic surgery (NOTES), it becomes popular and widely accepted. With the endoluminal technique, submucosal tunnel was created followed by endoscopic myotomy. POEM is not only indicated in classical achalasia but also other abnormal esophageal motility disorders. Moreover, failures of endoscopic treatment or surgical attempted cases are not contraindicated for POEM. The second attempted POEM is also safe and technically feasible. Even though the legend of success of POEM is fruitful, the possible complications are very frightened. Good training and delicate practice will reduce rate of complications. This review provides a summary of current state-of-the-art of POEM, including indication equipments, technique and complications. This perfect procedure may become the treatment of choice of achalasia and some esophageal motility disorders in the near future.

Keywords: Achalasia; peroral endoscopic myotomy (POEM)

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Background

The concept of natural orifice transluminal endoscopic surgery (NOTES) is widely accepted all over the world. The combination of the basic principle of the endoscopy and surgery make the marvelous concept of the less invasive surgical intervention. Peroral endoscopic myotomy (POEM) was recently introduced as the alternative treatment of Achalasia. Inoue H. (1) stated first POEM series in 2010 and widely spread to all over the world. Nowadays more than two thousand cases of POEM procedure had successfully done.

Achalasia is one of the esophageal motility disorders which impair relaxation of lower esophageal sphincter. In the North America, the estimated prevalence and incidence is 10.82 cases per 100,000 and 1.63 cases per 100,000 per year respectively (2). The choices of treatment are varies from medication to surgery. POEM is safe, scarless, and able to perform in various type of achalasia. It may replace standard procedure in the future.

Indication of POEM

Patients

All patients who diagnosed achalasia can be candidate for POEM. Since there is no direct contraindication of this procedure. The various types of achalasia and esophageal abnormalities are candidates for this procedure.

Disease condition

POEM can be performed in all types of achalasia [categorized by high resolution manometry (HRM)] especially in tortuous dilated sigmoid achalasia which is contraindication to surgical myotomy. Sigmoid achalasia was successfully performed more than sixty cases without complications in our series.

Previous procedures

POEM was indicated in prior endoscopic intervention or

surgical myotomy.

Even though palliative balloon dilatation in dysphagia patients makes some fibrosis, the following POEM is safe and feasible. The prior surgery or POEM is also possible to re-perform without any difficulty. Eleven cases of previous surgical myotomy and ten cases of second POEM were performed without any complications.

Equipments

A forward-viewing endoscope of outer diameter 9.8 mm, which is designed for routine upper gastrointestinal screening is used with a transparent distal cap attachment (DH-28GR, Fujifilm). This distal attached cap provided a better endoscopic vision even in submucosal space. With the smooth tapering cap, it takes the advantage to penetrate through the narrow part of submucosal tunnel. Air ventilation slit was designed to release smoke and provided clear vision during the procedure.

Mixture of 0.9% normal saline with 0.3% indigo carmine dye is usually used for submucosal injection. The concentration depends on the operator preference. This mixture offers a good plane for dissection and prevented unexpected injury to esophageal mucosa.

Injection needle: initially normal saline is injected with a 25 gauge injection needle. After that injection is repeated injection in the submucosal space by injection spray (non-needle type).

A triangle-tip knife (TT knife) (KD-640L, Olympus) was used to dissect the submucosal tissue and to divide circular muscle bundles. The maximum diameter for insertion portion of KD-640L is 2.6 mm.

A coagulating forceps (Coagrasper, FD-411QR; Olympus) is used for homeostasis and coagulated large vessels.

For electrosurgical energy generator, a VIO 300D electrogenerator (ERBE, Tübingen, Germany) is recommended. Generator mode of Spray coagulation in ERBE300D allows non-contact tissue dissection. It makes submucosal dissection much easier, faster and less bleeding.

Carbon dioxide insufflation is insufflated during the procedure with a CO₂ insufflator (UCR; Olympus). CO₂ insufflator with a regular insufflating tube (MAJ-1742; Olympus) offers controlled gas feeding of 1.2 liter/minute during procedure. Endoscopic CO₂ insufflation is beneficial for reducing the risk of both mediastinal emphysema and air embolization. During the procedure, the air insufflation had been strictly closed. If not, the pressure of air insufflation will overcome the carbon dioxide pressure

resulted in complication, e.g., pneumomediastinum, pneumoperitoneum. CO₂ insufflation is safe, rapidly absorption, decrease intra procedural, post procedural pain and recovery time (3-5). The CO₂ insufflation is safety as regular usage in laparoscopic and thoracoscopic surgery.

Gentamicin solution: 40 mg of Gentamicin diluted by 0.9% NSS 20 cc was injected before closing mucosal opening as a local antibiotic.

For final closure of the mucosal entry site, hemostatic clips (EZ-CLIP, HX-110QR; DF Olympus) are applied. Mucosal entry must securely be closed to avoid leakage of esophageal content into mediastinum.

Preoperative evaluation

Preoperatively, patients are evaluated with a history and physical examination, upper endoscopy, timed barium esophagogram (TBE), CT scan and HRM. TBE was performed using a 200-mL oral bolus of low-density barium, with radiographs taken at 1, 2, and 5 min after swallowing. CT scan is used not only to judge the degree of esophageal dilatation, but also to provide information on the anatomical features of adjacent structures. HRM was performed using a standard technique (6), and interpreted according to the Chicago Classification of esophageal pressure topography (7). An Eckardt symptom score (8) (which measures frequency of dysphagia, regurgitation and chest pain, and amount of weight loss, each on a scale of 0-3 resulting in a total scale of 0-12 with higher scores indicating more severe disease) and Vaezi symptom score (9) (which measure the height of barium column during TBE) were recorded preoperatively for POEM patients.

POEM operative technique

Patient is kept fasting overnight. Prior procedure started, residual food and liquid was clear to guarantee clear endoscopic view and avoided aspiration during induction of anaesthesia. The large channel endoscope (GIF-1T240, Olympus) is used for suction and irrigation with normal saline until clear. The antiseptic solution irrigation is not necessary. Prophylaxis intravenous antibiotic, 3rd generation cephalosporin is delivered beforehand.

Step 1: endotracheal intubation and CO₂ insufflation

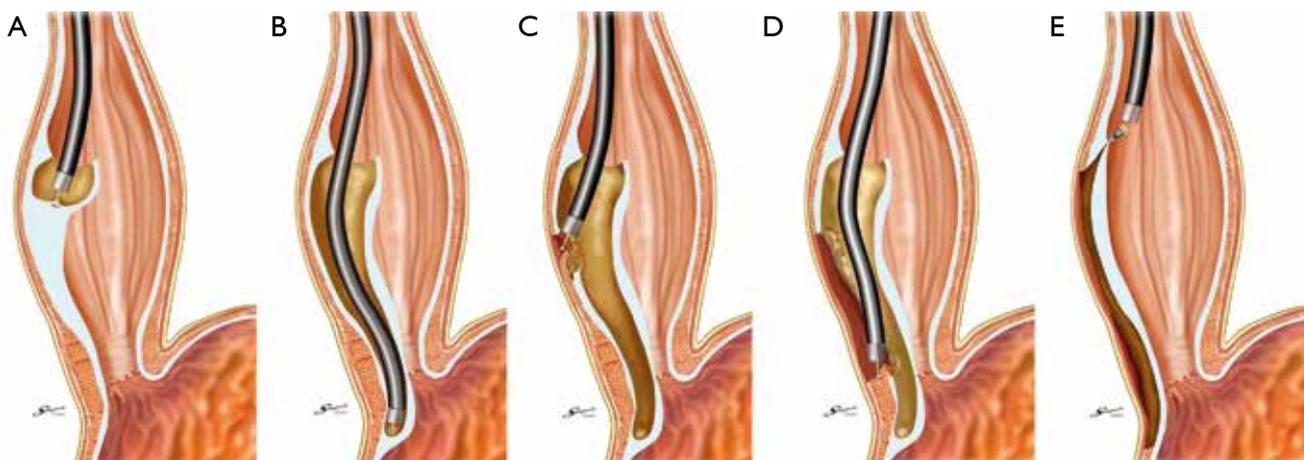
Patient was lying supine on the table with general anaesthesia. Positive pressure ventilation is recommended



Figure 1 Position of the patient.



Figure 2 Abdominal paracentesis.



Scheme 1 Steps of POEM. (A) mucosal entry; (B) create submucosal tunnel; (C,D) myotomy; (E) closure mucosal entry (©Inoue H. Showa University Northern Yokohama, 2010). POEM, peroral endoscopic myotomy.

for this procedure to prevent severe mediastinal emphysema. In our series, pneumoperitoneum occurred in eight cases. The abdomen was left exposed in order to detect abdominal distention and probably abdominal compartment syndrome (*Figure 1*). When abdominal wall is excessively extended, abdominal paracentesis using injection needle is the most effective to release abdominal pressure (*Figure 2*).

Step 2: creation of a submucosal tunnel mucosal entry

A total of 10 mL normal saline with 0.3% indigo carmine mixture is injected to the mucosa as a wheal before triangular knife is applied to open the mucosal surface (*Scheme 1A*). The recommended incision is anterior wall usually between 11 and 2 o'clock. A 2-cm longitudinal

mucosal incision was made on the mucosal surface to create a mucosal entry to the submucosal space (Endo cut Q mode, 50 W, effect 3). If the patient happens to have abnormal contraction of esophageal upper third much longer myotomy is expected. Longer myotomy can effectively control chest pain caused by spasm of hypertrophied circular muscle.

Submucosal tunnel: the tunnel is made downwards by using a technique similar to ESD, passing over the EGJ and enter the proximal stomach about 3 cm. Using TT knife (*Figure 3*), submucosal tissue is dissected by non-touching technique with spay coagulation 6mode, 50 W, effect 2 on ERBE 300D. Dissecting plane is definitely just beneath muscle layer surface (*Figure 3B*) (*Scheme 1B*). Mucosal injury may cause the serious complications because it is an only

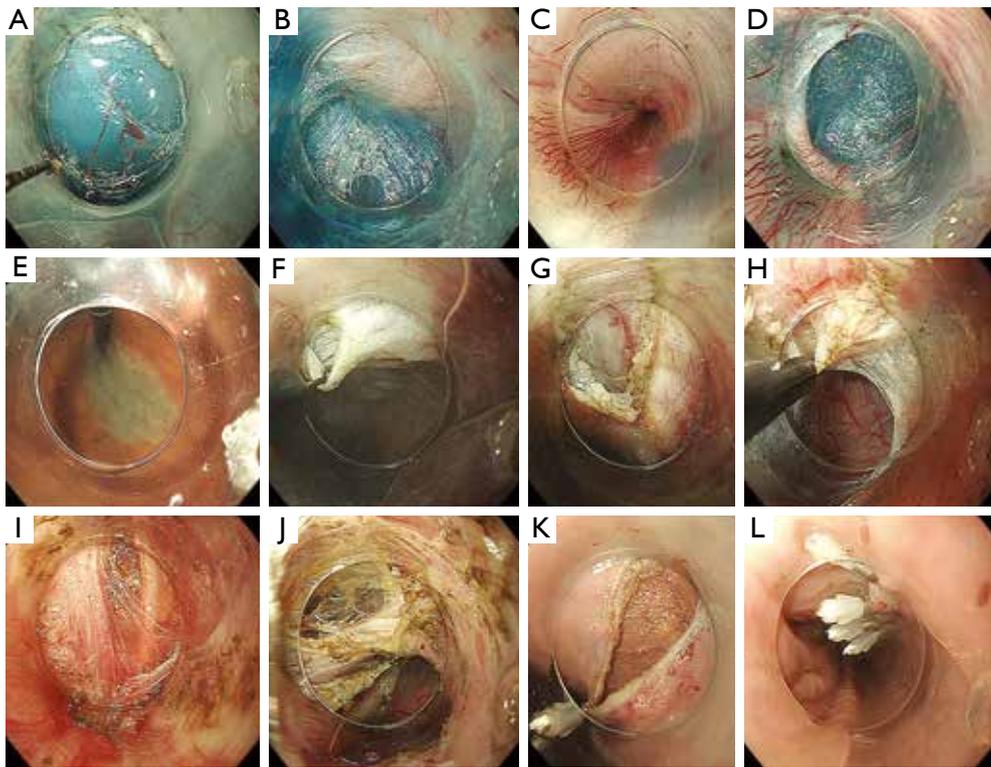


Figure 3 Step of POEM. (A) submucosal layer; (B) dissection plane just beneath muscle layer; (C) palisade vessels; (D) gastric site; (E) retroflex view showed dye stain; (F) initial myotomy site; (G) circular muscle was divided exposed longitudinal muscle; (H) narrow segment of LES; (I) exposed mediastinum due to total myotomy (vagus nerve seen); (J) myotomy was end about 2 cm below EGJ; (K,L) closure of mucosal inlet. POEM, peroral endoscopic myotomy.

Table 1 The landmark of the esophagogastric junction

Depth of the endoscope from the incisor
Submucosal lumen become narrow contained high resistance
The palisade vessels were identified
The aberrant innermost longitudinal muscle bundles was identified
Observed location of the scope by another small caliber trans nasal scope

barrier between esophageal lumen and mediastinum after completion of myotomy. During submucosal dissection, repeated submucosal injection makes submucosal tissue dissection easier. The width of the tunnel is about 1/3 of the circumferential of the tubular esophagus.

Identification of GEJ (*Table 1*): another interesting issue with the POEM technique concerns identification of the GEJ in submucosal space. As clear markers for

identifying the GEJ junction, the following indicators should be checked. The first indicator is insertion depth of the endoscope from the incisors. The position of the GEJ junction in the lumen of the esophagus itself is therefore recorded accurately in advance before we inserted the endoscope into the submucosal tunnel. Insertion depth of the endoscope in the submucosal space is almost the same as the accurate position of the endoscope in the true lumen. The submucosal tunnel created ends at least 3 cm long enough distal to the estimated GEJ. The second indicator is a marked increase of resistance when the endoscope approaches the GEJ, followed by a prompt easing when the endoscope passes through the narrow GEJ and enters gastric submucosal area. The working space in the submucosal tunnel also becomes gradually narrower when the endoscope approaches closely to the LES. At the LES segment, movement of the endoscope is obviously limited with high resistance. The third indicator is identification of palisade vessels in the submucosal layer (*Figure 3C*). Palisade vessels are located at the distal end of the esophagus.



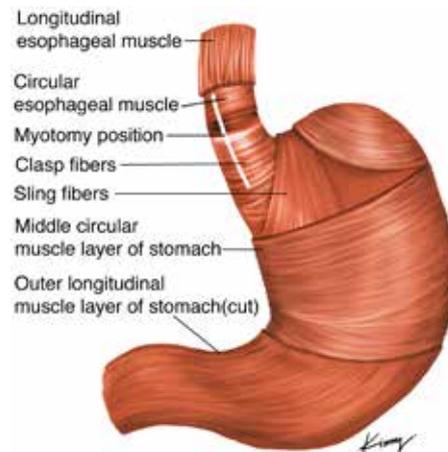
Figure 4 The aberrant innermost longitudinal muscle bundles.

The fourth indicator is a change of vasculature in the submucosal layer. There are plenty of gastric submucosal vessels compared to esophageal submucosal site. Finally, the aberrant innermost longitudinal muscle bundles in front of the circular muscle layer is one of the indicator for esophagogastric junction (10) (*Figure 4*). Large vessels in the submucosa are coagulated using the hemostatic forceps in soft coagulation mode (80 W, effect 5). Once tip of endoscope is getting into the cardia, submucosal space will be opened widely (*Figure 3D*). The distal margin of the tunnel can be easily checked by visualized the blue submucosal tattoo (*Figure 3E*) from retroflex view.

The recently published paper proposed to use a small caliber trans luminal scope inserted through natural lumen to observed real time dissection. It resulted in precise location but required another endoscopist and special instruments. It was useful in difficult cases (11).

Step 3: endoscopic myotomy

Dissection of the circular muscle bundle was begun at 2 cm distal to the mucosal entry, more than 10 cm above the GEJ (*Scheme 1C*). The sharp tip of the TT knife was used to first catch a couple of circular muscle bundles and then to lift them up toward the esophageal lumen. The captured circular muscle bundle was cut by spray coagulation current (50 W, effect 2). At the beginning of myotomy transverse muscle bundle should be caught and then gradually cut by electrocautery until longitudinal muscle layer was identified (*Figure 3F,G*). This inter-muscular space is the correct



Scheme 2 Anatomy of the stomach showed sling fibers (natural antireflux system) ©Inoue H. Showa University Koto-Toyosu Hospital 2014.

dissection plane. In any case outer longitudinal muscle layer is thin like a sheet of paper. It is regarded to have less special function of muscle contraction. Operator may reduce risk of surrounding structures injury by keep outer longitudinal layer intact. Division of the sphincter muscle was continued from the proximal side towards the stomach until the endoscope passed through the narrow segment of the LES (*Figure 3H*). Longitudinal muscle layer should be carefully preserved during the dissection procedure. The injured or torn longitudinal muscle, the mediastinal structures were exposed, does not caused any sequelae or complication if the mucosa was still intact (*Figure 3I*).

How to avoid symptomatic GERD?

Anterior myotomy in the two o'clock direction in the supine position seems most appropriate, as this leads to lesser curvature of stomach. In contrast, the angle of His is located at in the eight o'clock direction. Anterior myotomy potentially avoids damage to the sling muscle, and especially His angle (*Scheme 2*). In surgical myotomy an antireflux measure, such as a Dor procedure, is also carried out in order to avoid postoperative GERD, since adjacent structures surrounding the distal esophagus are inevitably dissected which may impair natural antireflux mechanisms. With POEM no antireflux procedure is carried out, since the endoscopist never touches surrounding structures. However, complete myotomy potentially may have a risk for post-therapeutic GERD. When the tip of the endoscope reached the stomach region, the submucosal space suddenly became

wider. Thickness of inner circular muscle layer is different in individual cases. Muscle layer cutting was continued for at least 2 cm distal to the EGJ (*Figure 3F*) (*Scheme 1D*). Complete division of the circular muscle bundle was confirmed by the endoscopic appearance. Any muscle bundle which runs transversely should not be remained. Complete hemostasis also achieved using coagulating forceps. After completion of the myotomy, smooth passage of an endoscope through the GEJ with minimal resistance was confirmed. The other abnormal esophageal motility patients, presented with odynophagia, need a very long myotomy which surgical myotomy cannot be performed. The myotomy length is approximately 10-15 cm depend on individual cases.

Step 4: closure of mucosal entry

Before closure mucosal entry, 40 mg gentamicin is infused into the submucosal tunnel. The mucosal entry site, usually 2-3 cm long, was closed with about 5-8 hemostatic clips (*Figure 3K,L*) (*Scheme 1E*). Whether mucosal entry is elongated over to myotomy site, tight mucosal closure only by clips avoids leakage of esophageal luminal content. Successful closure of the mucosal entry was confirmed by the endoscopic appearance (*Figures 1,4*). Over the scope clipping device was reported to use as the mucosal closure. Its wide mouth and ability to grasp large amount of tissue acquire secure closure of the mucosa. At the end of the procedure, the smooth passage through the gastrointestinal junction was checked by inserted scope in the natural lumen.

Post-operative care

Immediate post-operative period, Chest X-ray and abdominal plain X-ray was required. It is guarantee for non-clinical pneumomediastinum, pneumothorax nor pneumoperitoneum. Patient was kept fasting, intravenous antibiotic infusion and adequate pain killer.

1st day after POEM

Gastroscopy is needed to confirm the mucosal integrity. If mucosal was tightly closed without mucosal damage, water sipping is allowed. If mucosal defect existed or was questionable, continuing fasting for a few more days and repeated endoscopic examination would be advised. Fortunately, in our series we have no experience of mucosal damage.

TBE is also important to confirm smooth passage of

contrast media through EGJ with no leakage and stasis. Mucosal integrity is the premise of diet opening. Begin with drinking liquid on day 1, soft meal can be started on 2nd day post-POEM, and normal diet on 3rd day post-POEM. TBE provided an information for Vaezi score that can predict the prognosis and able to compare with pre-operative stage.

Antibiotics: intravenous infusion of antibiotics was prescribed for three days followed by four days oral antibiotics.

Complications

Pneumoperitoneum

Pneumoperitoneum during the procedure occurred in eight cases, all are treated with abdominal paracentesis to release abdominal pressure. The long 18 gauge needle with stylet is applied through abdominal wall. Carbon dioxide is released under the water.

Pneumomediastinum is managed by inserted small caliber of intercostal drainage (ICD) for couple days.

Mucosal injury

Cardia mucosal perforation is rarely occurred during the procedure. The management guideline is conservative with intravenous antibiotics, apply hemostatic clips and fibrin sealant spray (12). All reports receive successful treatment without any complications. A cover retrievable metallic stent was reported to place to prevent the inevitably stricture following mucosal injury in children (13). The choices of treatment depend on the preference of the endoscopist.

Bleeding

Acute bleeding or intraoperative bleeding manage by pressure the bleeding point with the cap, identified the bleeding point and coagulation with the coagrasper. The blind coagulation is avoided. In case of bleeding point cannot identified, pressure with the endoscopic tip in submucosal space or natural lumen in correspond level is advised. The postoperative hematoma may occur in this situation. Conservative treatment, keeping fasting with intravenous antibiotic is suggested. The hematoma will gradually resolve within one to two weeks. Diet will be stepping after solved hematoma.

Delay bleeding. A presence of postoperative hematemesis, melena, retrosternal pain, hypotension,

and/or tachycardia occurred, the postoperative bleeding should be suspected. CT scan and emergency endoscope are indicated to confirm this condition. Only 0.7% of delayed bleeding was reported (14). Emergency gastroscopy is performed to identify bleeding point in submucosal tunnel. If bleeding point cannot be identified, Sengstaken-Blakemore tube is directly placed into the stomach and lower esophagus to compress the bleeding sites. Bleeding always located at the edge of cut muscle and may related to history of predisposing bleeding factors, e.g., coagulation disorders, and history of antiplatelet/anticoagulant therapy.

Gasatrosophageal reflux (GER)

One of the complications after POEM is GER. The prevalence of mild GER is 46% (15,16) which comparable to 25-40% in laparoscopic heller myotomy (LHM) with Dor fundoplication and 20-30% after Toupet fundoplication (17,18). In our series, Over all post-operative GER was 63% but 80% is mild esophagitis [Los angeles classification (LA) 0, A, B] and symptom free. Only 4.89% (16/327 cases) need acid suppression treatment (LA C, D or symptomatic GER). However, risk factors for GER are still not identified yet. Fortunately, all patients' symptoms are well controlled by proton pump inhibitor (PPI). One of the hypotheses is the natural antireflux mechanism of the stomach (Angle of His). The fully mobilisation of the stomach during LHM disturb this mechanism while it is not involved by POEM. Thus, it is not necessary to add antireflux procedure.

POEM in children

In our institute, we experienced nine cases of children who diagnosed achalasia. The M:F ratio is 1:2. The major chief complaints are dysphagia. The onset varied from five months to eleven years and duration of disease between 31 months (5-72 months). All of them are type I or II. Only one case is sigmoid achalasia. After treatment, the Eckardt score was significantly reduced from 6.0 to 0.8. The procedure is conducted as same as regular. The obstacles during treatment are the obscure diagnosis, unsatisfied weight and small esophagus.

POEM after endoscopic intervention

Pneumatic dilatation (PD) or Botox injection is acceptable treatment for achalasia patient even though the recurrent rate is still high. However, some patients wish to choose

these options as a definite treatment in order to avoid surgery. The long term success of Botox injection and PD are 50% (19) in 1 yr and 40% in 5 yrs (20), respectively. Even the satisfactory result, there are some groups of patient need re-intervention or other treatments. It is generally accepted that the predictors of risk factors for relapse after PD include young age (<40-45 years), male sex, single dilation with a 3.0 cm balloon, post-treatment LES pressure >10-15 mmHg, poor esophageal emptying after timed barium swallow, and type I and type III achalasia pattern on HRM (21,22). It has been shown that POEM can be as safe and effective as first-or second-line treatment, even after the failure of Botox injection or PD. Regards to the technique, there are some difficulty due to existing adhesions from previous intervention. The delicate dissection with repeated normal saline injection leads us to the desirable plane. Coagulation forceps were applied to control unexpected bleeding from prior inflammatory induced vessels. The landmarks of the EGJ needs to clearly identified for adequate dissection plane. All of these techniques make POEM as a safety procedure. Besides of these, POEM also takes a role in esophageal motility disorder treatment. On the other hand, PD plays a good role for temporary treatment in dysphagic patients. It may improve nutritional status, reduced local esophagitis and prevented reflux complication during they are waiting for POEM.

POEM after laparoscopic heller myotomy (LHM)

LHM is expected as a treatment of choice for achalasia. The comparative study showed POEM has equivalent outcome to LHM regards to peri operative and short term outcomes (23,24). The failure of LHM need another intervention or surgery (redo myotomy or esophagectomy). Due to the difficulty to resect adhesions in redo surgery and high morbidity of esophagectomy, POEM is a better choice for treatment recurrence achalasia. The recently report demonstrated ten cases recurrence dysphagia was successfully treatment by POEM (25). The concept of treatment is to make another myotomy in different location from the prior surgery. Even though it showed only short term result, further study is required to define the long-term clinical outcomes.

Training in POEM

Performing POEM procedure requires two professional

skills. Basic anatomy beyond the esophageal mucosa and good manipulation of endoluminal procedures are needed. Both gastroenterologist as well as surgeon shared their experiences in this procedure. However, its complications risk serious adverse event including mediastinitis and sepsis. Thus, delicate skills are also needed. The porcine model, explant and living model, was proposed as a standard for POEM training (26). The porcine model has advantage as its similarity to the human anatomy, cheap and reproducible. In contrast, myotomy is limited due to the attenuated circular muscle. The cadaveric model has strong advantage as a real human anatomy but difficulty in mucosotomy and submucosal tunneling dissection due to tissue pliability and poor tissue distention (27). Till now, there is no standard training guideline for training. The training system is divided to two different systems. First is preclinical training which trainee has to practice in the animal or cadaveric model about 46 (range 12-154) hours. On the other hand, some center use clinical proctor system which done initial in human. The median number of proctored cases was 2 cases (1-7 cases) (28). However, the learning curve of POEM procedure was 20 cases in experienced hand (29).

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Human and animal rights and informed consent: this article does not contain any studies with animal subjects performed by any of the authors. With regard to the authors' research cited in this paper, all procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000 and 2008.

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Endoscopic submucosal dissection for superficial Barrett's esophageal cancer in the Japanese state and perspective

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Abstract: The incidence of Barrett's esophageal cancer is one of the most rapidly increasing among all cancers in the West, and it is also expected to increase in Japan. The optimal treatment for early Barrett's esophageal cancer remains controversial. *En bloc* esophagectomy with regional lymph node dissection has been considered the standard therapy. Endoscopic therapies are currently being evaluated as alternatives to esophagectomy because they can provide the least postoperative morbidity and the best quality of life. Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) allow for removal of visible lesions and histopathologic review of resected tissue, which help in diagnostic staging of the disease. EMR is limited with respect to resection size, and large lesions must be resected in several fragments. Piecemeal resection of lesions is associated with high local recurrence rates, probably because of minor remnants of neoplastic tissue being left *in situ*. ESD provides larger specimens than does EMR in patients with early Barrett's neoplasia. This in turn allows for more precise histological analysis and higher *en bloc* and curative resection rates, potentially reducing the incidence of recurrence. Detailed endoscopic examination to determine the invasion depth and spread of Barrett's esophageal cancer is essential before ESD. The initial inspection is usually conducted with white-light imaging followed by narrow-band imaging. The ESD procedure is similar to that for lesions in other parts of the gastrointestinal tract. However, the narrow space of the esophagogastric junction and contraction of the lower esophageal sphincter sometimes disturb the visual field and endoscopic control. Skilled endoscope handling, sometimes including retroflexion, is required during ESD for Barrett's esophageal cancer. Previous reports have shown that ESD achieves *en bloc* resection in >80% of lesions. Although promising short-term results are reported, a long-term, large-scale study is required for better understanding of ESD for Barrett's esophageal cancer.

Keywords: Barrett's esophageal cancer; Barrett's esophagus (BE); endoscopic resection; endoscopic submucosal dissection (ESD); endoscopic treatment

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Barrett's esophageal (BE) cancer

BE was first described in 1950 (1). This condition is thought to be a complication of chronic gastroesophageal reflux disease and may be found in both symptomatic and asymptomatic individuals (2). The annual incidence of adenocarcinoma arising from BE is 0.12% to 0.50% (3-7). There is geographic variation in the prevalence of BE, which

is much more common in the West than in the East (8). The increase in the incidence of BE has led to a four-fold increase in the incidence of BE cancer in the West (9). Similar data are not available from the East. However, it is suggested that the rate of BE and BE cancer will increase in Asia in the future (10,11) because of the decreasing prevalence of *Helicobacter pylori* infection and Westernization of the diet.

Barrett's esophageal cancer in Japan

BE is defined as replacement of the stratified squamous epithelium that normally lines the distal esophagus with columnar epithelium (12). Histological confirmation of intestinal metaplasia is not required for the diagnosis of BE in Japan. In Japan, there are few reports on the prevalence of BE and incidence of BE cancer. BE is usually classified into two categories according to the extent of columnar epithelium above the gastroesophageal junction: (I) long-segment BE, in which the extent of the columnar epithelium is ≥ 3 cm; and (II) short-segment BE, in which the extent of the columnar epithelium is < 3 cm (13). In Japanese patients, because the prevalence of long-segment BE (≥ 3 cm) is extremely low (11), most esophageal adenocarcinoma in Japanese patients arises from short-segment BE. The risk of cancer in BE appears to vary with the extent of BE; therefore, patients with long-segment disease may have a higher incidence of adenocarcinoma than those with short-segment BE (14). In a Spanish cohort, for example, the annual risk of BE cancer was 0.57% for patients with long-segment BE and only 0.26% for patients with short-segment disease (15).

Treatment for Barrett's esophageal cancer

BE cancer survival rates correlate with the disease stage. Locally advanced diseases show a 5-year survival rate of approximately 20% (16,17). Because of the poor 5-year survival rates for advanced BE cancer, surveillance and early detection of BE cancer has become a critical issue (18,19). Rigorous surveillance of BE and a systematic biopsy protocol improves detection of dysplasia and early cancer (20).

The optimal treatment for early BE cancer remains controversial. *En bloc* esophagectomy with regional lymph node dissection has been considered to be the standard therapy. Esophagectomy definitively eliminates all portions of the esophagus lined by BE and allows for the removal of associated lymph nodes that could harbor metastases. Nevertheless, *en bloc* esophagectomy is associated with high mortality (4-19%) (21), high postoperative morbidity (20-47%) (22), and low postoperative quality of life (23). The morbidity and mortality associated with surgical esophagectomy and the low rates of metastases associated with early esophageal cancer have led to an interest in newer, less invasive therapies as alternatives to esophagectomy.

New modalities such as endoscopic therapies or less

aggressive surgical operations are currently being evaluated in an effort to achieve the least postoperative morbidity and the best quality of life. Although limited data are available on the risk of metastasis related to subdivisions of T1 lesions, studies of esophagectomy specimens indicate that a low risk is present, ranging from 0.0% to 1.3% for T1a carcinomas and 18.0% to 22.0% for T1b tumors (24-26). This low rate of metastasis has provided a rationale for the endoscopic treatment of mucosal (T1a) BE cancer or high-grade dysplasia for curative intent. Endoscopic therapies can be further subdivided into tissue-acquiring and non-tissue-acquiring modalities. Tissue acquisition can be achieved through endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR), while thermal, photochemical, or radiofrequency energy is used to destroy the BE without providing a tissue specimen (27-29). Favorable outcomes have been reported after endoscopic ablative techniques such as photodynamic therapy, radiofrequency ablation, and cryotherapy. Modalities such as argon plasma coagulation, multipolar electrocoagulation, and laser therapy are not current mainstay therapies because of high BE relapse rates and their infrequent usage. In endoscopic eradication treatment, it is recommended that any visible abnormalities be removed by endoscopic resection followed by ablation of all remaining BE according to United States guidelines (30). However, this strategy is not commonly utilized in Japan because of the unknown risk of metachronous lesion development in the residual BE after endoscopic resection in the Japanese population.

ESD and EMR for Barrett's esophageal cancer

Endoscopic resection in the form of EMR and ESD allows for removal of visible lesions and histopathologic review of resected tissue, facilitating more accurate diagnostic staging of the disease. If submucosal invasion is found, patients can then be referred for surgical resection because these lesions have a substantial risk of metastasis. If the lesion is confined to the mucosa and the resection margins are clear, endoscopic resection can be curative because of the very low risk of lymph node metastases. Notably, most adverse events associated with endoscopic resection are amenable to endoscopic treatment (31-33).

The various modalities of EMR include the use of a transparent cap, two-channel endoscope, and ligation. These modalities are limited with respect to resection size, and large lesions must be resected in several fragments. In addition, the targeted area cannot be precisely controlled by



Figure 1 Endoscopic image of Barrett's esophageal cancer with small elevations and slightly reddish areas.



Figure 2 Narrow-band image of a slightly reddish area shows an irregular surface pattern.

the endoscopist, which might result in unnecessary resection of non-neoplastic mucosa. When lesions are resected in small fragments, histological assessment of cancer invasion depth can be inaccurate. Histological evaluation of several specimens cannot usually identify the outer margins of the neoplastic area, and thus complete resection cannot be confirmed. In addition, piecemeal resection of early neoplasia in BE is associated with a high local recurrence rate, probably because of minor remnants of neoplastic tissue left *in situ* (34-37). In one trial, the rate of complete resection (R0) was only 30% with a lesion diameter of <20 mm (36). Repeated sessions of EMR are sometimes needed to achieve complete local remission, and recurrent lesions develop in 10% to 30% of cases after EMR without eradication of the residual non-neoplastic BE (34-36,38,39).

In patients with early BE neoplasia, ESD provides larger specimens than does EMR, for more precise histological analysis and higher *en bloc* and curative resection rates, potentially reducing the incidence of recurrence. Variations of this method have been used increasingly more frequently for early gastrointestinal neoplasia, mainly in Asian countries. Although no large randomized prospective studies of ESD and EMR for neoplastic lesions have been performed, the results of several retrospective studies have been reported (40-42). A recent meta-analysis of nonrandomized studies showed that ESD for early gastrointestinal tumors is superior to EMR in terms of *en bloc* and curative resection rates, but that it is more time-consuming and is associated with higher rates of bleeding and perforation (43). Because limited data are available on ESD for BE cancer, we herein introduce our view of the Japanese standard practice of ESD for BE cancer.

Endoscopic examination before ESD

Detailed endoscopic examination to determine invasion depth and lesion spread is usually performed before ESD. Initial inspection is conducted with white-light imaging (*Figure 1*). Cancer invasion depth is diagnosed based on the lesion color, elevation, depression, and hardness. Spread of the lesion is determined by the presence of redness, an irregular surface, slight elevation, or slight depression. Non-magnifying white-light imaging observation is usually followed by magnifying narrow-band imaging observation. Lesion spread is determined by the presence of an irregular surface pattern or irregular vessel pattern with narrow-band imaging (*Figure 2*). Endoscopic diagnosis of the lateral extension of BE cancer is sometimes difficult because the margin can be unclear and the cancer can spread under the squamous epithelium. When these two modalities fail to delineate the lesion, biopsies are taken for further assessment. Screening for synchronous lesions is also performed with white-light imaging and narrow-band imaging. Autofluorescence imaging is commercially available, but the combination of this modality and random biopsy is not commonly used in clinical practice of BE cancer treatment in Japan.

Indication for ESD

ESD is indicated when a lesion is diagnosed as high-grade dysplasia or mucosal cancer during the pretreatment evaluation. The depth of cancer invasion is further assessed by histological examination of the resected specimen. When the lesion is identified as high-grade dysplasia or cancer limited to the lamina propria, ESD is regarded as



Figure 3 Endoscopic image of Barrett's esophageal cancer after marking.



Figure 4 Esophageal ulcer after endoscopic submucosal dissection.

curative. When the lesion invades the muscularis mucosa, a substantial risk of metastasis exists and additional surgical resection is considered based on the patient's condition. When submucosal invasion is confirmed histologically, additional surgical resection is usually performed. A lesion with a circumferential spread of two-thirds or less is a generally accepted indication for ESD. Lesions with a circumferential spread of more than two-thirds can be treated by ESD; however, surgical resection is sometimes indicated because of the risk of severe stricture after ESD.

Process of ESD

Marking dots are usually made 2 to 3 mm outside the margins of the lesion. However, the margin of BE cancer is sometimes unclear and difficult to delineate. Marking dots are made 5 to 10 mm outside lesions with unclear margins. When the

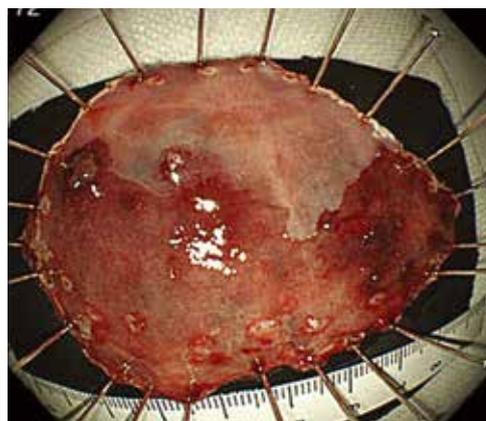


Figure 5 Endoscopic image of resected specimen.

oral side of the lesion is adjacent to the squamous epithelium, marking dots are made at least 10 mm outside the oral margins because the cancer can spread invisibly under the squamous epithelium (*Figure 3*). A solution such as glycerin solution or hyaluronic acid is injected into the submucosa, and the mucosa is incised outside the marking dots. In the lower part of the esophagus, most of the submucosal vessels run longitudinally. Mucosal incision in the transverse direction readily results in bleeding when longitudinally running vessels are cut. The submucosal layer beneath the lesion is then meticulously dissected until total removal of the lesion has been achieved (*Figures 4,5*). This part of the procedure is the most challenging and requires expert control and skill. Most BE cancers in Japan arise from short-segment BE, which is usually located near the esophagogastric junction. The narrow space of the esophagogastric junction and contraction of the lower esophageal sphincter sometimes disturb the visual field and control of the endoscope. Detailed handling of the endoscope, sometimes retroflexed handling, is required in the narrow space during ESD for BE cancer.

Management of adverse events associated with ESD

The adverse event profile of endoscopic resection includes stricture formation, bleeding, and perforation. Perforation is usually treated by endoscopic clipping, and bleeding is treated by ablation with hemostatic forceps. The risk of stricture rises with the extent of the resection area. When more than three-fourths of the circumference is resected by ESD, the risk of stricture increases (44). Repeated balloon dilatation was previously required to treat stricture after ESD. However, triamcinolone injection (45,46) or oral

prednisolone (47) can reportedly reduce the stricture after wide spread endoscopic resection.

Outcome after endoscopic resection for Barrett's esophageal cancer

Only two English-language case series of ESD for BE cancer (48,49), and four peer-reviewed English articles on ESD for esophagogastric junctional cancer have been published (50-53). BE cancer is probably included within the group of esophagogastric junctional cancers; however, the actual number of cases of BE cancers is not described in these articles. Some non-peer-reviewed Japanese articles involving five to six patients with BE cancer have also been published (54,55). Short-term outcomes were evaluated in these Japanese articles. *En bloc* resection was achieved in 80% to 83% of lesions, and *en bloc* resection with cancer-free margins was achieved in 80% to 83% of patients.

Comparison of long-term survival after surgical resection and endoscopic resection would provide helpful information with regard to the most optimal standard treatment. Although the ideal design would be a randomized controlled trial to compare outcomes between these two treatment modalities, this would be difficult to achieve given the small number of cases of mucosal BE cancer and the difficulty in randomizing patients to these two radically different treatment approaches. The available literature suggests that the long-term outcomes of endoscopic therapy for early esophageal cancer, including the median cancer-free survival period, are similar to those of surgical therapy but with fewer adverse events (37,56-58). ESD allows for detailed histologic examination and a reduced risk of recurrence. Improved outcomes are expected with the use of an ESD-based treatment strategy for BE cancer. Although previous reports show promising short-term results (48-55), a long-term, large-scale study is required for better understanding of ESD for BE cancer.

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Endoscopic therapies for Barrett's neoplasia

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Abstract: The standard of care for treatment of Barrett's esophagus (BE) with early esophageal neoplasia, including high-grade dysplasia (HGD) and intramucosal adenocarcinoma (IMC), has undergone a revolution over the past several years. With the introduction and popularization of endoscopic ablative technologies, along with the refinement of endoscopic mucosal resection (EMR) techniques, the majority of cases of early neoplasia in the setting of BE now are managed by endoscopic approaches. As a result, many patients who previously would have been referred for esophagectomy now may be spared from this major surgical procedure with its inherent morbidity, potential for mortality, and negative impact on long-term gastrointestinal function. The esophageal surgeon must be knowledgeable about the indications for such endoscopic therapies, as well as their limitations and potential pitfalls, so as to apply them in the appropriate clinical scenarios.

Keywords: Endoscopic surgical procedure; Barrett's esophagus (BE); esophagectomy

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Introduction

Esophageal cancer is a highly lethal disease of which relatively few are cured. Data from the American Cancer Society predict an overall 5-year survival of only 17% for patients diagnosed with esophageal carcinoma in 2014 (1). Similar to other gastrointestinal malignancies, cancer of the esophagus is usually asymptomatic in its early stages, a fact that explains the common presentation of patients with the manifestations of advanced, incurable disease. The link between gastroesophageal reflux disease (GERD), Barrett's esophagus (BE), and esophageal adenocarcinoma (EAC) has been well established (2). Fortunately, patients found to have BE with early esophageal neoplasia, such as high-grade dysplasia (HGD) [synonymous with high-grade intraepithelial neoplasia (HGIN) or carcinoma in situ (CIS)] or intramucosal adenocarcinoma (IMC), can be treated with the expectation of cure; this fact should not be lost in the pessimism surrounding the treatment of more advanced EAC. In addition, the frequency of detection of esophageal neoplasia at an early, curable stage appears to be increasing,

an observation that may be explained by a number of factors (*Table 1*). Given the anticipated long-term survival for patients with early esophageal malignancy, quality of life considerations become important in deciding upon a management strategy that avoids morbidity while still assuring eradication of disease.

Contemporaneous to the increasing detection of early esophageal neoplasia has been the introduction of technologies that have improved the ability to eliminate such disease by endoscopic approaches. As a result, a revolution in the standard of care for the treatment of early neoplasia in the setting of BE has occurred. While only a few years ago, the recommended therapy for cases of BE with HGD or IMC was esophagectomy, assuming a medically suitable patient and the availability of an expert surgical team, the treatment paradigm has shifted such that most cases now are treated by endoscopic approaches. Guidelines recently proposed by the American Gastroenterological Association recommend endoscopic resection (ER) and ablation as the procedures of choice

Table 1 Factors leading to the increased detection of esophageal adenocarcinoma at an early stage

- The liberal use of flexible upper endoscopy to investigate foregut symptoms
- The recognition of the potential for gastroesophageal reflux disease to cause BE, a malignant precursor, and esophageal adenocarcinoma
- Structured screening and surveillance programs for BE to detect early neoplasia prior to the onset of sentinel signs or symptoms
- The establishment of formal biopsy protocols for the assessment of dysplasia or occult invasive cancer in the setting of known BE
- Advancements in endoscopic imaging technologies (e.g., narrow-band imaging, confocal laser endomicroscopy) and vital staining dyes that have facilitated the detection of subtle esophageal mucosal abnormalities harboring early neoplasia

BE, Barrett's esophagus.

for BE with HGD in the majority of patients (3). Due to the widespread adoption of these effective and low-risk endoscopic therapies, many individuals who previously would have been referred for surgery are now spared from esophageal resection, with its high rate of morbidity, potential for mortality, and negative impact on long-term alimentary function.

Esophagectomy for early esophageal neoplasia

For decades, esophagectomy was the standard of care for BE with HGD or IMC. As a result, the indications, surgical techniques, perioperative outcomes, cure rates and long-term quality of life relative to esophageal resection and reconstruction have been extensively studied and elucidated. With the recent, rapid changes in treatment recommendations for early esophageal neoplasia, the physician must be mindful of this surgical experience so as to have a basis against which endoscopic alternatives should be compared. In the course of therapy for early neoplasia, the treating physician runs the risk of being over aggressive, recommending esophagectomy when less invasive endoscopic therapies would have been appropriate. Alternatively, the physician may risk being under aggressive, continuing on a course of endoscopic treatment when it should have been abandoned, leading to the development of incurable locoregionally advanced cancer or systemic metastases from what started as a readily curable disease process.

The rationale for esophageal resection in cases of BE with HGD has been based on two factors: (I) occult invasive carcinoma has been found in a significant proportion of esophagectomy specimens, averaging approximately 37% in multiple large surgical series, when surgery has been undertaken for the preoperative diagnosis of HGD (4); and (II) invasive cancer may arise within dysplastic BE over

the short to medium term if the esophagus is left *in situ*. Esophagectomy, therefore, is both curative and prophylactic relative to the treatment of invasive disease. Of course, the ability to eliminate pathologic mucosa by surgical extirpation must be weighed against the invasiveness of the procedure and its implications with regards to perioperative morbidity, mortality, recovery time, and long-term impact on quality of life. Thus, esophagectomy in this circumstance may rightly be considered “radical prophylaxis” for a microscopic disease process (5).

The morbidity and mortality associated with esophagectomy fortunately have improved over recent decades, a trend that is likely to continue. While several well-publicized, population-based studies have reported perioperative mortality of 9% or more following esophagectomy (6-8), these data reflect outcomes ten years or older when surgery was performed for all stages of esophageal cancer in non-specialty centers. Accordingly, such results are not appropriate for comparisons to endoscopic therapies, most studies of which were more recently undertaken for early disease in specialty units.

More relevant for comparison are reports specific to esophagectomy for early esophageal neoplasia. A literature review from 2007 detailed the experience with esophagectomy for HGD over the 20-year period from 1987-2007 and found an overall perioperative mortality of 0.94% (4), roughly one-tenth the mortality rate quoted above for all cases of esophagectomy for cancer. In addition, when operating for early disease with a low potential for lymph node metastasis and high expectation for cure, the surgeon should consider operative approaches, such as transhiatal esophagectomy (THE) (9), minimally invasive esophagectomy (MIE) (10) or vagal-sparing esophagectomy (VSE) (11), that avoid some of the morbidity and negative impact on long-term alimentary function associated with more aggressive procedures.

Endoscopic therapies for early esophageal neoplasia

Endoscopic mucosal resection (EMR)

Inoue, Endo and other surgeons in Japan initially described EMR for curative treatment of superficial squamous cell carcinomas of the esophagus (12). The term “EMR” is a misnomer in that the excision typically occurs at the interface between the submucosa and muscularis propria. As a result, the specimen contains both mucosa and submucosa. The term ER is more appropriate, but has not gained widespread acceptance.

Based on the findings from series of patients undergoing esophagectomy with regional lymphadenectomy, early squamous cell carcinomas were determined to be at low risk of distant intramural spread or metastasis to regional lymph nodes; such tumors were considered amenable, therefore, to cure by endoscopic approaches. The selection criteria for undergoing EMR in Japan include tumors ≤ 30 mm in diameter, infiltration no deeper than the lamina propria, superficial tumor spread \leq one-half the esophageal circumference, and the absence of lymphatic or venous invasion (12).

Physicians in Europe and the United States (U.S.) adopted EMR for excisional biopsy of small mucosal irregularities or discrete nodules in the setting of BE, as well as for potentially curative treatment of small foci of HGD or IMC. Two main applications exist for EMR: (I) provision of a wide and deep biopsy, particularly of small, discrete, mucosal nodules, for diagnosis and staging of metaplasia/neoplasia and to guide subsequent tailored therapies; and (II) excision with curative intent (with or without subsequent mucosal ablative therapy of surrounding non-nodular metaplasia/dysplasia) for neoplasia deemed to be at low-risk for metastasis to regional lymph nodes or systemic sites. Treatment adjuncts in such situations include radiofrequency (RF) ablation, cryotherapy, argon plasma coagulation (APC), multipolar electrocautery (MPEC) or photodynamic therapy (PDT).

In contrast to ablation, EMR possesses the obvious advantage of providing a generous specimen for histologic assessment, including a determination of the presence of invasive carcinoma, the depth of invasion, the degree of differentiation of the tumor, the presence of lymphovascular invasion, and the status of disease at the lateral and deep resection margins. EMR improves the staging of early esophageal neoplasia compared to standard biopsy techniques and imaging modalities such as endoscopic

ultrasonography (EUS). While EUS commonly is utilized to assess the depth of tumor invasion in cases of EAC, particularly for bulky T3 or T4 lesions, it is quite inaccurate at determining the depth of invasion of superficial epithelial or mucosal neoplasms, where important differences are measured in microns and involve landmarks not ultrasonographically discernible.

A feature of EAC is its propensity to spread to regional lymph nodes, the likelihood of which is dependent upon the depth of tumor penetration. Several series from the surgical literature have evaluated outcomes after esophagectomy with regional lymphadenectomy for EAC and have correlated the incidence of nodal metastasis with the depth of tumor invasion. Neoplasia limited to the epithelium (HGD/HGIN/CIS) has no potential for nodal metastasis. Invasive tumors penetrating the basement membrane to involve the lamina propria or muscularis mucosa (IMC; T1a) appear to have a limited potential for nodal disease, in the range of 2-5% (13-18). For EAC penetrating just slightly deeper through the muscularis mucosa to involve the submucosa (submucosal carcinoma; T1b), the incidence of nodal metastasis appears to increase significantly to approximately 25%. The muscularis mucosa, therefore, appears a critical barrier to nodal spread. Tumors involving the muscularis propria or beyond (T2-4) have an even higher probability of nodal involvement, in the range of 50-80%.

The general consensus is that endoscopic therapies are appropriate with curative intent only when the neoplastic process appears to be limited to the epithelium or mucosa and the potential for lymph node metastasis or systemic spread is low. In select circumstances, however, such as the patient at high risk for undergoing esophagectomy, EMR may be considered the best therapeutic option even for submucosal tumors, accepting the modest risk of occult nodal disease.

Endoscopic mucosal resection techniques

A number of EMR techniques have been described, all sharing the basic strategy of endoscopic localization of a specific mucosal nodule or irregularity for excision using a snare cautery device. Differences in technique relate to the use of submucosal injection of saline (with or without dilute epinephrine) to lift the target lesion from the underlying muscle layer, and the manner in which the lesion subsequently is prepared for snare application.

The simplest variant of EMR is snare resection alone



Figure 1 “Suck and ligate” endoscopic mucosal resection technique. (A) Endoscopic image of a small esophageal mucosal nodule in a long segment of Barrett’s esophagus. The nodule is situated at the 8 o’clock position; (B) Variceal banding device attached to the tip of a flexible endoscope; (C) The targeted mucosal lesion is sucked into the cap to facilitate application of a variceal band.



Figure 2 Variceal band applied to the esophageal mucosa with resultant pseudopolyp.

without elevation or submucosal injection. This technique is best applied to polypoid lesions of the esophageal mucosa, in that flat lesions cannot be snared without some form of mucosal elevation, though is infrequently applicable. A common resection method has been the use of submucosal injection of saline with dilute epinephrine (10–20 mL injectate, 1:100,000 solution) to separate the mucosa from the underlying muscularis propria. The target lesion can then be aspirated into a specially designed cap (Olympus EMR-001, Olympus America, Center Valley, Pennsylvania) attached to the end of a standard flexible adult endoscope (“cap-assisted” EMR). The cap is manufactured with an inner groove that allows seating of a standard electrocautery snare. Once the mucosa is within the cap, the snare can be tightened around the base of the lesion and cautery applied, amputating the specimen in the submucosal plane. Prior to application of cautery, the lesion should be gently

tugged to give the endoscopist a sense of mobility from the muscularis propria and to prevent inadvertent full-thickness injury to the esophageal wall. The resected specimen typically remains within the cap and can be extracted as the endoscope is withdrawn.

A similar technique, and perhaps the one most commonly employed, utilizes a variceal banding device with supplied cap system to facilitate excision of the target lesion (*Figure 1A–C*). Various single-use multiband systems (Duette Multiband Mucosectomy System, Cook Medical, Bloomington, Indiana or Bard Six-Shooter, Bard Interventional Products, Billerica, Massachusetts) are commercially available. The procedure involves suction of the nodule or lesion into the cap (without prior submucosal injection) and application of a rubber variceal band to the base of the elevated mucosa (*Figure 2*) creating a pseudopolyp (“suck and ligate” EMR). The lesion is excised either above or below the band using snare electrocautery (*Figure 3A,B*). The specimen can then be retrieved using any of a variety of devices such as a net or polypectomy grasper (*Figure 4*).

An important principle underlying this technique is that the elasticity of the rubber band is not sufficient to hold the muscularis propria within it; excision of the pseudopolyp can proceed with confidence that only mucosa and submucosa are being removed and that a full-thickness perforation should not result (*Figure 5*). Advantages of this technique compared to cap-assisted resection are that submucosal injection is not necessary and that the snare does not need to be seated in the cap, a process that may be time-consuming and difficult to master. Disadvantages of the banding technique are the need to reintroduce the

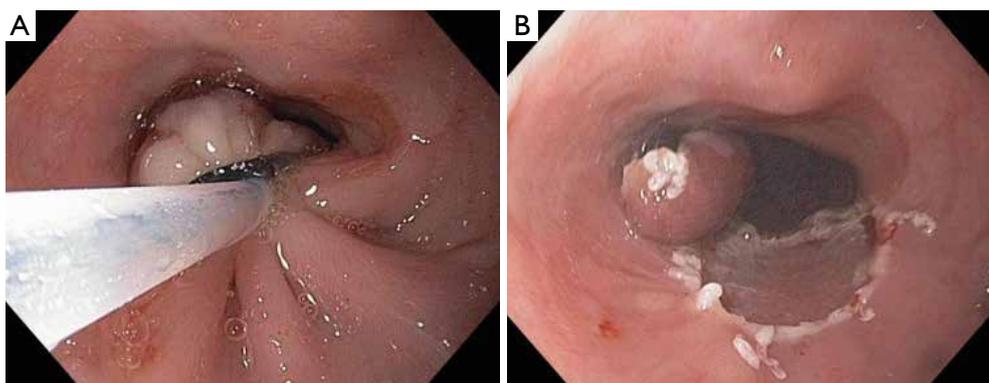


Figure 3 Snare excision of pseudopolyp. (A) Electrocautery snare placed just deep to the variceal band for amputation of the pseudopolyp; (B) Resultant specimen and mucosal/submucosal defect.

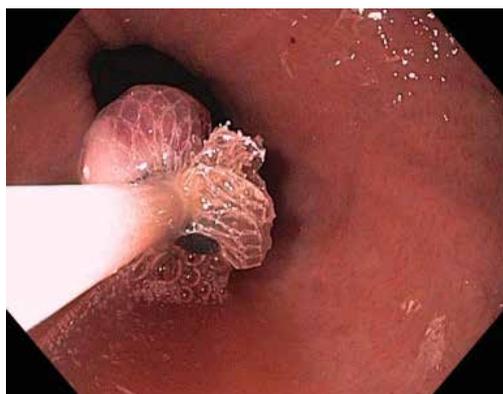


Figure 4 The specimen being retrieved with an endoscopic net.



Figure 5 Defect in mucosa and submucosa created by endoscopic resection. The resection plane is typically at the interface between the submucosa and muscularis propria.

endoscope to position the snare, as well as the requirement of an additional instrument to retrieve the excised specimen. A prospective, randomized trial demonstrated equivalency between “cap-assisted” EMR and “suck and ligate” EMR in terms of the maximum diameter of the resected specimen, the resection area and complication rates (19).

Ell *et al.* from Germany reported in 2007 on their initial experience with EMR for early EAC. Their cohort consisted of 100 patients selected from 667 referred with suspected intraepithelial neoplasia (20). Their criteria for an endoscopic treatment approach are listed in *Table 2*. The majority of tumors (69%) occurred in the setting of short-segment BE. EMR was combined with either APC for short-segment BE or PDT for long-segment BE in 49 patients. Complete local remission was noted in 99 out of the 100 patients by a mean of 1.9 months and a maximum of three resections. Metachronous or recurrent disease occurred in 11% of patients during a mean follow-up period of 36.7 months, though repeat treatment with EMR was successful in all cases. The calculated 5-year survival was 98%, with no cancer-related deaths during the surveillance period.

In a follow-up report published in 2008, their patient cohort had increased to 349 patients with a mean follow-up of 63.6 months (21). The majority of patients underwent EMR, though only 20% were treated with some form of mucosal ablation. Perhaps due to this infrequent use of ablative therapies, the metachronous neoplasia rate increased to 21.5%. The complete response rate was 97%, however, and only 3.7% of patients required esophagectomy

Table 2 Eligibility criteria for endoscopic mucosal resection in the setting of Barrett's esophagus

Tumor characteristics suggesting a low-risk of lymphatic or systemic spread:

- Lesion diameter ≤ 20 mm
- Macroscopically polypoid or flat nodule without ulceration
- Well-differentiated or moderately differentiated adenocarcinoma
- Tumor limited to the mucosa on the basis of staging procedures (e.g., endoscopic ultrasonography) and proven on histologic examination of the resected specimen
- No invasion of lymphatics or veins on histologic examination of the resected specimen

No evidence of lymph node involvement or systemic metastasis on staging evaluation

[Adapted from: Ell C, May A, Pech O, *et al.* Curative endoscopic resection of early esophageal adenocarcinomas (Barrett's cancer). *Gastrointest Endosc* 2007;65:3-10.].

Table 3 Features of an ideal esophageal mucosal ablation technology

- Endoscopic
- Automated, quick and reliable
- Inexpensive
- Removes all Barrett's esophagus in a single session
- Re-treatment possible
- Uniform treatment depth limited to mucosa
- No subsequent buried glands
- No complications
- Eliminates the need for surveillance

for failed endoscopic therapy. The five-year survival was 84% with no EAC-related deaths. Risk factors for recurrent disease included piecemeal resections, long-segment BE, lack of ablative therapy after EMR, and multifocal neoplasia. The data prove the efficacy and safety of EMR in a highly select subgroup of patients referred with IMC and treated at a high-volume specialty center.

Mucosal ablation

Several mucosal ablative technologies have been introduced in recent years for elimination of esophageal metaplasia or early neoplasia. The result of such therapies, however, is that the pathologic epithelium is destroyed, preventing subsequent histopathologic assessment and staging of the disease. The ideal mucosal ablation technology should fulfill a number of criteria (*Table 3*). As newer devices have been introduced into the marketplace, the fulfillment of these criteria has significantly improved, though none to date has proven perfect.

PDT and APC were the two endoscopic ablative techniques most studied in years past. Both procedures, however, had significant shortcomings in that the depth of penetration was limited, variable and difficult to predict, complete elimination of pathologic mucosa was not guaranteed, buried BE under squamous epithelium was observed, and a significant complication rate from esophageal strictures, perforations and photosensitivity (with PDT) was reported. The point-and-shoot nature of APC also made it both unreliable and potentially dangerous. As a result of these limitations, the technologies were not widely adopted and endoscopic ablation with them did not supplant the role of esophagectomy for the vast majority of cases of BE with HGD or IMC.

With the recent introduction into clinical practice of RF ablation, and to a lesser extent cryotherapy, the landscape of endoscopic ablative therapies has undergone dramatic change. These modalities have proven quite effective while overcoming many of the limitations of their precursors. Endoscopic ablation of non-nodular ("smooth") BE with RF, coupled with EMR of discrete mucosal lesions, has clearly been the most significant advance in the treatment of BE and associated early neoplasia over the past decade. The high rate of histologic complete response, along with an excellent safety profile, reasonable cost, and durability of treatment effect, make RF a nearly ideal ablation modality. Eradication of all BE appears to be associated with a lower rate of metachronous neoplasia than resection alone of focal dysplastic or invasive lesions.

Five RF ablation devices (the Barrx 360, Barrx Ultralong, Barrx 90, Barrx 60, and Barrx Channel catheter) are currently manufactured by Covidien Medical (Minneapolis, MN) (*Figure 6*). Each device consists of tightly approximated electrodes (250 μ m spacing) that deliver high-frequency



Figure 6 The five radiofrequency ablation devices made by Covidien Medical (from left to right: Barrx 360, Barrx Ultralong, Barrx 90, Barrx 60 and Barrx Channel catheter).

radio waves, generating heat. The established energy density and dosimetry have been shown to cause a reliable depth of tissue injury to the level of the muscularis mucosa, deep enough to destroy the target epithelium, yet not so deep as to injure the submucosa and cause subsequent esophageal stricture formation.

The balloon-based Barrx 360 is typically used for ablation of circumferential BE. The ablation catheters, consisting of 3 cm of circumferential electrodes wrapped over a 4 cm balloon, come in a variety of diameters (18, 22, 25, 28 and 31 mm). A sizing balloon is initially passed through the esophagus at 1 cm increments to select an ablation catheter of an appropriate diameter. The ablation catheter is then advanced over a guidewire and positioned under endoscopic control at the upper limit of the target epithelium. Dosimetry studies have led to the use of an energy level of 10 Joules/cm² for NDBE and 12 Joules/cm² for cases of LGD/HGD (22,23). If the length of BE is greater than 3 cm, the ablation catheter is advanced, positioned to have slight overlap with the initial segment, and ablation is repeated. Once all targeted areas have been treated, the ablation catheter is withdrawn and the coagulum is debrided from the esophageal mucosa. A specially designed cap that fits on the tip of the endoscope is available to facilitate the debridement process. The ablation catheter is similarly cleaned then re-inserted. Ablation is repeated at each level such that two ablations are achieved across the entire segment of BE.

For smaller tongues or islands of BE, the Barrx 90, Barrx Ultralong, Barrx 60, or Barrx Channel Catheter may be utilized. The Barrx 90 is 13 mm wide and 20 mm in length (Figure 7A,B) while the Barrx Ultralong is the same width but 40 mm in length. Each device is designed to fit over the

tip of a standard flexible adult upper endoscope while the Barrx Channel catheter is designed to fit down the biopsy channel (Figure 8). An energy level of 12 J/cm² (40 W/cm²) is appropriate with these devices for both non-dysplastic and dysplastic BE. The endoscope with attached device is inserted transorally, the target epithelium is ablated under direct endoscopic visualization, and ablation is repeated. The ablation catheter is repositioned to the next target zone, and the process carried out until all regions have been ablated twice. The coagulum is debrided using the tip of the device, the scope withdrawn, the ablation catheter cleaned, and the process repeated. Thus, four ablations are performed to each zone. Patients typically are brought back at 2-month intervals for repeat endoscopy and ablation until a complete response, as confirmed by endoscopic biopsies, has been achieved.

Multiple studies have demonstrated the safety and efficacy of RF ablation for both dysplastic and nondysplastic BE (NDBE). The most significant study to date relative to dysplastic BE was a multicenter, randomized (2:1), sham-controlled trial from 20 centers in the U.S. One hundred twenty-seven patients with BE and HGD or LGD underwent RF ablation or sham treatment (24). At a median follow-up of 12 months, 81.0% of treated patients achieved complete eradication (CE) of HGD (compared to 19.0% in the sham group), 90.5% had CE of LGD (compared to 22.7% in the sham group), and 77.4% had CE of IM (compared to 2.3% in the sham group) on intention-to-treat analysis. Patients who underwent RF ablation also had less disease progression (3.6% versus 16.3%, P=0.03) and developed fewer cancers (1.2% versus 9.3%, P=0.045) compared to the sham control group. The complication rate and side effect profile associated with treatment were quite low, with 6% developing an esophageal stricture after ablation.

In a subsequent report from this trial, the durability of response to RF ablation was assessed (25). At 2 years follow-up, CE of dysplasia was noted in 95% of patients, while CE of NDBE was found in 93%. By 3 years follow-up, the CE of dysplasia was 98%, while the CE of NDBE was 91%. The development of invasive EAC was found in 0.55% of patients per year, while an esophageal stricture occurred in 7.6%. Finally, in a recent meta-analysis assessing 18 studies of efficacy and 6 studies of durability, the CE of dysplasia was 91% and the CE of NDBE was 78% (26). Progression to EAC was found in 0.2% of patients, and the stricture rate was 5%.

The use of circumferential EMR for excising entire

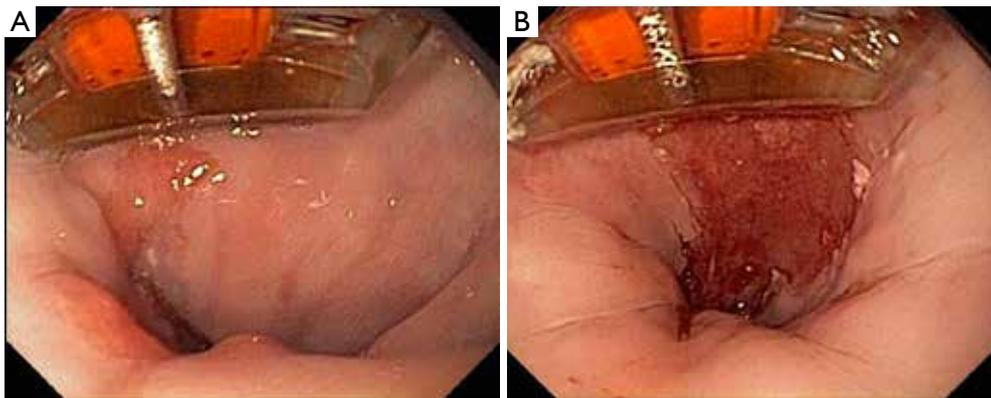


Figure 7 Focal ablation. (A) Barrx 90 attached to the tip of a flexible endoscope with targeted tongue of Barrett's esophagus; (B) Coagulum that results after radiofrequency ablation ($\times 2$) of targeted mucosa. The coagulum is debrided with the tip of the device and the ablation is repeated ($\times 2$).

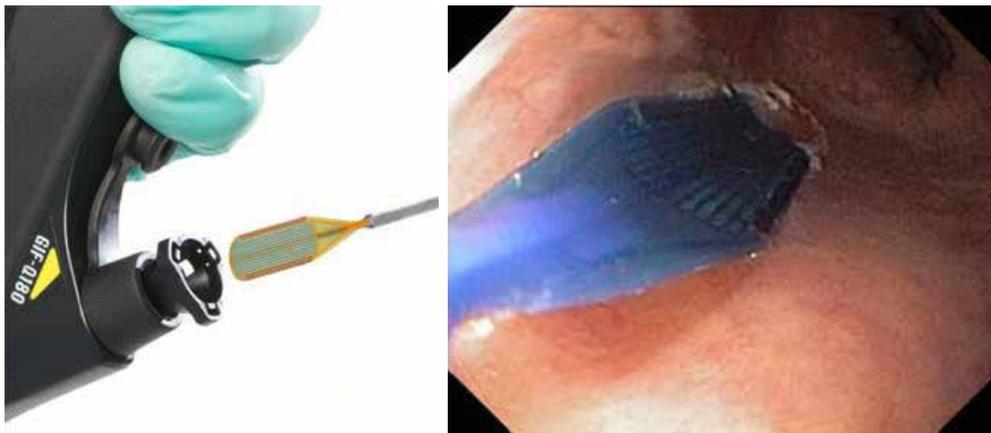


Figure 8 Barrx Channel catheter designed to pass through the biopsy channel of a flexible endoscope.

short or long segments of BE has also been evaluated. While complete circumferential excision is feasible, a high rate of subsequent esophageal stenosis has been found [up to 88% in a recent multicenter trial (27)], particularly if the excisions are performed in a single session. Based on these reports, ablation of residual BE appears preferable to stepwise circumferential resection.

Cryotherapy

Cryotherapy also has been utilized for endoscopic ablation of BE with or without dysplasia. The current technology (truFreeze[®] Spray Cryotherapy, CSA Medical, Lutherville, Maryland) consists of a 7 French catheter advanced via the biopsy channel of a flexible upper endoscope through which liquid nitrogen (-196°C) is delivered at a low pressure (2-3 pounds per square inch) (Figure 9). The technique

requires placement of a specialized decompressive tube into the esophagus and stomach to prevent perforation from barotrauma. Dosimetry is based upon the time the mucosa is exposed to the cryogen and is a matter of some debate. The target lesion is treated under direct visualization and may be smooth or nodular, increasing the applicability of the technology to cases not suitable for RF ablation. In addition, the treatment zone may be focal or diffuse. Another advantage of spray cryotherapy over RF ablation is that non-cellular connective tissue elements, such as collagen and fibrin, are relatively resistant to freezing, thus allowing selective necrosis of cellular elements while preserving the extracellular matrix.

The available data supporting the safety and efficacy of cryotherapy in the ablation of BE are much more limited than the experience reported for RF ablation. A small, multi-institutional case series reported on 23 patients



Figure 9 Spray cryotherapy delivering liquid nitrogen at a low pressure via a catheter advanced through the biopsy channel of a flexible endoscope.

undergoing cryotherapy for BE or cancer, 17 for the diagnosis of HGD (28). The safety profile was excellent, and the CR rates were 94% for HGD, 88% for all dysplasia, and 53% for NDBE, similar to the results reported by others following RF ablation.

Studies comparing esophagectomy and endoscopic therapies for early esophageal neoplasia

Three retrospectively reviewed case series have compared surgical and endoscopic treatment of BE with HGD or esophageal IMC. The first report, from the Mayo Clinic group published in 2009, compared outcomes in 178 patients with IMC treated between 1998 and 2007 (29). Endoscopic therapy was undertaken in 132 patients (74%) and 46 patients (26%) underwent an initial esophagectomy. Endoscopic therapy consisted of EMR alone in 75 (57%) and a combination of EMR with PDT in 57 (43%). At a mean follow-up of 43 months in the endoscopic cohort, 24 patients (18.2%) experienced persistent or recurrent cancer, 9 requiring esophagectomy, 1 undergoing chemoradiation, and 14 being treated with repeat EMR. The overall mortality during the follow-up interval was 17%. For the cohort undergoing an initial esophagectomy, the mean follow-up was 64 months and the overall mortality was 20%. The survival was thought to be comparable between the two groups.

The second report, from 2011, described the experience at the University of Southern California (30). Their cohort consisted of 101 patients with either HGD or IMC, 40 treated via endoscopy and 61 undergoing esophagectomy. The endoscopic treatment group underwent a total of

109 EMRs and 70 ablation sessions. The median number of endoscopic interventions per patient was three. The metachronous neoplasia rate was 20%, with three patients (7.5%) subsequently requiring esophagectomy for endoscopic treatment failure. Comparing endoscopic and surgical therapy, the former was associated with lower morbidity (0% versus 39%), though similar overall (94% in both groups) and disease-free survival at 3 years.

The third report, also from 2011, assessed outcomes at two high-volume specialty centers in Germany between 1996 and 2009 (31). Seventy-six patients who underwent EMR and APC in Wiesbaden were compared to 38 patients who underwent transthoracic esophagectomy with two-field lymphadenectomy for IMC at the University of Cologne. The groups were matched for age, gender, depth of invasion, and differentiation. Similar to the prior studies, endoscopic treatment was associated with equivalent cure rates compared to esophagectomy, but with lower morbidity and no mortality.

Conclusions

Esophageal cancer remains a highly lethal disease, a fact due mainly to the frequency with which patients present in an advanced stage. Early detection, therefore, is critical, underscoring the importance of the liberal use of endoscopy for assessment of foregut symptoms, screening of patients at high-risk for development of EAC, and surveillance of BE, a known malignant precursor.

The recommended treatment strategy for early esophageal neoplasia in the setting of BE has undergone a revolution in the span of just a few years. With the introduction, refinement, and popularization of EMR techniques and ablative technologies, the vast majority of cases of BE with HGD or IMC now can be treated successfully by endoscopic means. While esophagectomy for early neoplasia can be undertaken with a low mortality rate in appropriate candidates and by experienced centers, the morbidity of such a major surgical procedure remains considerable, as does the potential for negatively impacting long-term quality of life and gastrointestinal function. An endoscopic treatment approach, in carefully selected patients and by expert endoscopists, has been shown to provide cure rates equal to esophagectomy for early stage disease, but with lower morbidity, virtually no mortality, and fewer side effects.

A few comments are relevant, however, when considering a curative endoscopic strategy. The initial endoscopic assessment is critical for detection, mapping and staging

of disease, including a meticulous visual inspection of the esophagus for suspicious nodules or subtle irregularities that might harbor a focus of invasive cancer, and perhaps utilizing advanced technologies such as narrow-band imaging, confocal laser endomicroscopy, or vital stains to highlight mucosal detail. Multiple biopsies should be taken of non-nodular BE, as per established protocols, and EMR should be used liberally for excision of suspicious focal lesions. Careful assessment of biopsy and EMR specimens by an experienced gastrointestinal pathologist is critical, as major treatment decisions may hinge on subtle interpretations of histopathologic findings. If such expertise is not available locally, the specimens should be sent to a recognized expert in the assessment of esophageal pathology for a second opinion. Compliance on the part of the patient and rigorous follow-up on the part of the treating physician both are essential, as multiple endoscopic sessions are required for the initial diagnosis, eventual treatment, and subsequent surveillance. As persistent or metachronous neoplasia is not infrequent, the patient must understand that they are agreeing to a prolonged process of evaluation and therapy spanning over years, not merely a single intervention. The patient must also be aware that endoscopic treatment might ultimately fail, leading to esophagectomy at some point in the future or even, rarely, the development of incurable malignancy.

Esophagectomy will continue to play a role for a minority of cases of BE with HGD or IMC, such as for patients unwilling to stay the course of a prolonged endoscopic treatment regimen, tumor characteristics portending a significant risk of nodal metastasis, or cases difficult to manage by endoscopic means, and offers definitive therapy in a single intervention. Surgeons should offer resection options such as THE, MIE or VSE, with low perioperative morbidity and mortality while providing a good long-term quality of life, in order for esophageal resection to remain competitive as a treatment alternative.

The esophageal surgeon must be well-versed in the indications for endoscopic resective and ablative therapies so that they are appropriately applied. Before any treatment decisions are made, the patient should be evaluated and counseled by both an experienced endoscopist and an esophageal surgeon on the available management options, including the pros and cons of each. The best treatment decision for a given patient will depend upon patient factors, such as their desires, their comorbidities, the specifics of their disease, and the salvageability of their esophagus, physician expertise, and local or regional institutional resources.

While the science of endoscopic therapies has progressed

a long way in recent years, much is still unknown. Long-term outcome data spanning a decade or more are lacking. Factors predicting failures of ablation, as well as ways to prevent recurrence of neoplasia or metaplasia, require further study. The frequency and duration of surveillance in patients having achieved a complete response to endoscopic treatment is still a topic of debate, as is the cost effectiveness of therapy for various indications including dysplasia and NDBE. Improved methods for detecting submucosal invasion and, more importantly, lymphatic spread would be ideal, as would the identification of biologic or genetic markers predicting a high risk of occult carcinoma or progression to invasive malignancy.

Endoscopic therapies for early esophageal neoplasia are the new standard of care. In few areas of thoracic surgery has a treatment paradigm changed so dramatically and so rapidly with such promising results.

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Photodynamic therapy for esophageal cancer

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Abstract: Photodynamic therapy (PDT) is a treatment that uses a photosensitizing drug that is administered to the patient, localized to a tumor, and then activated with a laser to induce a photochemical reaction to destroy the cell. PDT using porfimer sodium followed by excimer dye laser irradiation is approved as a curative treatment for superficial esophageal cancer in Japan. While endoscopic submucosal dissection (ESD) is currently more popular for esophageal cancer, there is evidence to support PDT as an alternative treatment and as a salvage treatment for local failure after chemoradiotherapy (CRT). A photosensitizing agent has also been developed that requires a shorter sun shade period after administration, and studies are currently underway to establish an esophageal cancer indication for this next-generation PDT in Japan.

Keywords: Esophageal cancer; photodynamic therapy (PDT); salvage therapy

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What is photodynamic therapy (PDT)?

PDT is a laser treatment involving photosensitizer, which is a photosensitive molecule such as porphyrin, and light of a specific wavelength. The photosensitizer is administered via an oral or intravenous route, and is localized to a target tumor cell; then, light of a specific wavelength activates the sensitizer (1). This photodynamic reaction induces a chemical destruction of the tumor tissue mediated by singlet molecular oxygen and other reactions. Damage to the tissue occurs through several pathways, including cell necrosis, apoptosis, and ischemia with vascular shutdown (2). The most popular photosensitizer is porphyrin, and PDT is an effective treatment and is being tested to treat many cancers, such as those of the skin, head and neck, brain, lung, bladder, gastrointestinal (GI) tract, and others.

Present state of PDT for esophageal cancer

In Japan, PDT using porfimer sodium (Photofrin, Pfizer Japan Inc., Japan) followed by 630 nm wavelength excimer dye laser irradiation (EDL-1 or 2, Hamamatsu Photonics, Hamamatsu, Japan) is approved for early stage of lung cancer, esophageal cancer, gastric cancer, and cervical cancer. Between September 1990 and March 1992, a clinical

trial of PDT for patients with superficial esophageal cancer was conducted, and 9 of 10 patients achieved complete response (CR) (CR rate: 90%) (3). Because of the favourable results of this study, PDT using porfimer sodium was approved as a curative treatment for superficial esophageal cancer in 1994.

PDT procedures using porfimer sodium commence with the intravenous administration of 2 mg/kg of Photofrin. Subsequently, laser treatment using the 630 nm wavelength excimer dye laser is performed 48-72 hours after drug administration. The excimer dye laser is delivered via a microlens fiber through the operative channel of the endoscope, and was positioned in front of the lesions. The distal tip of the fiber is maintained to keep approximately 1 cm from the lesion, and laser is irradiated using total light density of 60-150 J/cm² with a maximum pulse energy of 4 mJ per pulse and a 40 Hz pulse frequency. If the lesions are large, laser irradiation is performed on overlapping sections as the Olympic symbol. The manufacturer recommends the use of porfimer sodium as PDT for esophageal cancer lesions with the following characteristics: (I) smaller than half of the circumference of the lumen and 2 cm in diameter; (II) limited to within the submucosal layer in depth; and (III) judged as difficult to remove with endoscopic resection.

Endoscopic submucosal dissection (ESD) was developed initially in gastric cancer to improve the curability of endoscopic resection for large lesions. However, use of the ESD procedure for superficial esophageal cancer has dramatically spread in Japan recently; therefore, the number of superficial lesions that are considered to be difficult to remove with ESD, and indicated for PDT has decreased. Although PDT for superficial esophageal cancer is not popular in Japan, some investigators have reported the results of using PDT for patients with superficial esophageal squamous cell carcinoma (ESCC). Nakamura *et al.* reported the results of PDT for seven patients with relatively small lesions (5-30 mm), all lesions were cured with no recurrence or severe complications (4). Tanaka *et al.* reported the results of PDT used against wide-spread lesions for which curative resection was considered to be difficult even with ESD (5). They treated 38 patients with superficial ESCC (31 lesions of T1a and 7 lesions of T1b without lymph node metastasis), and complete remission was achieved in 33 (87%) patients with PDT. There was no major complication and treatment related death, and at the median follow up period of 64 months, the 5-year survival rate was 76%. They concluded that PDT could be a possible curative treatment option for large superficial ESCC.

In contrast, palliative treatment for obstructive advanced esophageal cancer and curative treatment for precancerous lesions in Barrett's esophagus are the major indications for PDT in US and European countries. Litle reported the treatment results of palliative PDT for 215 patients with symptomatic advanced or recurrent esophageal cancer, and approximately 85% of patients improved their dysphagia (6). They achieved a median of 2 months of dysphagia-free survival, and 4.8 months of overall survival (OS) time. The major complications were perforation (2.3%), photosensitivity (6%), and aspiration pneumonia (1.8%). Lindenmann *et al.* published a retrospective analysis of 171 patients who received multimodal palliative treatment for inoperable esophageal cancer and who achieved sufficient dysphagia relief and improved survival (7). They concluded that PDT could be a beneficial initial treatment for patients with inoperable advanced cancer without gross infiltration into other organs.

Furthermore, several reports of PDT for high grade dysplasia of Barrett's esophagus were published, and a sufficient eradication rate of dysphagia was confirmed using not only porfimer sodium, but also aminolaevulinic acid (ALA) (8,9). Advantages of ALA compared with porfimer

sodium were a shorter period of photosensitivity and a lower rate of esophageal strictures when used for short segments of Barrett's esophagus. ALA is a natural amino acid and a pro-drug of protoporphyrin IX; it has been used as a photosensitizer mainly in European countries.

PDT for local failure after chemoradiotherapy (CRT)

CRT is one of the curative treatment options for ESCC, even at an advanced stage. However, local failure without distant metastasis after completion of CRT remains a major problem that must be overcome to achieve a cure. Although salvage esophagectomy is now indicated for such patients, it has a higher morbidity and mortality rate compared with primary or planned esophagectomy (10-12). In addition, lymph node recurrence within the radiation field is negligible, if the local is under controlled (13). The development of curative and safe salvage treatment options for local failure is needed to improve the survival of patients treated with CRT. Although we have reported that endoscopic resection could be a curative salvage treatment option for carefully selected patients with local failure, the indication was limited to only for tiny local failure lesions (14). We considered that PDT could be more powerful procedure compared with endoscopic treatment, because PDT is indicated not only superficial cancer, but also palliative treatment for advanced esophageal cancer as described earlier.

We have introduced PDT as a salvage treatment for local failure after CRT, and reported that acceptable short term results could be achieved (15). The indication criteria of salvage PDT were determined to be the follows: (I) absence of lymph node or distant metastases by computed tomography (CT) before PDT; (II) residual or recurrent tumor at the primary site with a stage limited to within uT2 by endoscopic ultrasound (EUS); (III) endoscopic resection of ESD was not indicated for reasons of either concomitant deep ulceration or severe fibrosis due to radiation or lesion invading to the deep submucosal layer; and (IV) patient refusal of surgery or physical complications that would have made surgery intolerable. A CR was achieved in 22 of 37 patients (CR rate: 59.5%) after PDT (*Figure 1*). Moreover, the 5-year progression free survival (PFS) and OS were 20.7% and 36.1%, respectively (16).

Subsequently, we conducted a prospective study to confirm the efficacy and safety of salvage PDT for local failure after CRT. A total of 25 patients with local failure limited to within the submucosal layer were enrolled, and

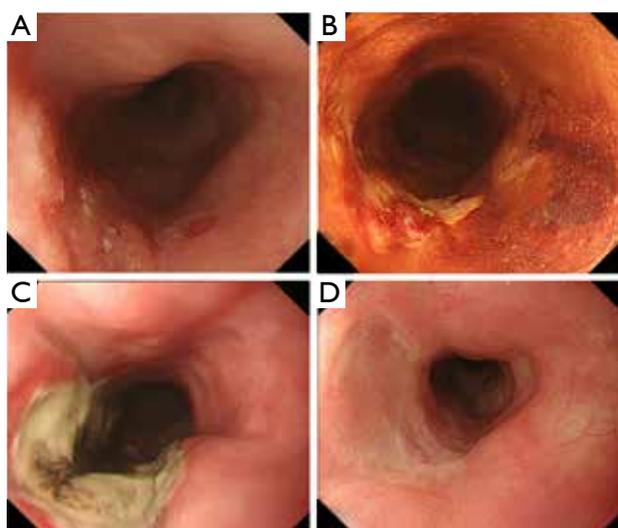


Figure 1 A case with local failure after CRT was treated with salvage photodynamic therapy (PDT). (A) a local failure lesion limited to within T1b; (B) a lesion was well demarcated after Lugol's staining; (C) deep ulceration was present one week after PDT; (D) complete response (CR) was achieved and continued one year after PDT.

a CR was attained in 19 patients with PDT (CR rate, 76%; 95% CI, 55-91%). One treatment related death (4%) was experienced caused by GI bleeding that was suspected to be due to an esophago-aortic fistula at the irradiated site approximately one month after PDT. With the median follow up period of approximately three years, the PFS and OS at three years were approximately 40%, and we concluded that PDT could be a curative option as salvage treatment for carefully selected patients without any metastasis.

PDT using next generation photosensitizer

First generation PDT using porfimer sodium has had some problems, such as a high risk of skin phototoxicity requiring a long sun shade period (4-6 weeks), and the need for a large and expensive excimer dye laser system. In fact, we have found that 34% of patients experience phototoxicity even with 2 weeks hospitalization and 8 weeks sun shade period (17). In contrast, talaporfin sodium (Laserphyrin for Injection, Meiji Seika Pharma Co., Ltd., Tokyo, Japan) is a second generation photosensitizer that is developed in Japan and featured as possessing more rapid clearance from the skin compared with porfimer sodium. Therefore, PDT

using talaporfin sodium is expected to reduce phototoxicity even with a short sun shade period of two weeks or less. Furthermore, the diode laser system (PD laser, Panasonic Healthcare Co., Ltd., Ehime, Japan), which was also developed in Japan and emits 664 nm laser light to excite the talaporfin sodium, is a much smaller and less expensive system compared with the excimer dye laser system. PDT using talaporfin sodium and the diode laser system demonstrated a high response rate and similar efficacy compared with first generation PDT, with modest skin phototoxicity, in a clinical trial for early lung cancer (18). However, PDT using talaporfin sodium and the diode laser is confirmed of its efficacy and approved only for lung cancer and malignant brain tumors. While we had wanted to introduce this new combination of PDT for esophageal cancer, its safety and efficacy for this use had not yet been evaluated even in animal models. First, we have evaluated the tissue damage of a normal esophagus caused by photoactivation with talaporfin sodium and a diode laser in a living canine model (19). In this pre-clinical study, laser irradiation was escalated with three levels of fluence (25, 50, and 100 J/cm²) after administration of talaporfin sodium for three dogs at each level; the canine tissues were then evaluated one week after laser irradiation. From the results of the pathological evaluation we found that the tissue damage had worsened in a stepwise fashion at every increase in the fluence levels. Next, we conducted a phase I study to find the appropriate intensity of the diode laser for patients with local failure after CRT for esophageal cancer (20). In that study, no patient experienced severe adverse events or phototoxicity, and we established that 100 J/cm² was the recommended fluence for treating local failure after CRT. The next generation PDT also demonstrated promising efficacy. From the results of this study, we are now conducting a multi-institutional phase II study of PDT using talaporfin sodium and a diode laser to acquire the approval for its use in the treatment of esophageal cancer in Japan.

Conclusions

While PDT is approved as a curative treatment for superficial esophageal cancer in Japan, it lost the popularity due to the dramatic spread of ESD. Recently, the advantages of PDT are being reconsidered after favorable results of salvage treatment in patients with local failure after CRT. Furthermore, photosensitizers that require only a short sun shade period have been developed, and promising results

of PDT as a salvage treatment for esophageal cancer were observed in our study. If this new PDT is approved for esophageal cancer in Japan, salvage PDT may become a popular and effective option, and could contribute to increasing quality of life for esophageal cancer survivors through organ preservation.

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Cell sheets engineering for esophageal regenerative medicine

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Abstract: Recently, cell-based therapies, regenerative medicine, and tissue engineering have been progressing rapidly. We have developed a novel strategy for regenerative medicine to recover tissue functions using temperature-responsive cell culture surfaces. To overcome of conventional methods such as the usage of single-cell suspension injection, we have applied transplantable cell sheets fabricated with temperature-responsive culture surfaces for cell delivery. In the field of gastroenterology, transplantable cell sheets from autologous oral mucosal epithelial cells can prevent esophageal stricture following extensive endoscopic mucosal resection.

Keywords: Cell sheet; cell sheet engineering; temperature responsive polymer; regenerative medicine; clinical research; stricture

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Tissue engineering using cell sheet

Regeneration of tissues and organs offers an innovative approach to the treatment of injury and disease with substituted artificial organs and organ transplantations. The term “tissue engineering” was first utilized in the late 1980s, the use of cultured cells as a therapeutic modality was initiated by Howard Green and associates, who transplanted cultured sheets of autologous epidermis to patients resulting from severe burns, giant congenital nevi, and skin ulcers. The key technology is the use of biodegradable polymer scaffolds, preformed in the target tissue shape, for seeding cells, as demonstrated in the well-publicized reconstruction of cartilage tissues for the growth of human ears on mouse back. Since the mid-1990s, significant progress from basic science has resulted in clinical applications of tissue engineering for the replacement of a variety of tissues and organs. An innovative approach to tissue engineering using a thermo-responsive culture surface has been developed from 1990s (1). Poly (*N*-isopropylacrylamide) (PIPAAm) exhibits a lower critical solution temperature (LCST) in aqueous media at the vicinity of 32 °C. While they hydrate and form an expanded structure in an aqueous media below the LCST, they dehydrate and form a compact structure above the LCST.

Such a conformational change in response to temperature has been extensively used to modulate the physicochemical properties of polymeric thin surfaces. At 37 °C, PIPAAm-grafted surface is slightly hydrophobic, allowing cells to proliferate under normal conditions and become a confluent cell sheet, which is regularly found on usual tissue culture polystyrene. A decrease in temperature lower than 32 °C, however, results in the hydration of the polymer surface, giving the spontaneous detachment of the cells as a monolithic tissue-like cell sheet for less than 1 h without any enzymes such as trypsin. Since PIPAAm is covalently immobilized onto the culture surfaces, PIPAAm remains bound to the surfaces even after cell sheet detachment, realizing the non-invasive harvest of cultured cells as an intact cell sheet having deposited ECM. This technology allows us to transplant cell sheets to host tissues without using biodegradable scaffolds. PIPAAm thickness on the order of nanometers is necessary for expressing such interesting properties as temperature-controlled cell attachment or detachment. For example, a PIPAAm layer of approximately 20 nm is optimal for cell adhesion and detachment properties in response to temperature change for a PIPAAm-modified tissue culture polystyrene system. Since the PIPAAm-grafted surfaces facilitate spontaneous cell detachment, the use of

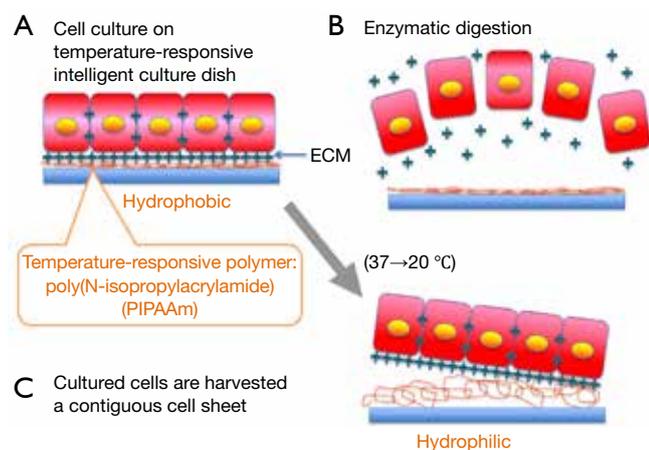


Figure 1 (A) Cell sheet detachment from temperature-responsive culture surfaces. Cells attach to hydrophobic culture surface via ECM, and connect to each other via cell-to-cell junction proteins; (B) when enzymatic digestion is used, cell-to-cell connections and ECM are disrupted and cells are released separately; (C) when cells are cultured on thermo-responsive culture surfaces, the interconnection between ECM and hydrophilic culture surface is released only by low temperature. Cell-to-cell connections are completely preserved and the cells are detached as a contiguous cell sheet. ECM retained underneath the cell sheets works as an adhesive agent.

conventional proteolytic enzymes such as dispase, trypsin, and collagenase, can be avoided. With noninvasive cell harvest, cell-to-cell junction and ECM proteins can therefore be maintained (2) (*Figure 1*).

Numerous cell types including epidermal keratinocytes (3), vascular endothelial cells (4), renal epithelial cells, periodontal ligaments (5,6), and cardiomyocytes (7,8) have shown the maintenance of differentiated functions after low-temperature cell sheet harvest, due to the preservation of cell surface proteins, such as growth factor receptors, ion channels, and cell-to-cell junction proteins. Additionally, due to the presence of deposited ECM that is produced during *in vitro* incubation, cell sheets can be easily transplanted and attached to the site such as culture dishes and even host tissues. To fabricate thick tissues, cell sheets can be stacked in layers because cell sheets connect each other in a short time. Therefore, cell sheet technology enables us to avoid scaffolds, fixation, or sutures which are needed by conventional tissue engineering approaches using isolated cell injections and scaffold-based technologies, which is the limitation of applicability.

Cell sheet regenerative medicine following endoscopic submucosal dissection (ESD) for esophageal neoplasm

Endoscopic treatments for early esophageal cancer and Barrett's esophagus with high-grade dysplasia have gained widespread acceptance as minimally invasive therapies (9). In particular, ESD makes it possible to resect superficial cancer *en block* regardless of size and allows for an accurate histological assessment for diagnosis. However, severe postoperative esophageal stricture is inevitably observed when ESD is performed for widespread superficial neoplasms that remove a large area of mucosa, i.e., >75% of the esophageal lumen (10). Severe esophageal stricture after endoscopic treatment is difficult to treat and often requires repeated endoscopic balloon dilations (10,11) or a temporary stent (12). It has been reported that fibrosis of the submucosa and atrophy of the muscularis contribute to esophageal stricture following endoscopic treatment (13). Therefore, the prevention of esophageal stricture requires intervention aimed at reducing mucosal defects, calming inflammation, and preventing excess fibrosis. For solving the demand, our laboratory has developed a method combining ESD with the endoscopic transplantation of autologous oral mucosal epithelial cell sheets (14) (*Figure 2*). The purpose of our approach is to cover the surface of mucosal defects to promote re-epithelialization and to reconstruct the esophageal luminal surface by using cell sheets. Results showed the effectiveness of a novel combined endoscopic approach for the potential treatment of esophageal cancers that can effectively enhance wound healing and possibly prevent postoperative esophageal stenosis. In addition, we reported using fabricated autologous skin epidermal cell sheet, as another epithelial cell source, prevent severe stricture following full-circumferential ESD in a porcine model (15) (*Figure 3*). These transplantable epithelial cell sheets are fabricated on temperature-responsive culture surfaces, which allow noninvasive harvesting of the cell sheets simply by reducing the temperature below 32 °C; the fabricated cell sheets retain all of the cell membrane proteins and extracellular matrices deposited during culture. Therefore, these cell sheets can easily adhere to and integrate into transplanted tissue sites within a short period. Additionally, the placement of cell sheets into the mucosal defect does not require sutures or other adhesives. Furthermore, several studies revealed epithelial cell sheets can be fabricated with temperature-responsive culture inserts without feeder layers (16), which can exclude xenogeneic factors for animal-free cell transplantation.

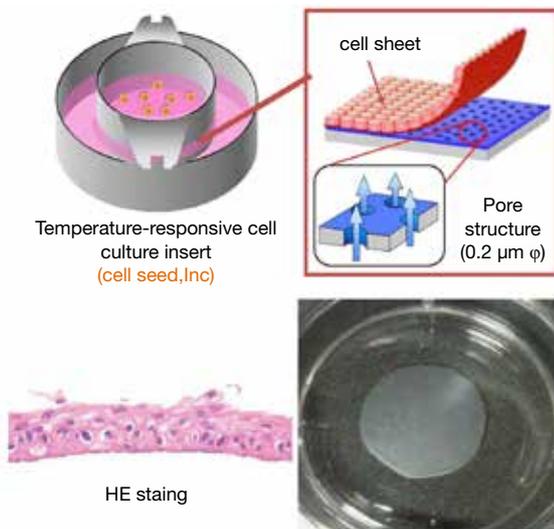


Figure 2 Fabricated multilayered oral mucosal cell sheet using temperature responsive cell culture insert.

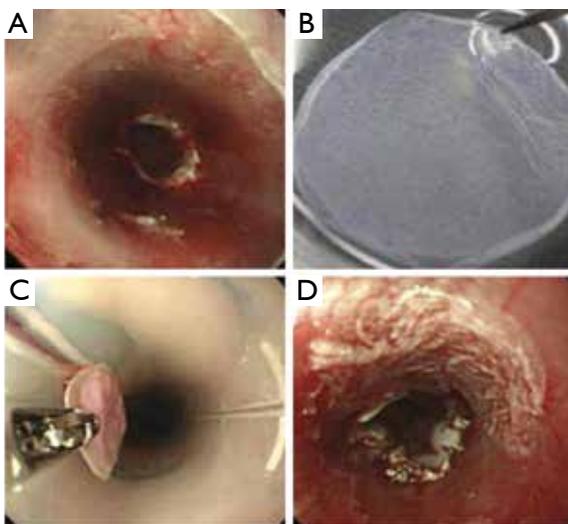


Figure 3 (A) An artificial circumferential mucosal defect (4 cm in length); (B) a harvested epidermal cell sheet; (C) the polyvinylidene difluoride support membrane with an attached autologous epidermal cell sheet was grasped by using endoscopic forceps; (D) an epidermal cell sheet that was endoscopically transplanted to the center of an ulceration without sutures. [Reprinted with permission from (15), Copyright © 2014 Elsevier. All rights reserved].

Based on these animal studies, human autologous oral mucosal epithelial cell sheets are fabricated with the UpCell-Insert technology (17). The first clinical study was esophageal regeneration using autologous oral mucosal cell sheets following a large-size removal ESD for superficial esophageal

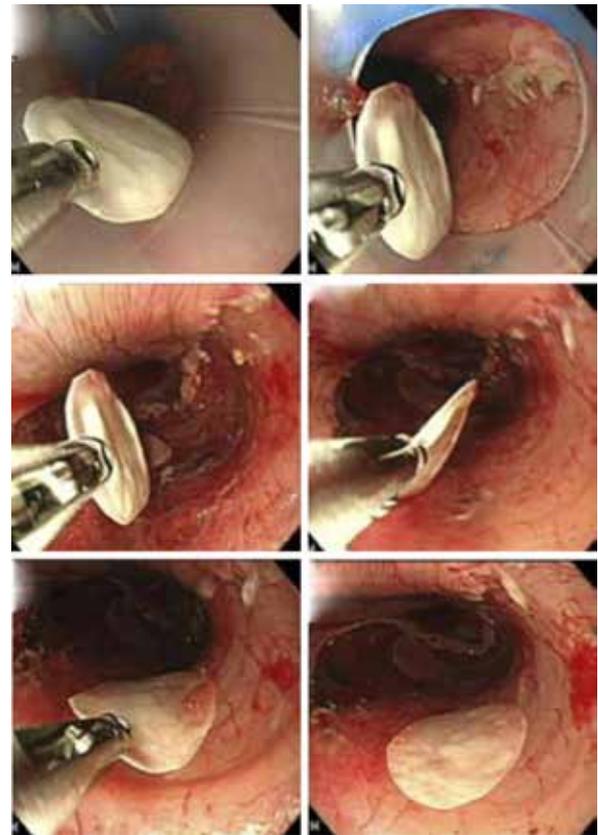


Figure 4 Autologous oral mucosal epithelial cell sheets on a support membrane were transplanted with endoscopic forceps onto the bed of the esophageal ulceration immediately after ESD. [Reprinted with permission from (18), Copyright © 2014 Elsevier. All rights reserved].

neoplasms and the results were published in 2012 (18). The preliminary results showed that early re-epithelialization of the ulcer site and the results suggested its efficacy for preventing stricture in case of circumferential ESD (Figure 4). Currently, we are preparing for a further randomized study to fully assess the potential benefits of regenerative medicine using cultured autologous cell sheets therapies.

Conclusions

We described the technology of “Cell Sheet Engineering” and its current applications following endoscopic therapy for esophageal neoplasm. Cell sheet engineering has already been tested in clinical settings for several incurable diseases. We believe that methods that can effectively apply cell sheet engineering will provide new possibilities in the field of regenerative medicine.

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McKeown esophagogastrectomy

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Abstract: Esophageal cancer is increasing in incidence faster than other cancers in the US. Outcomes after esophagectomy may be related to many factors, including the age of the patient, the stage of the tumor, the operative approach, and the incidence of postoperative morbidity. Pulmonary complications are the major source of morbidity and mortality following esophageal resection, and numerous studies have identified various factors associated with these complications. Various operative approaches have been applied to the management of esophageal cancer, with the goal of optimal oncologic results with the lowest possible morbidity and mortality. The McKeown esophagogastrectomy is applicable for most patients with esophageal cancer, and the technique and results are reviewed.

Keywords: Esophageal cancer; esophagogastrectomy; outcomes; minimally invasive surgery

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Introduction

The incidence of esophageal cancer is increasing faster than other cancers in the US (1). Esophageal resection remains the treatment standard for resectable esophageal cancer and for some benign esophageal conditions (2). However, despite surgical and anesthetic advances over the years, morbidity and mortality rates of ER have been consistently higher than those associated with other commonly performed general and thoracic surgical procedures (3). Despite improvements in perioperative care, surgical techniques, and anesthetic techniques, ER remains a formidable operation.

Many analyses have been performed to identify the most important risk factors for complications after ER (4-12). Based upon these data, it is clear that the most important cause of significant morbidity and mortality after ER is the development of pulmonary complications (10-18). Several factors have been associated with pulmonary complications after esophagectomy, including issues related to the preoperative status (age, nutritional status, induction therapy, baseline pulmonary function, ethanol use, smoking history, poor performance status), intra-operative details (stage/location of tumor, surgical approach, estimated blood

loss, length of surgical procedure, entry into two separate body cavities; disruption of bronchial innervation and lymphatic circulation), and postoperative details (pulmonary toilet, vocal cord paralysis or recurrent laryngeal nerve palsy, postoperative respiratory muscle dysfunction) (4-12). The purpose of this review is to describe the McKeown esophagectomy and its role in the management of esophageal cancer.

McKeown esophagogastrectomy

The most common surgical approaches to accomplish resection of esophageal cancer include transhiatal, Ivor Lewis, and McKeown (3 incision) esophagogastrectomy (1). While the issue of 2-field *vs.* 3-field lymph node dissection is important, it will not be addressed in this review (1,19). The Ivor Lewis approach is defined by the following sequence: abdominal exploration, stomach mobilization; lymph node dissection; feeding jejunostomy (laparoscopic or open); thoracic esophageal mobilization; lymph node dissection; anastomosis (thoracoscopic or open). Potential advantages of the Ivor Lewis approach includes lower stricture, leak, and aspiration rates (1). McKeown esophagectomy is defined by: thoracic esophageal mobilization; lymph node

dissection; ligate thoracic duct (thoracoscopic or open); abdominal exploration (laparoscopic or open); stomach mobilization; lymph node dissection; feeding jejunostomy; left cervical incision for anastomosis (1). Potential advantages of the McKeown approach compared to the Ivor Lewis include less chance of local recurrence, anastomosis in neck easier to manage if leak occurs, and less need to expand the thoracic incision since the anastomosis is in the neck instead of the chest.

Choosing the operative approach

One of the important principles of surgery is that the Siewert tumor type should be assessed in all patients with adenocarcinomas involving the gastroesophageal junction prior to surgical resection in order to choose the correct approach (1,20). The Siewert tumor types are summarized as: Siewert type I: adenocarcinoma of the lower esophagus (often associated with Barrett's esophagus) with the center located within 1 cm above and 5 cm above the anatomic gastroesophageal junction; Siewert type II: true carcinoma of the cardia at the gastroesophageal junction, with the tumor center within 1 cm above and 2 cm below the gastroesophageal junction; Siewert type III: subcardial carcinoma with the tumor center between 2 and 5 cm below gastroesophageal junction, which infiltrates the gastroesophageal junction and lower esophagus from below.

McKeown esophagectomy is appropriate for all patients with Siewert type I and II patients, as well as all patients with tumor above the gastroesophageal junction, up to the level of the clavicle. Ivor Lewis esophagectomy is also appropriate for Siewert I and II tumors, and perhaps some Siewert III tumors, although many of these patients are treated with sub-total gastrectomy as a gastric as opposed to esophageal cancer (1). Most importantly, Ivor Lewis should not be applied to tumors at or above the level of carina due to the risk of a positive esophageal surgical margin.

Minimally invasive approaches

Minimally invasive esophagectomy (MIE) strategies have been proposed to decrease morbidity and improve quality of life after esophagectomy (21-24). MIE approaches include the use of thoracoscopy with or without laparoscopy for Ivor Lewis or McKeown resections, as it is likely that omission of thoracotomy is more important than the omission of open abdominal incision. In a study of MIE in 222 patients, mortality rate was 1.4% and hospital stay was only seven

days (22). However, larger multi-institutional analyses have not been successful in demonstrating major advantages for the MIE approach. In one study, retrospective comparison of 446 patients was performed, including 114 open, 309 thoracoscopic assisted, and 23 totally MIE. The median hospital stay was not statistically different (14 vs. 13 vs. 11 d, respectively). In addition, there was no difference in lymph node retrieval or survival. The authors conclude that MIE appears to be safe with equivalent survival, but with no advantages identified (23). Another large study analyzed esophagectomies performed in the UK from 2005-2010. There were 7,502 esophagectomies, including 15.4% MIE. Of note, the percentage of esophagectomies performed minimally invasively increased over time, and between 2009 and 2010, 24.7% of resections were MIE. There was no difference between open and MIE approaches (4.3% vs. 4.0%, respectively; $P=0.61$). Furthermore, there was no difference in postoperative complication rate (38% vs. 39%; $P=0.46$) in open and MIE groups, respectively. A higher reintervention rate was associated with the MIE group than with the open group (21% vs. 17.6%, $P=0.006$; odds ratio, 1.17; 95% confidence interval, 1.00-1.38; $P=0.040$) (24).

Conclusions

The multidisciplinary evaluation of patients with esophageal cancer is essential. Induction therapy esophagogastrectomy is the best option for most patients with T2N0 disease or greater (1). Centers and surgeons with more extensive experience have the best outcomes (3). The choice of operative approach should be based on tumor location and surgeon experience, and the McKeown approach is likely the most versatile, with numerous advantages over other approaches. Minimally invasive strategies are proliferating, although the advantages of MIE have not yet been demonstrated to the degree that advantages for other minimally invasive procedures, such as thoracoscopic lobectomy. Nevertheless, as more experience and data is gathered for MIE, approaches that avoid thoracotomy are preferable.

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Minimally invasive and robotic Ivor Lewis esophagectomy

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Abstract: Esophageal cancer is the eighth most common malignancy and the sixth most common cause of cancer-related death worldwide. Esophagectomy provides a curative treatment but carries significant morbidity and mortality. Ivor Lewis esophagectomy (ILE) is one of the most commonly employed open techniques of esophagectomy. Minimally invasive approaches have been explored in ILE in an effort to reduce operative morbidity. This article reviews recent literature of minimally invasive Ivor Lewis esophagectomy (MI-ILE), discusses its clinical outcomes, and introduces the robotic approach in MI-ILE. MI-ILE has demonstrated comparable postoperative outcomes to open ILE, and it has shown potential to reduce blood loss and length of hospitalization. Due to limited studies, no significant improvement of long-term survival has been reported in MI-ILE. Robotic ILE is safe and feasible, but more studies are needed to prove identifiable benefits. Randomized controlled trials comparing MI-ILE or robotic ILE with conventional open ILE are warranted to determine the optimal surgical procedure for the treatment of esophageal cancer.

Keywords: Esophageal cancer; Ivor Lewis esophagectomy (ILE); minimally invasive surgery

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Introduction

Esophageal cancer is the eighth most common malignancy and the sixth most common cause of cancer-related death in the world. An estimated 482,300 new cases and 406,800 cancer deaths occurred in 2008 worldwide (1), showing a high mortality-to-incidence rate ratio of 0.84. Incidence rates vary internationally, and China has the fourth highest rate of esophageal cancer according to the GLOBOCAN 2008 Database. In the United States, approximately 17,990 patients are diagnosed with esophageal cancer in 2013 with a mortality of 15,210 (2). The overall 5-year survival rate for esophageal cancer remains poor, despite the modest improvement from 5% between 1975 and 1977 to 19% between 2002 and 2008 (2). Several surgical techniques are available, and the choice of technique depends on tumor location, extent of lymphadenectomy, the patient's overall condition and surgeon's preference. The two most frequent open techniques are transhiatal esophagectomy (THE) and transthoracic esophagectomy (TTE). THE involves laparotomy with blunt dissection of the esophagus (without

thoracotomy) and cervical esophagogastric anastomosis (3). Ivor Lewis esophagectomy (ILE) is the classic TTE, which consists of laparotomy and right thoracotomy with intrathoracic anastomosis (4). The 3-incision McKeown approach is a modified TTE, which utilizes the right thoracic and abdominal portions of ILE with an added left cervical anastomosis. Compared to THE, TTE allows the removal of the intrathoracic esophageal tumor with a wider radial margin, and the oncologic resection of extensive mediastinal lymph nodes (5), but is associated with significant in-hospital morbidity (but not mortality), predominantly respiratory complications (6,7). THE carries a lower complication rate, but only a limited lymphadenectomy can be performed with no dissection of the carinal and paratracheal lymph nodes (6,7). Although no significant difference in 5-year survival was seen between the THE and TTE groups, there was a trend towards survival benefit: overall survival was 29% in the THE group, as compared with 39% in the TTE group (6).

To reduce the surgical morbidity and mortality, multiple minimally invasive approaches have been explored in

esophagectomy. Several studies have shown a substantial decrease in blood loss, complication rate and hospital stay when minimally invasive esophagectomy (MIE) was applied (8,9). However, MIE has several intrinsic limitations, including 2-dimensional view, reduced eye-hand coordination and a decrease in degrees of freedom of movement (10). These may create difficulties in mediastinal dissection and anastomosis during thoracoscopic esophagectomy. Robotic systems have been designed to overcome some disadvantages of standard minimally invasive surgery. The *da Vinci*[®] robotic system (Intuitive Surgical, Inc. California, USA) provides a magnified 3-dimensional vision system and special wristed instruments that offer more degrees of freedom (10). It translates the surgeon's hand movement into precise real-time movements of surgical instruments, filters the tremor and restores the natural eye-hand coordination. These technical improvements facilitate precise dissection in a confined operating field, and may benefit mediastinal dissection of esophagus and surrounding lymph nodes.

This article reviews development and techniques of minimally invasive ILE (MI-ILE), and introduces robotics in the management of esophageal cancer.

Minimally invasive Ivor Lewis esophagectomy (MI-ILE)

The conventional ILE consists of a laparotomy and a right thoracotomy for esophageal resection (and lymphadenectomy) followed by an intrathoracic anastomosis of the gastric conduit with the proximal esophagus at the level of the proximal mediastinum (4). The following components of ILE may differ from surgeon to surgeon: technique of pyloric drainage (pyloromyotomy versus pyloroplasty versus Botox injection versus none); inclusion of jejunostomy; width of the gastric tube; technique of anastomosis (mechanical versus hand sewn). The advantages of ILE include excellent visualization of all parts of the operation, ability to perform 2-field lymphadenectomy, and potential prevention of cervical dissection of the esophagus and consequent complications, such as stenosis, leakage and recurrent laryngeal nerve injury. The disadvantages are the need for single lung ventilation, morbidity associated with a thoracotomy, higher risk for respiratory complications, and the potential danger caused by a postoperative anastomotic leak (11).

To reduce surgical trauma and overcome some of the disadvantages, various minimally invasive approaches

have been explored in ILE, including any combination of laparoscopy instead of laparotomy, thoracoscopy instead of thoracotomy and intrathoracic anastomosis. Watson *et al.* first described a totally endoscopic ILE in two patients, which incorporated a hand-assisted laparoscopy for gastric mobilization and a right thoracoscopy for esophageal dissection and anastomosis (12). Nguyen *et al.* then reported a series of three patients receiving a completely MI-ILE of combined laparoscopic and thoracoscopic resection of the distal esophagus with an intrathoracic anastomosis reconstruction (13,14). All patients had an uneventful postoperative course. In 2006, Bizekis and colleagues described their experience in 50 patients who underwent MI-ILE from 2002 to 2005 (15). Thirty five patients (70%) underwent a hybrid ILE (laparoscopic gastric mobilization combined with a minithoracotomy); the remainder (30%) had a completely MI-ILE (laparoscopy and thoracoscopy). A circular stapled anastomosis was performed in all patients. The operative mortality rate was 6% (3/50). Three patients (6%) developed an anastomotic leak; all were successfully managed nonoperatively. Four patients (8%) developed postoperative pneumonia (15). There were no recurrent laryngeal nerve injuries. They concluded that a MI-ILE is technically feasible. MI-ILE approach could minimize the gastric mobilization, avoid recurrent laryngeal nerve injury, and allow a more extensive gastric resection in the case of cardia extension of gastroesophageal junction tumors (15). Similarly, Nguyen and coworkers later reported a series of 104 MIE procedures performed between 1998 and 2007, in which 51 cases were MI-ILE and 47 cases were combined laparoscopic and thoracoscopic McKeown esophagectomy (MI-McKeown, cervical anastomosis) (16). In the MI-ILE group, the mortality rate was 1.96% (1/51) and leak rate was 9.8%, which was comparable to the other group. Interestingly, the MI-ILE group had significant shorter operative time and less blood loss (16). They again showed MIE is feasible with acceptable morbidity and low mortality. They also preferred MI-ILE due to the important advantages of constructing a tension-free intrathoracic anastomosis and the ability to resect the tip of the gastric conduit (16). Other groups also reported successful completion of MI-ILE procedures with comparable outcomes (17-24). In a recent review of Luketich *et al.*, they compared the results of 481 patients undergoing MIE-McKeown to 530 patients undergoing MI-ILE (25). Both approaches resulted in acceptable lymph node resection, postoperative outcomes and low mortality. They proposed MI-ILE as their preferred approach because

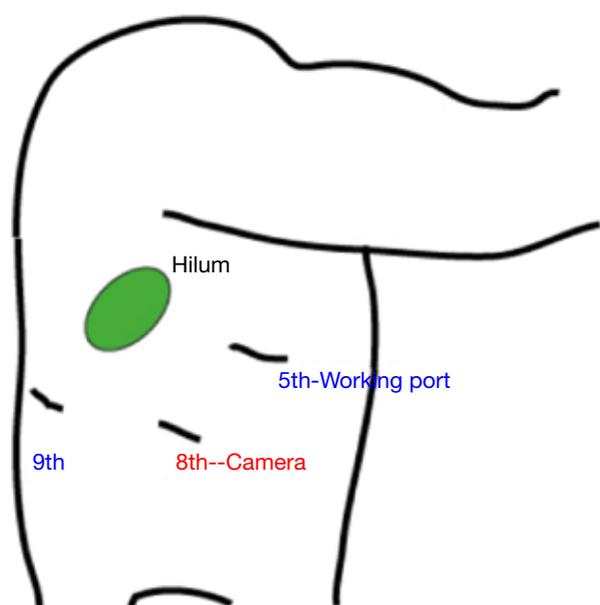


Figure 1 Port positions for right thoracoscopic esophageal mobilization, lymph node dissection, and anastomosis.

it was associated with decreased recurrent laryngeal nerve injury and mortality rate of 0.9%.

Techniques of the MI-ILE

As pioneers in MIE, Luketich and the Pittsburgh group described the modified MI-ILE procedures in recent publications (26,27). For the laparoscopic portion of the procedure, the patient is initially positioned in a steep reverse Trendelenburg position, and a double lumen endotracheal tube is placed in preparation for the later thoracoscopic stage. Five abdominal ports are used. A 10-12 mm port is first placed via a Hasson technique in the epigastrium between the xiphoid and umbilicus to the right of midline. Subsequent ports are placed under direct laparoscopic visualization. A 5 mm camera port is placed just to the left of the midline at the same level as the 10 mm port. Two additional 5 mm ports are inserted at the right and left subcostal margins. The final 5 mm port is placed at the right flank for liver retractor. After an abdominal inspection to rule out advance disease, the gastrohepatic ligament is divided. The exposed right crus is dissected, followed by dissection of the left crus until the gastroesophageal junction is freed. The greater curvature of the stomach is mobilized by dividing the short gastric vessels using the ultrasonic coagulation shears. The gastrocolic

omentum is then divided, with care taken to preserve the right gastroepiploic arcade. Posterior gastroesophageal attachments are divided after retraction of the stomach anteriorly. A complete celiac node dissection can be performed before division of the left gastric vessels with a vascular stapler. Next, Luketich *et al.* perform a pyloroplasty whereas some other groups do not. A gastric tube is created with a stapling device from the lesser curvature towards the fundus of stomach, preserving the right gastric vessels. There are some variations regarding the diameter of the gastric tube. Luketich *et al.* reported an increase of ischemia and high leak rate with a too narrow tube (3-4 cm in diameter), and hence they emphasized the importance of creating a gastric tube of 5-6 cm in diameter (8). Berrisford *et al.* also observed a high gastric tube ischemia and leak rate by using a 4 cm gastric tube (28). Currently, creating a 5 cm wide gastric tube is recommended in MIE by Wee and Morse (29). Next, a jejunostomy tube is placed before division of the phrenoesophageal membrane. The abdomen is inspected and the incisions are closed.

In the thoracoscopic phase, the patient is placed in a left lateral decubitus position. The position of the double-lumen tube is verified, and single-lung ventilation is used. In our hands, three thoracoscopic ports are used (*Figure 1*). A 10 mm camera port is placed in the eighth intercostal space, just posterior to the posterior axillary line. Access incisions are placed in the 5th and 10th/11th intercostal spaces. After division of the inferior pulmonary ligament, the mediastinal pleura is divided up to the level of the azygous vein to expose the thoracic esophagus, and the vein is divided with an endovascular stapler. The esophagus is circumferentially mobilized from the diaphragm to the level about 2 cm above the carina, and a Penrose drain is placed around it. Mediastinal lymph node dissection is performed. The distal esophagus and previously constructed gastric conduit are brought up into the chest. The proximal esophagus is then transected above the azygous vein. The eighth posterior interspace port is enlarged to 5 cm to remove specimen and complete construction of intrathoracic anastomosis. The redundant portion of the gastric conduit is then excised with endostapler and the thoracic cavity is drained. There are various intrathoracic anastomotic techniques in MI-ILE, including handsewn and stapled techniques. The stapled techniques varied with regard to transthoracic circular stapled, transoral circular stapled and side-to-side liner stapled. Anastomotic leak rates ranged from 0% to 10%, and anastomotic stenosis rates ranged from 0% to 27.5% (30).

Table 1 Review of MI-ILE operative parameters

Study	Surgical type	No. patients	Total operative time (min)	Estimated blood loss (mL)	No. lymph nodes	Length of hospital stay (day)
Watson <i>et al.</i> [1999] (12)	HAL, T	2	210, 300 respectively	50, 300 respectively	NR	10
Nguyen <i>et al.</i> [2001] (13)	MI-ILE	1	450	200	11	8
Bizekis <i>et al.</i> [2006] (15)	L, mini-T	35	NR	NR	16*	9
	MI-ILE	15				7
Thairu <i>et al.</i> [2007] (22)	MI-ILE	18	NR	NR	NR	NR
Nguyen <i>et al.</i> [2008] (16)	MI-ILE	51	249±72	146±117	13.8±8.6	9.7±8.1
Campos <i>et al.</i> [2010] (19)	L, mini-T	23	275*	NR	15*	10*
	MI-ILE	14				
Cadière <i>et al.</i> [2010] (31)	MI-ILE	1	337	170	25	6
Ben-David <i>et al.</i> [2010] (20)	MI-ILE	6	360	NR	18	8
Gorenstein <i>et al.</i> [2011] (21)	MI-ILE	31	NR	NR	NR	NR
Ben-David <i>et al.</i> [2011] (17)	MI-ILE	16	330-420*	125-150*	14*	7.5-10*
	MI-McKeown	82				
Tapias <i>et al.</i> [2011] (24)	MI-ILE	40	364±46	205±68	21	7
Merritt [2012] (32)	MI-ILE	15	468±54	182±67	11.4±1.1	10
Thomay <i>et al.</i> [2012] (23)	MI-ILE	30	535±120	278	27.1±11.4	10.7±4
Luketich <i>et al.</i> [2012] (25)	MI-ILE	530	NR	NR	23.5	7

HAL, hand-assisted laparoscopy; T, thoracoscopy; MI-ILE, minimally invasive Ivor Lewis esophagectomy; L, laparoscopy; mini-T, minithoracotomy; MI-McKeown, combined laparoscopic and thoracoscopic McKeown esophagectomy; NR, not reported; *, data is evaluated based on total cases of both approaches.

MI-ILE outcomes

As with many novel procedures, the initial publications involving MI-ILE were mostly institutional series. Operative parameters, including operating time, estimated blood loss, number of lymph nodes harvested and length of hospital stay, were evaluated in MI-ILE (*Table 1*). Post-operative mortality and major complications of MI-ILE were also reviewed in *Table 2*. Theoretically, obviating the need of the thoracotomy, laparotomy, or both may reduce surgical pain, wound infections, cardiopulmonary complications, intensive care unit and hospital stays, and mortality rates. Although MI-ILE has been shown to be safe and feasible, a clear advantage with MI-ILE over conventional ILE has not been demonstrated. The ultimate answer to this important question is complicated by the lack of well-designed trials, the small number of institutional series, publications bias of satisfactory outcomes and the technical variations. Recently, there are several studies aiming to compare open transthoracic with MIE (33-36) (*Tables 3,4*). Patients in

both groups underwent similar pre-operative and post-operative protocols. Operative data and post-operative data were collected. These studies demonstrate the feasibility and safety of MI-ILE, and show its potential of reducing blood loss, pulmonary complications and length of hospital stay. Prospective multi-center, randomized and controlled studies would be needed to draw definite conclusions.

Another controversial issue with MI-ILE is whether its long-term survival rate is comparable with the open procedure, because the extent of lymphadenectomy may be compromised. Many series did not report on lymph node dissection, and the quality of lymph node dissection is difficult to evaluate. From the studies comparing open and MIE (*Table 3*), lymph node dissection is comparable between two groups. However, most of the major complications of MI-ILE were described within the perioperative period, and the long-term survival and disease progression data from large patient cohorts is absent (*Table 4*). Therefore, the potential of MI-ILE may not have been fully realized.

Table 2 Review of MI-ILE post-operative outcomes

Study	Surgical type	No. patients	30-day mortality	Pneumonia	Leak	Stricture	RLN injury
Watson <i>et al.</i> [1999] (12)	HAL, T	2	0	0	0	0	0
Nguyen <i>et al.</i> [2001] (13)	MI-ILE	1	0	0	0	0	0
Bizekis <i>et al.</i> [2006] (15)	L, mini-T	35	2 (5.7%)	4 (11.4%)	3 (8.6%)	6 (12%)*	0
	MI-ILE	15	1 (6.7%)	0	0		0
Thairu <i>et al.</i> [2007] (22)	MI-ILE	18	NR	NR	0	NR	NR
Nguyen <i>et al.</i> [2008] (16)	MI-ILE	51	1 (1.96%)	NR	5 (9.8%)	14 (27.5%)	NR
Campos <i>et al.</i> [2010] (19)	L, mini-T	23	0	3 (8.1%)*	1 (2.7%)*	5 (13.5%)*	NR
	MI-ILE	14					
Cadière <i>et al.</i> [2010] (31)	MI-ILE	1	0	0	0	0	0
Ben-David <i>et al.</i> [2010] (20)	MI-ILE	6	0	NR	0	0	NR
Gorenstein <i>et al.</i> [2011] (21)	MI-ILE	31	NR	NR	1 (3.2%)	NR	NR
Ben-David <i>et al.</i> [2011] (17)	MI-ILE	16	1 (1%)*	9 (9%)*	8 (8%)*	4 (4%)*	7 (7%)*
	MI-McKeown	82					
Tapias <i>et al.</i> [2011] (24)	MI-ILE	40	0	1 (2.5%)	0	6 (15%)	0
Merritt [2012] (32)	MI-ILE	15	0	0	1 (6.7%)	0	0
Thomay <i>et al.</i> [2012] (23)	MI-ILE	30	0	2 (6.7%)	3 (10%)	NR	1 (3.3%)
Luketich <i>et al.</i> [2012] (25)	MI-ILE	530	5 (0.9%)	NR	23 (4.3%)	NR	5 (1%)

RLN injury, recurrent laryngeal nerve injury; HAL, hand-assisted laparoscopy; T, thoracoscopy; MI-ILE, minimally invasive Ivor Lewis esophagectomy; L, laparoscopy; mini-T, minithoracotomy; MI-McKeown, combined laparoscopic and thoracoscopic McKeown esophagectomy; NR, not reported; *, data is evaluated based on total cases of both approaches.

Table 3 Studies comparing ILE and MI-ILE operative parameters

Study	Surgical type	No. patients	Operative time (min)	Estimated blood loss (mL)	No. lymph nodes	Length of hospital stay (day)
Pham <i>et al.</i> [2010] (33)	MI-ILE	44	543 ^a	407 ^a	13 ^a	15
	ILE	46	437	780	8	14
Sihag <i>et al.</i> [2012] (34)	MI-ILE	38	360.5	200 ^c	19	7 ^b
	ILE	76	365.5	250	21	9
Biere <i>et al.</i> [2012] (35)	MIE	59	329 ^a	200 ^b	20	11
	Open	56	299	475	21	14
Noble <i>et al.</i> [2013] (36)	MI-ILE	53		300 ^c	19	12
	ILE	53		400	18	12

MI-ILE, minimally invasive Ivor Lewis esophagectomy; ILE, conventional Ivor Lewis esophagectomy; MIE, minimally invasive esophagectomy; open, open esophagectomy; ^a, P<0.01; ^b, P<0.001; ^c, P<0.05.

Robotic ILE

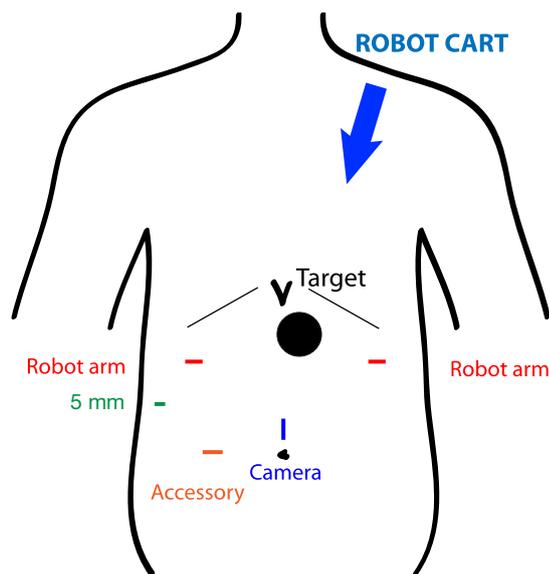
Some limitations of the minimally invasive approaches to esophagectomy include the 2-dimensional view, decreased freedom of movement, narrow field of the mediastinum and reduced eye-hand coordination. Robotic system provides

the possibility to overcome some of these limitations by offering 3-dimensional camera with 10× magnification and wristed instruments (37). The robotic system can be used during the thoracic dissection of the esophagus, gastric mobilization and intrathoracic anastomosis. It can also

Table 4 Studies comparing ILE and MI-ILE post-operative outcomes

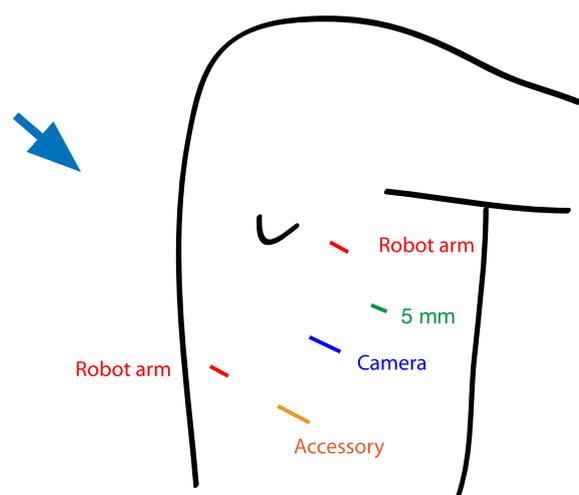
Study	Surgical type	No. patients	30-day mortality	Pneumonia	Leak	Stricture	RLN injury
Pham <i>et al.</i> [2010] (33)	MI-ILE	44	3 (6.8%)	11 (25%)	4 (9%)	3 (6.8%)	6 (13.6%)
	ILE	46	2 (4.3%)	7 (15%)	5 (10.9%)	0	0
Sihag <i>et al.</i> [2012] (34)	MI-ILE	38	0	0 ^a	2 (5.3%)	NR	NR
	ILE	76	2 (2.6%)	16 (21.1%)	4 (5.3%)	NR	NR
Biere <i>et al.</i> [2012] (35)	MIE	59	1 (2%)	7 (12%) ^a	7 (12%)	NR	1 (2%) ^b
	Open	56	0	19 (34%)	4 (7%)	NR	8 (14%)
Noble <i>et al.</i> [2013] (36)	MI-ILE	53			5 (9%)		
	ILE	53			2 (4%)		

RLN injury, recurrent laryngeal nerve injury; MI-ILE, minimally invasive Ivor Lewis esophagectomy; ILE, conventional Ivor Lewis esophagectomy; MIE, minimally invasive esophagectomy; open, open esophagectomy; NR, not reported; ^a, P<0.01; ^b, P<0.05.

**Figure 2** Port positions for laparoscopic robotic gastric mobilization and lymph node dissection.

be used in combination with laparoscopy, hand-assisted laparoscopy or thoracoscopy. Several groups have reported their early experience with robot-assisted ILE (38-40).

At our institution, we have begun to utilize the robotic system with MI-ILE. *Figure 2* illustrates the port placement for the robotic abdominal procedure. The patient is placed in the supine position. A camera port is placed above the umbilicus, and a 12 mm accessory port is placed to the right of umbilicus. A liver retractor is placed through a 5 mm port in the low right subcostal space. Two additional ports for robot arms are placed in the right and left subcostal space at least a handbreadth from the camera port. The robotic

**Figure 3** Port positions for right thoracoscopic robotic esophageal mobilization, lymph node dissection, and anastomosis.

cart comes over the patient's left shoulder. The abdominal operation for gastric mobilization, gastric tube construction and jejunostomy tube placement is performed as described in MI-ILE procedure. In the robotic thoracoscopic stage, the patient is turned to the left lateral decubitus position and the right lung is deflated. Chest port placement is shown in *Figure 3*. The camera port is placed in the eighth intercostal space, posterior to the posterior axillary line. One robot instrument port is placed a handbreadth superior and a handbreadth anterior to the camera port. The other robot port is placed a handbreadth inferior and a handbreadth posterior to the camera port. A 5 mm port is placed between superior incisions, and a 12 mm port is placed between inferior incisions. The robotic cart comes

over the patient's right shoulder posteriorly. The thoracic operation for esophageal mobilization, lymphadenectomy and intrathoracic anastomosis is performed as in the above-mentioned MI-ILE procedure. However, we have preferred to use a stapled side-to-side anastomosis using an endoGIA stapler (45 mm purple load) and then to oversee the resulting defect with two layers of running suture (using the wristed robotic instruments).

Robotic ILE outcomes

As a relatively new technology, data regarding the safety and the oncologic efficacy of robotic ILE are limited. de la Fuente *et al.* reported their initial experience with robotic ILE in 50 patients, which were comparable to open ILE and MI-ILE approaches (39): the mean operative time was 445±85 min. The estimated blood loss was 146±15 mL. The mean number of lymph nodes retrieved during surgery was 20±1.4. The mean length of hospitalization was 10.9±6.2 days. Mortality was 0 and main postoperative complications included pneumonia (10%) and anastomosis leak (2%). Study of Cerfolio *et al.* described similar results in 22 patients with robotic ILE with 40 mL blood loss, 18 lymph nodes harvested, 7 days of hospitalization, 0% mortality, and 4.5% anastomosis leak (40). These data suggest robotic ILE is safe, feasible and associated with perioperative outcomes similar to open ILE and MI-ILE. However, no evidence to date demonstrates improved outcomes of robotic over MI-ILE. The cost of equipment, specialized training, prolonged set up time and limited instrumentation are barriers to more widespread use. The fact that the surgeon is separated from the patient and the lack of tactile feedback raise potential safety concerns. For this procedure to be ultimately widely adopted, future studies are needed to prove identifiable benefit of robotic ILE relative to other approaches to offset inherent disadvantages and financial concerns.

Conclusions

MI-ILE has proven to have equivalent postoperative outcomes to open ILE, and thus represent a safe and feasible alternative for the surgical management of esophageal cancer. It also shows potential to reduce blood loss, postoperative pain and length of hospitalization. Improved long-term survival has not been documented in MI-ILE compared to conventional ILE. Prospective and randomized controlled trials comparing open ILE with MI-ILE are necessary if a

definite conclusion is to be made about the superiority of one surgical technique over the other. Robotic approach may offer advantages to MI-ILE over conventional procedure. Further studies of MI-ILE and robotic ILE are warranted to determine the ideal esophagectomy procedure.

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Robotic assisted Ivor Lewis esophagectomy in the elderly patient

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Objective: Robotic assisted approaches to esophagectomy have demonstrated decreased complications and length of hospitalization. We sought to examine the impact of age on outcomes in patients undergoing robotic assisted Ivor Lewis esophagectomy (RAIL).

Methods: A retrospective review of all patients undergoing RAIL from 2009–2013 was conducted. Statistical analysis was performed for the entire cohort and by stratifying patients into three age cohorts: ≤ 49 , 50–69, ≥ 70 .

Results: We identified 134 patients and found no statistically significant difference for operative time, length of hospitalization, adverse events (AE), or mortality. There was a higher median blood loss (150 cc) seen in cohorts 1 (50–600 cc) and 3 (50–400 cc) compared to cohort 2 [100 (range, 25–400) cc; $P < 0.01$]. The overall AE rate was 10% (cohort 1), 22% (cohort 2), 35% (cohort 3), $P = 0.13$. There were 5 (4%) leaks and 2 (1.5%) deaths, but this was not significantly different between cohorts ($P = 0.40$, $P = 0.91$, respectively).

Conclusions: RAIL is a safe surgical technique for use in an aging patient population. There was no increased risk of AE or death in the elderly patients compared to younger patients undergoing the robotic approach.

Keywords: Esophageal cancer; elderly; robotic esophageal

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Introduction

Esophageal cancer continues to increase in incidence worldwide (1–4). In the United States in 2013 there were 17,990 new cases of esophageal cancer and 15,210 deaths (4). The average age at the time of diagnosis continues to rise, and men and women are both presenting at an advanced age at the time of diagnosis, with a peak incidence between 75 and 79 years of age (1). The long-term survival for patients with locally advanced esophageal cancer remains poor despite improvements in multi-modality care over the last several decades. The current approach to locally advanced esophageal cancer includes neoadjuvant chemoradiation followed by surgical resection (5). Traditionally, older age has been associated with a presumed frailty and there is a concern that the elderly may not be able to tolerate the complex treatment regimen now recommended for

esophageal cancer.

Minimally invasive esophagectomy (MIE), including robotic assisted techniques, offer several potential advantages over traditional open esophagectomy. MIE has been found to result in faster recovery time, shorter hospitalization, and diminished post-operative pain. Biere *et al.* demonstrated favorable results for MIE in their open label controlled trial in which patients were randomized to either open esophagectomy or MIE. They reported patients undergoing MIE were less likely to have pulmonary infections and had shorter hospital stays compared to patients undergoing open esophagectomy (6). Additionally, retrospective reviews have demonstrated MIE does not compromise oncologic principles and is safe compared to traditional open esophagectomy for esophageal cancer (7–11). Robotic assisted Ivor Lewis esophagectomy (RAIL) is a new technique that allows the surgeon a broader three-

dimensional view of the operative field with the added benefit of improved instrument articulation and motion over standard thoracoscopy.

We have previously described the development and implementation of RAIL, however, the specific use of this technique in the elderly has not been extensively reviewed (12). We sought to evaluate outcomes after RAIL across all age groups to determine if this approach is safe in the elderly.

Methods

A retrospective review of all consecutive patients undergoing RAIL from 2009 to 2013 was conducted after obtaining study approval from our Institutional Review Board. All patients regardless of age, race, tumor stage or location, or receipt of neoadjuvant therapy were included in the cohort. Patients were required to have a tissue diagnosis of cancer, but were not excluded based upon histologic variant. Basic demographics, tumor characteristics, operative details, and post-operative outcomes were recorded.

The patients were analyzed as an entire cohort and then divided into three separate cohorts based upon age. Cohorts were defined as follows: cohort 1, ≤ 49 years old; cohort 2, 50 to 69 years old; and cohort 3, ≥ 70 years old. A separate analysis was performed evaluating outcomes of the elderly, defined as patients ≥ 70 years of age, compared to those patients ≤ 69 years of age.

Endpoints and statistical analysis

The primary endpoints were median operating room (OR) time, estimated blood loss (EBL), intensive care unit (ICU) days following surgery, and length of hospitalization (LOH). Secondary end-points included peri-operative adverse events (AE) less than 30 days following surgery; including pneumonia, cardiac arrhythmia, deep vein thrombosis (DVT)/pulmonary embolism (PE), wound infection, leak, and death.

Statistical analysis was performed using SPSS[®] version 21.0 (IBM[®], Chicago, IL, USA). Continuous variables were compared using the Kruskal Wallis or the ANOVA tests as appropriate. patients Chi-square test was used to compare categorical variables. All statistical tests were two-sided and an α (type I) error < 0.05 was considered statistically significant.

Results

We identified 134 patients (106 men, 28 women) who

underwent RAIL during the study period. The average patient age was 66 ± 10 years (*Table 1*). Adenocarcinoma was the predominant histology and was diagnosed in 115 (86%) patients. Only 14 (10%) patients had squamous cell histology and 5 (4%) patients had other histology. Neoadjuvant therapy was administered to 102 (76%) patients. All patients underwent a complete resection (R0) and the median tumor size was 3.0 (range, 0.1-15.1) cm. The median OR time was 407 (range, 239-694) minutes with a median EBL of 150 (range, 25-600) mL. There were 5 (4%) leaks and 2 (1.5%) deaths in the entire cohort.

The patients were divided into three cohorts by age for comparison (*Table 1*). Ten patients were ≤ 49 years old (8 men, 2 women), 67 patients were 50 to 69 years old (53 men, 14 women) and 57 patients were ≥ 70 years of age (45 men, 12 women). The only statistically significant difference among the cohorts at baseline was the receipt of neoadjuvant therapy. Only 65% of patients ≥ 70 years old received neoadjuvant therapy compared to 90% of patients ≤ 49 years old and 84% of patients 50 to 69 years of age ($P=0.03$).

There was no significant differences between the three cohorts with respect to median or time, ICU days, or LOH ($P=0.65$, $P=0.85$, $P=0.42$, respectively, *Table 2*). There was, however, a significant difference in median EBL between the three age groups; patients aged 50 to 69 had the lowest amount of blood loss [100 (range, 25-400) mL] while patients ≤ 49 and ≥ 70 had a median EBL of 150 mL (range, 50-600 and 50-400 mL, respectively; $P=0.004$). Re-admission rates were low at 5.2% and did not vary amongst age groups. There were 0 (0%) in the ≤ 49 , 4 (5.6%) in the 50-69, and 3 (5.7%) in the ≥ 70 age group $P=0.52$.

The rate of overall complication after surgery was not significantly different among the three cohorts (*Table 3*). Patients ≥ 70 years old had a higher absolute rate of overall complications (35%), although the difference in overall complication rate was not significant ($P=0.13$). Cardiac arrhythmias were the most frequent complication and were seen in 17 (12.7%) patients. Additionally, there was no significant difference in rate of pneumonia ($P=0.43$), wound infection ($P=0.51$), DVT or PE ($P=0.91$), leak ($P=0.40$), or death ($P=0.91$) among the three cohorts. Excluding cardiac arrhythmia, the overall rate of complications remained low and there was still no statistically significant difference between the three cohorts (≤ 49 years old 10%, 50 to 69 years old 18%, ≥ 70 years old 23%; $P=0.58$).

A separate analysis was done to compare the elderly (≥ 70 years old) to the non-elderly (≤ 69 years old). The only

Table 1 Pre-surgical patient, tumor and treatment characteristics

Characteristics	All patients (N=134), n (%)	≤49 years (N=10), n [%]	50-69 years (N=67), n (%)	≥70 years (N=57), n (%)	P value
Mean age (±SD)	66.4±10.1	43.1	62.3	75.3	
Mean BMI (±SD) (kg/m ²)	27.6±4.8	27.6±4.5	27.6±5.1	27.7±4.6	0.98
Sex					0.99
Male	106 (79.1)	8 [80]	53 (79.1)	45 (78.9)	
Female	28 (20.9)	2 [20]	14 (20.9)	12 (21.1)	
Race					0.50
Caucasian	126 (94.0)	10 [100]	64 (95.5)	52 (91.2)	
Black	6 (4.5)	0 [0]	3 (4.5)	3 (5.3)	
Other	2 (1.5)	0 [0]	0 (0)	2 (3.5)	
Tumor location					0.16
Cervical	1 (0.7)	0 [0]	0 (0)	1 (1.8)	
Upper & mid-thoracic	6 (4.5)	1 [10]	5 (7.5)	0 (0)	
Lower thoracic & GE junction	109 (81.3)	6 [60]	53 (79.1)	50 (87.8)	
Unknown	18 (13.4)	3 [30]	9 (13.4)	6 (10.5)	
Tumor histology					0.56
Adenocarcinoma	115 (85.8)	9 [90]	57 (85.1)	49 (86.0)	
Squamous	14 (10.4)	0 [0]	7 (10.4)	7 (12.3)	
Other	5 (3.7)	1 [10]	3 (4.5)	1 (1.8)	
Median clinical tumor size (range) (cm)	3.0 (0.1-15.1)	3.0 (2.0-10.0)	3.0 (0.7-10.0)	2.6 (0.1-9.0)	0.95
Clinical T stage					0.63
1	38 (28.4)	2 [20]	17 (25.3)	19 (33.3)	
2	17 (12.7)	1 [10]	9 (13.4)	7 (12.3)	
3	67 (50.0)	7 [70]	36 (53.7)	24 (42.1)	
4	1 (0.7)	0 [0]	1 (1.5)	0 (0)	
Unknown	11 (8.2)	0 [0]	4 (6.0)	7 (12.3)	
Clinical N stage					0.19
0	55 (41.0)	3 [30]	24 (35.8)	28 (49.1)	
1	56 (41.8)	6 [60]	33 (49.3)	17 (29.8)	
2	6 (4.5)	1 [10]	3 (4.5)	2 (3.5)	
3	0 (0)	0 [0]	0 (0)	0 (0)	
Unknown	17 (12.7)	0 [0]	7 (10.4)	10 (17.5)	
Neoadjuvant treatment	102 (76.1)	9 [90]	56 (83.6)	37 (64.9)	0.03*

*, denotes significant P value; SD, standard deviation; GE, gastroesophageal.

Table 2 Comparison of surgical and hospital outcomes between age cohorts

Outcomes	≤49 years (N=10)	50-69 years (N=67)	≥70 years (N=57)	P value
Median OR time [range] [minutes]	412 [328-573]	400 [239-694]	411 [293-621]	0.65
Median EBL [range] [cc]	150 [50-600]	100 [25-400]	150 [50-400]	0.004*
Median ICU stay [range] [days]	1.5 [1-13]	1 [0-23]	2 [0-30]	0.85
Median length of hospitalization [range] [days]	9.5 [7-21]	9 [4-35]	11 [6-38]	0.42

*, denotes significant P value; OR, operating room; EBL, estimated blood loss; ICU, intensive care unit.

Table 3 Comparison of perioperative complications between age cohorts

Complication	≤49 years (N=10), n (%)	50-69 years (N=67), n (%)	≥70 years (N=57), n (%)	P value
Pneumonia	0 (0)	3 (4.5)	5 (8.8)	0.43
Cardiac/arrhythmia	0 (0)	7 (10.4)	10 (17.5)	0.23
DVT/PE	0 (0)	1 (1.5)	1 (1.8)	0.91
Wound Infection	0 (0)	0 (0)	1 (1.8)	0.51
Leak	1 (10.0)	3 (4.5)	1 (1.8)	0.40
Death	0 (0)	1 (1.5)	1 (1.8)	0.91
Overall rate	1 (10.0)	15 (22.4)	20 (35.1)	0.13
Overall rate (excluding atrial fibrillation)	1 (10.0)	12 (17.9)	13 (22.8)	0.58

Patients who had a complication in addition to atrial fibrillation were counted in the overall rate (excluding atrial fibrillation) category.
DVT, deep vein thrombosis; PE, pulmonary embolus.

difference in baseline demographics between the two cohorts was once again receipt of neoadjuvant therapy ($P=0.01$) (Table 4). Median EBL was higher in the elderly cohort, but not statistically significant [100 (range, 25-600) *vs.* 150 (range, 50-400) mL; $P<0.4$]. There was also a trend toward longer LOH in the elderly [9 (range, 4-25) *vs.* 11 (range, 6-38) days; $P=0.23$ (Table 5)]. AE and mortality were not significantly different, although there was a trend towards increased AE (20.8% *vs.* 35.1%, $P=0.06$) in the cohort of patients ≥ 70 years of age, again with cardiac arrhythmia being the most common. There was a higher rate of cardiac arrhythmias in the patients who were ≥ 70 years old; 7 (9.1%) in the ≤ 69 group and 10 (17.5%) in the ≥ 70 cohort ($P=0.15$). The overall AE rate excluding cardiac arrhythmias was 13 (16.9%) in the ≤ 69 cohort *vs.* 13 (22.8%) in the ≥ 70 cohort $P=0.39$ (Table 6). Additionally, patients that developed a cardiac arrhythmia had a median length of hospitalization of 1.5 days longer than those who did not, 9 (range, 4-38) and 10.5 (range, 7-28) days respectively ($P=0.07$).

Discussion

We report our series of 134 RAIL cases comparing outcomes

by increasing age. While the AE rates were higher amongst the ≥ 70 population, this was predominated by cardiac arrhythmias and was not statistically significant. When accounting for these arrhythmias, overall AE rates were no different between cohorts. Additionally, there were no significant differences in operative outcomes and LOH between the elderly *vs.* younger cohorts.

Surgical resection is an integral part of the treatment algorithm for early stage and locally advanced esophageal cancer. Unfortunately, the morbidity associated with esophagectomy can be high and is estimated in the literature to be between 25% and 50% (2,13,14). Pulmonary and cardiovascular complications such as atelectasis, pneumonia, and atrial fibrillation, in addition to wound infection, anastomotic leak, and chylothorax are among the most commonly seen post-operative complications and may increase the risk of mortality (13,15). As life expectancy increases, the average age at time of diagnosis is expected to continue to increase. This trend may have a significant impact on the treatment algorithm for elderly patients if age alone is determined to be an operative risk factor. Given that treatment regimens now call for multi-modality approaches including chemoradiation prior to surgery, the

Table 4 Pre-surgical patient, tumor and treatment characteristics elderly versus non-elderly

Characteristics	≤69 years (N=77), n (%)	≥70 years (N=57), n (%)	P value
Mean age (±SD)	60±8.1	75±3.6	<0.001*
Mean BMI (±SD) (kg/m ²)	28±5	28±4.6	0.96
Sex			0.97
Male	61 (79.2)	45 (78.9)	
Female	16 (20.8)	12 (21.1)	
Race			0.23
Caucasian	74 (96.1)	52 (91.2)	
Black	3 (3.9)	3 (5.3)	
Other	0 (0)	2 (3.5)	
Tumor location			0.07
Cervical	0 (0)	1 (1.8)	
Upper & mid-thoracic	6 (7.8)	0 (0)	
Lower thoracic & GE junction	59 (76.6)	50 (87.7)	
Unknown	12 (15.6)	6 (10.5)	
Tumor histology			0.51
Adenocarcinoma	66 (85.7)	49 (86.0)	
Squamous	7 (9.1)	7 (12.3)	
Other	4 (5.2)	1 (1.8)	
Median clinical tumor size (range) (cm)	3 (0.7-10)	2.6 (0.1-9)	0.44
Clinical T stage			0.30
1	19 (24.7)	19 (33.3)	
2	10 (13.0)	7 (12.3)	
3	43 (55.8)	24 (42.1)	
4	1 (1.3)	0 (0)	
Unknown	4 (5.2)	7 (12.3)	
Clinical N stage			0.07
0	27 (35.1)	28 (49.1)	
1	39 (50.6)	17 (29.8)	
2	4 (5.2)	2 (3.5)	
Unknown	7 (9.1)	10 (17.5)	
Neoadjuvant treatment	65 (84.4)	37 (64.9)	0.01*

*, denotes significant P value; SD, standard deviation; GE, gastroesophageal.

Table 5 Comparison of surgical and hospital outcomes between elderly versus non-elderly

Outcomes	≤69 years	≥70 years	P value
Median OR time [range] [minutes]	400 [239-694]	411 [293-621]	0.67
Median EBL [range] [cc]	100 [25-600]	150 [50-400]	0.4
Median ICU stay [range] [days]	1 [0-23]	2 [0-30]	0.62
Median length of hospitalization [range] [days]	9 [4-25]	11 [6-38]	0.23

OR, operating room; EBL, estimated blood loss; ICU, intensive care unit.

Table 6 Comparison of perioperative complications between the elderly versus non-elderly

Complication	≤69 years (N=77), n (%)	≥70 years (N=57), n (%)	P value
Pneumonia	3 (3.9)	5 (8.8)	0.24
Cardiac arrhythmia	7 (9.1)	10 (17.5)	0.15
DVT/PE	1 (1.3)	1 (1.8)	0.83
Wound infection	0 (0)	1 (1.8)	0.24
Leak	4 (5.2)	1 (1.8)	0.30
Death	1 (1.3)	1 (1.8)	0.83
Overall rate	16 (20.8)	20 (35.1)	0.06
Overall rate (excluding atrial fibrillation)	13 (16.9)	13 (22.8)	0.39

Patients who had a complication in addition to atrial fibrillation were counted in the overall rate (excluding atrial fibrillation) category. DVT, deep vein thrombosis; PE, pulmonary embolus.

age of a patient has been called into question further as a potential risk factor for poor outcomes after treatment for esophageal cancer. The data to support this theory, however, is controversial.

Age has been demonstrated in several studies to correlate with higher rates of morbidity and mortality as well as worse survival (16-20). In their study of 474 patients undergoing esophagectomy between 2002 and 2011, Tapias *et al.* demonstrated an increased risk of morbidity and mortality in the elderly. The overall major complication

rate was highest in the cohort over the age of 80 at 62.5% compared 47.6% for those 70 to 79 years of age, and 37.2% for patients less than 70 years old ($P=0.016$). Mortality was also significantly different, 0.6% for patients less than 70, 3.2% for those 70 to 79 years old, and 6.3% for the patients over age 80 ($P=0.032$). The majority of these cases were performed using an open Ivor Lewis technique (45.7%) and only 8% were MIE (19). Similarly, in an analysis of the Society of Thoracic Surgeons General Thoracic Database by Wright *et al.* in which 2,315 esophagectomy cases were reviewed, the authors found that age, cardiovascular disease, diabetes, and smoking were independent risk factors on multivariate analysis for increase morbidity and mortality (16).

Several other studies, however, have found that when adjusted for comorbid conditions, age itself is not a predictor of post-operative morbidity (2,21-26). In a review of 685 patients undergoing esophagectomy between 1994 and 2012 at a single institution cancer center, McLoughlin *et al.* found that the only significant predictor of overall survival and disease free survival on multivariate analysis was neoadjuvant therapy. Age was not found to be a significant predictor of adverse outcomes ($P=0.66$) (2). Pultrum *et al.* also concluded in their analysis of 234 patients that comorbid conditions, not age, were predictors of complications, and they found no difference in rates of in-hospital mortality or overall number of complications. Additionally, the presence of a comorbid condition, not age, was an independent prognostic factor for survival (21).

Age and comorbid status may have an impact on outcomes after open esophagectomy, however, MIE may provide a reduction in the risk of complications to this patient population. Outcomes after MIE have been well-studied and found to be equivalent in safety and efficacy when compared with open procedures while providing shorter hospitalization, reduction in pain and need for narcotic medication, and a faster return to normal activity. In an early analysis of fifty patients undergoing RAIL at our institution, we found that lymph node yield (20.6 ± 9.3) and percentage of microscopically negative margins (100%) indicated equivalence of robotic to open approach (1). In their 3-year results of robotic-assisted transhiatal esophagectomy, Dunn *et al.*, achieved a similar lymph node yield [20 (range, 3-38)] and a 94.7% R0 resection rate (27). A study by Sihag *et al.* evaluated perioperative outcomes in 38 patients undergoing Ivor-Lewis MIE (combination of laparoscopy and thoracoscopy) compared to 76 patients undergoing open Ivor Lewis esophagectomy. They found

no difference in adequacy of oncologic outcomes: median number of lymph nodes, resection margins, and 60-day mortality. The MIE group, however, had a significantly reduced risk of developing pulmonary complications and were also found to have reduced length of ICU and hospital stay (15).

The robotic approach does require technical expertise by the operating surgeon and an OR team familiar with the intricacies of using the robot such as set-up, docking, and instrument exchange. Efficacy and feasibility of robotic surgery for complex esophageal surgery has been evaluated and found to offer enhanced three-dimensional visualization and advanced articulation with wrist-like motion. The potential draw-back to adoption of this technique is the steep learning curve required to achieve proficiency (27-30). In our experience, there was a significant reduction in operative time after completing twenty cases (514 *vs.* 397 minutes, $P<0.005$). During our initial evaluation of outcomes after our first 52 cases, we reported one case of anastomotic leak, no deaths and the overall complication rate was low at (26.9%). However, once the learning curve was reached (after 29 cases) the overall morbidity decreased, [n=10 (34%) *vs.* 4 (19%); $P=0.07$]. Additionally, there were no conversions to open thoracotomy and all patients in the series received an R0 resection (29).

Age alone has not been definitively proven to contribute to worse outcomes for open esophagectomy, and MIE has demonstrated reduction in post-operative pulmonary complications and shorter hospitalization, however, the impact of age on MIE, specifically RAIL, has not been thoroughly evaluated. The purpose of this study was to demonstrate that RAIL is a safe and reasonable operative approach in elderly patients with esophageal cancer. We acknowledge the limitations of this study that include the retrospective nature of the review. This cohort includes all consecutive patients undergoing RAIL at a single institution where all procedures were performed by a single surgeon thereby minimizing selection bias or variation in operative technique or learning curve as a factor in analyzing outcome data.

Conclusions

In our series of 134 patients, we were able to demonstrate that RAIL is a safe surgical technique for use in elderly patients. This represents the largest series to date with the RAIL technique and we demonstrated that elderly patients undergoing RAIL do not experience longer operative times,

length of time in an ICU or the hospital overall, nor have they been shown to suffer increased risk of complication or death. When separating the study groups into those greater than 70 and those less than 70 years old, there were trends toward significant differences in LOH and AE although this was related to the increasing incidence of cardiac arrhythmias in patients who are older than 70. Close monitoring and vigilant post-operative care are required to ensure safe outcomes after esophagectomy for all patients regardless of age.

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Salvage esophagectomy

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Abstract: Patients with locally advanced esophageal cancer are treated with definitive chemoradiation (dCXRT) for a number of reasons. Some patients are never referred to a surgeon for a conversation about surgery, others decline surgery, and some are not candidates for surgery due to a sag in performance status secondary to therapy. Regardless of method of arrival at dCXRT, the risk of local/regional recurrence during follow-up is significant. Many of these patients are faced with limited options for therapy once dCXRT has failed. Salvage esophagectomy has historically been considered a morbid procedure and poor choice for local/regional recurrence. This chapter reviews the recent literature arguing the relevance of salvage resection. We recommend that any patient suffering from persistent or recurrent local/regional only disease after dCXRT should be referred to an experienced esophageal center to consider surgical options.

Keywords: Esophageal cancer; surgery; salvage; definitive chemoradiation (dCXRT); selective

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Definitions

Planned resection: esophagectomy that occurs after preoperative therapy, usually within three months of therapy.

Salvage resection: surgical therapy after local-regional recurrence.

Observation: an active process of patient re-evaluation after definitive medical therapy. Optimally this involves PET imaging and EGD with endoscopic ultrasound at q4 monthly basis for the initial two years after therapy.

Introduction

Salvage esophagectomy can be defined in different ways, such as time elapsed from therapy or intent to treat. Patients with esophageal cancer who were treated with chemoradiation as definitive therapy (dCXRT) but are later identified as having local-regional recurrence or persistent disease and are resected satisfy the definition of salvage. Other definitions are included in the literature, such as patients who underwent resection in a delayed manner after induction chemoradiation, usually with a 3-month or greater interval from completion of therapy to resection. It

is important to understand the basic definitions to interpret the available data. Patients treated with definitive intent will have avoided surgery by design; thus, when recurrence is detected, the decision to proceed to resection is dependent on the knowledge of disease, rather than patient fitness. On the other hand, patients who were delayed from undergoing a planned resection because of poor performance status after completion of chemoradiation (CXRT), and who later were identified as having persistent disease and sufficient performance improvement to tolerate a resection represents a different patient population with different risks and outcomes.

Thus, patients arrive at dCXRT by different routes. Decreased performance after preoperative CXRT can result in a “watch and wait” strategy rather than proceeding to the planned resection. This is a method of backing in to definitive therapy by risk/necessity. If a patient is not cured by the initial therapy, recurrence noted during a period of observation should stimulate a discussion for salvage surgery. One very important caveat is that the method and frequency of observation in patients treated with this strategy effects the surgeon’s ability to offer resection. Local-regional recurrences that go unrecognized will

Table 1 Randomized controlled trials on definitive non-surgical therapy for esophageal cancer

Reference	Study interval	Histology	N	Schema	Results
Cooper, <i>et al.</i> (RTOG 85-01) (2)	1986-1990	SCCA/ACA	129	CRT vs. RT	26% vs. 0% 5-yr OS
Minsky, <i>et al.</i> (RTOG 94-05) (3)	1995-1999	SCCA/ACA	236	CRT with Higher dose RT vs. Standard	56% vs. 52% persistence of disease
Bedenne <i>et al.</i> (4)	1993-2000	SCCA/ACA	259	CRT vs. CRT + S	17.7% vs. 19.3% MS
Stahl <i>et al.</i> (5)	1994-2002	SCCA	172	CCRT vs. CCRT + S	24% vs. 31% 3-yr OS (P=0.02) surgery improves DFS

SCCA, squamous cell carcinoma; ACA, adenocarcinoma; CRT, chemoradiotherapy; OS, overall survival; CCRT, chemo + chemoradiation; DFS, disease free survival; S, surgery; RT, radiation therapy; QOL, quality of life.

progress to a point of non-resectability even in the situation where there is no evidence of distant disease. From the standpoint of clinicians, this should be recognized as the ultimate failure of therapy; death from local-regional disease.

The optimal management of locally advanced cancer of the esophagus remains controversial. Published results of pathologic complete response after combined concurrent chemoradiation therapies for esophageal cancer have caused some medical and radiation oncologists to question the additional benefit of surgical resection in patients that respond to non-surgical therapy. To that end, patients may not ever see a surgeon to consider the option of resection until after there is a recurrence, and sometimes not until the recurrence has failed multiple attempts at systemic or combined non-operative therapy.

Finally, to be complete we should clarify the definition of selective surgical approach. In this strategy, patients treated with CXRT to a complete response would be observed, those in whom there is residual disease, as judged by the med/surgical team, would proceed to planned resection. All of these pathways to salvage resection may result in subtle or even significant differences in patients and potential risk/benefit ratio for surgery. These differences need to be carefully considered prior to embarking on a physician-patient discussion about surgery.

Definitive chemoradiation therapy

When patients present with what appears clinically to be locally advanced disease on staging work up, they actually have a variety of potential outcomes. The biologic heterogeneity of esophageal cancer and lack of accurate staging technologies results in an inability to recognize patients with systemic disease versus those who are

curable by local-regional treatment modalities. It has been assumed that resection in this group of patient's results in discouraging long-term outcomes, primarily as a result of an inability to predict who will ultimately die of systemic disease. Optimally, we would offer surgery to only patients that would benefit, without omitting patients who need surgery, and every patient who underwent resection would have an excellent outcome. But, as long as esophagectomy is regarded as an operation carrying significant potential for morbidity, mortality, and changes in quality of life, patients who are either incapable or unwilling to undergo resection will opt to be treated medically.

This is precisely what occurred. Clinicians treating patients who were omitted from surgical therapy found some limited success with innovative combined therapies (chemotherapy and concurrent radiation). This led to a paradigm shift; the inevitable conclusion that patients with better performance status and potentially curable disease may also perform well with medical therapy as an alternative to resection (1). In fact, there are a number of phase II and III trials illustrating the potential of non-surgical therapy to produce short and long-term survival (*Table 1*) (1-10). One landmark study of medical-only therapy in a cohort of potentially curable patients describes the long-term results of patients treated with chemotherapy with concurrent radiation versus radiation alone. This study by the Radiation Therapy Oncology Group (RTOG 85-01/INT 0123) reported median and 5-year survival of 14.1 months and 27% in the group treated with definitive chemotherapy and radiation (6). In follow up to INT 0123 was a publication of mature data from both the randomized cohort and an additional group of non-randomized patients, the majority of who had squamous cell carcinoma (2). The authors reported 5-year survival between 14-26% in the non-randomized and randomized patient cohorts

respectively. The ability to achieve prolonged survival with medical therapy was somewhat encouraging in the randomized group, but intermediate to poor in the non-randomized group.

Most significant was number of patients that failed local-regionally in that trial: 56%. The RTOG 94-05 trial was designed to address this issue by utilizing higher levels of radiation, presumably to help sterilize the local-regional tumor fields (3). The results were disappointing; this trial illustrated that higher radiation levels, in the manner in which they were dosed in this trial, failed to improve local-regional control or survival, and therefore the 50.4 Gy dose of radiation described in the original INT-0123 trial became the standard for definitive dose for radiation for thoracic esophageal carcinoma treated with concurrent chemotherapy. This dose has since been adopted by many centers as the standard for preoperative chemoradiation therapy as well. The advantage being that a selective approach to surgery could be employed should that become the more attractive treatment option.

There was further evidence in surgical series illustrating that with modern chemoradiation protocols, patients treated with multi-modality therapy reached a pathologic complete response frequently (20-40%) (2-5,7-9). Given this response there were clinician groups that were of the opinion that surgery was merely documenting the response to therapy rather than complementing the outcome (11). The ensuing controversy led to an opinion shift in treatment approach. Rather than seeking to improve upon surgical outcomes with pre or post-operative therapy, the question arose: what is the additional benefit of esophagectomy in patients who have responded to definitive chemoradiation?

Chemoradiation with or without surgery

There are two randomized controlled trials comparing the benefit of adding surgery to definitive chemoradiation therapy (4,5). Both trials primarily involve squamous cell carcinoma of the esophagus. The study by Bedenne *et al.* randomized patients that responded to chemoradiation either to a surgery or observation arm. Two hundred fifty patients were evaluated (129 surgical, 130 definitive chemoradiation therapy; 11% adenocarcinoma). Median survival in the surgical and non-surgical groups was 17.7 months versus 19.3 months, respectively, and 2-year overall survival was 34% versus 40%, respectively (P= NS). There were notable benefits found in the surgical arm such as improved local-regional control and increased freedom from palliative procedures

(such as stents), but the trade-off was significantly higher treatment related toxicity in the surgical arm. Mortality analyzed at 90 days was 9.3% in the surgical group versus 0.8% in the non-surgical group (4). The fact that improved local control in the surgical arm did not lead to an increase in overall survival in this study may exemplify the difficulty with adequately staging patients pretreatment and the biologic heterogeneity that is inherent with esophageal cancer. Further, the data exemplifies that esophagectomy after concurrent chemoradiation in a multi-institutional setting can lead to higher than expected mortality which will decrease the value of resection.

The study by Stahl *et al.* employed induction chemotherapy prior to chemoradiation presumably in an effort to decrease distant failure (5). All patients in this trial had squamous cell carcinoma. This study randomized 172 patients (86 to chemoradiation followed by surgery versus 86 treated with definitive chemoradiation). The results showed freedom from local-regional recurrence was better with surgery and disease-free survival was reported to be significantly improved with surgery compared to observation (64% versus 41% at 2 years; P=0.003). However in contrast to the Bedenne trial (4), the Stahl trial (which randomized all patients rather than responders only) did demonstrate a survival advantage in the surgery arm (31% versus 24% at 3 years; P=0.02). Again, there was a significant increase in treatment-related mortality reported in the surgical arm (12.8% versus 3.5%; P=0.03). Overall this study illustrated that patients who underwent surgery were less likely to die of cancer but were at increased risk for treatment-related toxicity. Another finding of interest on sub-group analysis was that non-responders who achieved a complete (R0) resection reached 32% three-year survival. This was in contrast to responders who achieved greater than 50% three-year survival regardless of the treatment arm.

Taken together, these two studies demonstrate that in patients who respond to medical therapy, the risk of increased toxicity seen in multi-institutional trials involving combined modality therapy including surgery may detract from a potential advantage in disease-free survival obtained by the addition of surgery. A second observation is that non-responders may derive more benefit from surgery than responders.

Salvage esophagectomy

Definitive chemoradiation therapy as a treatment strategy has created a unique subgroup of patients who eventually

manifest regrowth of residual viable tumor or re-present with recurrence in a local-regional distribution in the absence of metastatic disease. These patients face limited treatment alternatives that can lead to cure, and should absolutely be evaluated by an esophageal surgeon to discuss the option of salvage esophagectomy. Other methods of therapy such as retreatment with chemoradiation may be possible for previously untreated regional disease, but tumor that regrows within the radiation field after medical therapy is resistant and unlikely to respond well to retreatment.

There are many prospective, non-randomized and retrospective publications describing the feasibility of salvage esophagectomy (Table 2). Whereas most focus on squamous cell carcinoma, there is also published experience on salvage resection for adenocarcinoma (12-24). Most of the published data are small retrospective series ranging from 10 to 65 patients. A comprehensive review by Gardner-Thorpe summarizes nine published series totaling 105 patients (Table 3) (27). The indication for salvage in over 50% of the resected cases was for persistent disease, while local-regional recurrence in the absence of metastatic disease was the indication in 43%. One of the interesting

questions about definitive CXRT is the percentage of patients that will ultimately require surgery, and how many will have missed an opportunity for cure because planned surgery was avoided. Based on available data the absolute percentage of patients that will present for salvage resection after definitive medical therapy is not known. Selection for salvage resection depends on many factors such as initial stage, indications for resection, patient demographics, referral patterns, etc. However, there is one report by Nishimura *et al.* that reported on 16% of the thoracic esophageal cancer patients that underwent definitive CXRT at their institution who were referred for salvage resection (18).

Regarding surveillance for patients undergoing observation after definitive CXRT, patients whose recurrence is discovered because of symptoms are generally further advanced than those that are discovered by imaging or endoscopy. Often this means that the patient will not be amenable to salvage resection. In contrast, patients who are followed closely with imaging and endoscopy are probably (observational data from author) more likely to have recurrence detected at an early enough stage to potentially benefit from salvage resection. Therefore, it is recommended that patients undergo endoscopy with ultrasound (to detect nodal disease, not wall thickness) along with PET imaging every four months during the first 1-2 years after CXRT, followed by surveillance at 6-12 months intervals thereafter. Up to 95% of patients will recur within two years of definitive CXRT, and almost all within three years (99%) (25).

Patient selection

Patients who present persistent or recurrent local-regional disease after definitive CXRT and have no evidence of systemic disease are candidates for salvage resection. Similarly, for a patient whose surgery was cancelled due

Table 2 Retrospective reviews on salvage resection

Reference	Study interval	N	Histology
Swisher <i>et al.</i> (12)	1987-2000	13	SCCA/ACA
Nakamura <i>et al.</i> (13)	1992-2002	27	SCCA
Tomimaru <i>et al.</i> (14)	1985-2004	24	SCCA
Chao <i>et al.</i> (15)	1997-2004	27	SCCA
Oki <i>et al.</i> (16)	1994-2005	14	SCCA
Borghesi <i>et al.</i> (17)	1999-2005	10	SCCA/ACA
Nishimura <i>et al.</i> (18)	2000-2006	46	SCCA
Marks <i>et al.</i> (19)	1997-2010	65	ACA

SCCA, squamous cell carcinoma; ACA, adenocarcinoma.

Table 3 Reviews of interest

Reference	Year published	Topics/comments
Ishikura <i>et al.</i> (21)	2003	Reviews toxicity of definitive CRT
Urschel <i>et al.</i> (25)	2003	Excellent general review of salvage esophagectomy
Urschel and Sellke (26)	2003	Complications of salvage resection
Adams <i>et al.</i> (9)	2007	Retrospective review of outcomes on 330 pts treated with definitive CRT, CRT + S, surgery, or chemo + surgery
Gardner-Thorpe <i>et al.</i> (27)	2007	Excellent review, combines data from previously published manuscripts

CRT, chemoradiotherapy.

to a decline in performance status but has since improved, recognition of disease should prompt a re-evaluation for surgery. A re-staging work up should be performed prior to considering salvage resection, and this would include methods to rule out systemic disease such as high definition CT to rule out metastatic disease in the lungs and integrated PET/CT for the whole body. Endoscopy is used to assess the proximal and distal extent of tumor involvement for resection and reconstruction planning. Endoscopic ultrasound is not reliable for assessing esophageal wall invasion after radiation treatment but can be very helpful when combined with transesophageal or transbronchial fine needle aspiration to assess regional and non-regional nodes of interest. These low risk diagnostic methods can offer histologic confirmation of disease where there is question of non-regional lymph node or adrenal gland involvement for example, that would preclude the indication for salvage resection. Bronchoscopy is necessary in patients with proximal tumors above or around the carina when there is suspicion for direct invasion into the airway. Endobronchial ultrasound (EBUS) can be helpful in this situation as well. A physiologic work up consisting of serum laboratory analyses, cardiac and pulmonary evaluations should be considered prior to resection. In patients where elevated CEA was a marker for disease, drawing baseline levels can be helpful for later surveillance.

Surgical resection

Reported series have consisted of resections performed with transhiatal, McKeown and Ivor Lewis approaches (12-28). There is no literature supporting a limited lymphadenectomy for salvage resection and therefore we advocate a complete resection with a two-field lymph node dissection when possible. However, one review does describe significantly fewer 3-field lymphadenectomies performed for salvage compared to planned esophagectomy (41% vs. 91%) (20). Two-field lymphadenectomy has been described, and there is no direct evidence that this contributes to significant morbidity (12). We perform salvage resection exactly as a standard esophagectomy (including the use of minimally invasive techniques) with some caveats. Alternative methods of reconstruction and the possibility for resection of primary tumor with a second, staged reconstruction effort at a later date either due to poor patient performance or for lack of an appropriate conduit should be considered (14).

One of the more striking morbidities that have been

reported in multiple series describing salvage esophagectomy is the rate of conduit necrosis, quoted as high as 25% (13,28). Although ours is the largest series on salvage for adenocarcinoma (65 patients) our rate of conduit loss is still a bit higher than our historical data and in comparison to planned resection (4.6% compared to 1%) (19). Most surgeons would agree that the stomach is the most robust and straight-forward esophageal replacement, however, for patients with lower esophageal tumors review of the radiation treatment plan will often reveal inclusion of the entire stomach within the treatment field, usually to full dose. The latent period between the completion of radiation and the surgical resection may affect the extent of small-vessel radiation damage and potentially jeopardize the viability of the stomach when transposed into the chest. In these situations we make a practice of carefully examining the stomach intra-operatively for signs of damage or suitability as a reconstruction conduit. Similarly, fashioning the anastomosis within the radiated field in the chest has been shown by our group to result in a higher than acceptable leak rate (29). When the potential viability of the stomach is in question, one or more of several responses should be prompted: harvest of omentum to transpose into the chest to wrap the gastric and anastomotic suture/staple lines (30), consideration for use of a different conduit such as a colon or long segment jejunal interposition with microvascular augmentation, or esophageal resection with delayed reconstruction. We recommend that the esophageal anastomosis be placed above the previous radiation field when at all possible. Another potential drawback to salvage resection is the potential for incomplete resection. Available data reports that 10-70% of resections performed in a salvage situation are R1 or R2 (12-14,17,19). In our series 91% (59/65) of patients had an R0 resection (19).

Toxicity

Another barrier to adopting salvage resection as the primary treatment modality for thoracic esophageal cancer is the described toxicity associated with salvage resection. This is summarized in *Table 4*. In-hospital deaths range from 2% to 33% (12-28); the upper range being significantly higher than optimal. In some series hospital stays were longer in general (14 to 47 days) and this may be due to an increased incidence of conduit necrosis, pulmonary toxicities and/or anastomotic leak. As previously mentioned, conduit necrosis, when described, was seen in up to 25% and anastomotic leak in 15% to 39% of patients undergoing

Table 4 Toxicity of salvage resection

Reference	N	R1 (%)	Leak (%)	Length of stay (days)	30-day mortality (%)
Swisher <i>et al.</i> (12)	13	20	38*	29.4*	15
Nakamura <i>et al.</i> (13)	27	33	22	40	8
Tomimaru <i>et al.</i> (14)	24	33*	21	NS	13
Chao <i>et al.</i> (15)	27	37*	15*	22.4	29*
Oki <i>et al.</i> (16)	14	50	29	NS	7
Borghesi <i>et al.</i> (17)	10	70*	20	21	10
Nishimura <i>et al.</i> (18)	46	0	22	47	15
Tachimori <i>et al.</i> (20)	59	15	31*	38	8*
Marks <i>et al.</i> (19)	65	5	18	12	3

*, denotes a significant difference from reported comparison group when applicable; NS, not specified.

salvage resection. In fact, many of the perioperative deaths described in these series were related to anastomotic leak or conduit necrosis despite aggressive medical and surgical efforts to rescue these patients. Other reported discrepancies from standard, planned resection include potential for more blood transfusion and ICU stay. In order to explore the potential reasons for any differences in our series we performed a matched pair analysis between a planned and salvage resection cohort. Those results showed that salvage resection was not the predictor of complication above and beyond co-morbidity (controlled for in matched pair) and disease stage. Variables such as length of stay, ICU admission, OR time, blood loss and leak rate were comparable. With careful selection patients can achieve an excellent outcome in experienced centers (19).

Outcome

Patients who have undergone salvage resection represent a highly selected group of patients with potentially favorable biology. Less fortunate patients with poor performance status, progressive systemic disease, or unresectable local-regional recurrence are, by definition, eliminated from this group thus improving the appearance of the overall outcome for this selected group. With this in mind, the reported 5-year overall survival is up to 60% in patients who were fortunate enough to undergo an R0 resection (12). However, as a group that includes R0-1 resections long term survival is intermediate, ranging from 0-35% at five years (12-24,27).

The data for patients with adenocarcinoma undergoing salvage resection is similar to squamous histology. We

presented a series describing salvage for exclusively adenocarcinoma; 65 patients who presented for resection after definitive chemoradiation for adenocarcinoma of the esophagus achieved a 32% overall 5-year survival. The median survival was not statistically different from a comparison group of 521 patients who underwent planned resection (48 versus 32 months, P=0.22) (19).

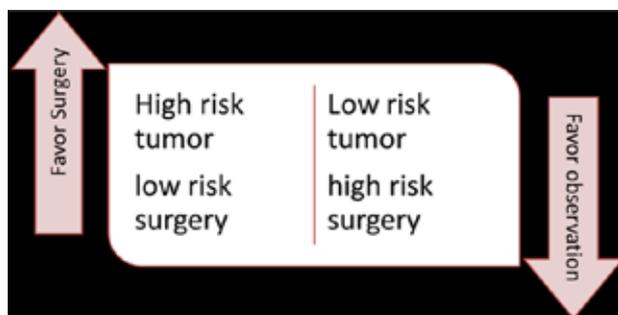
Selective surgery

Trials comparing chemoradiation with or without surgery have illustrated that cure is possible without surgical resection. Choosing the patient that requires further local-regional therapy after chemoradiation as opposed to one who would not benefit from resection compels the possibility of selective surgical resection; incomplete responders would go for surgery and patients that are clinical complete responders or progressed to distant disease on therapy would avoid resection. There have been two recent prospective, nonrandomized trials that sought to evaluate a selective surgical approach as an adjunct to definitive medical therapy in patients with squamous histology (*Table 5*) (31,32). Both show high clinical response rates to therapy suggesting that a selective surgical approach using chemoradiotherapy represents a survival advantage over surgery alone. Similarly, a phase II study including patients with adenocarcinoma was completed by the RTOG (protocol 0246) showing feasibility of this approach in a multi-institutional study albeit with high medical mortality (5/41) (33). None of these studies were designed to show superiority over a planned tri-modality chemoradiotherapy + surgery approach and therefore conclusions cannot be

Table 5 Non-randomized phase II trials utilizing selective surgery

Reference; [Study interval]	Patients	N	Histology	Endpoints	Results
Wilson and Lim; [1993-1996] (31)	T ₁₋₃ , N ₀₋₁ , M ₀	32	SCCA/ACA	Path response, survival, organ preservation, toxicity	Endoscopic response 77%, selective approach was feasible
Ariga <i>et al.</i> ; [2001-2005] (32)	T ₁₋₃ , N ₀₋₁ , M ₀	99	SCCA	OS, DFS, QOL, toxicity	26% cross-over to salvage surgery
Swisher <i>et al.</i> ; [2003-2006] (33)	T ₁₋₃ , N ₀₋₁ , M _{0-1a}	41	SCCA/ACA	Treatment response, organ preservation, toxicity, feasibility	1-yr survival goals not met, but feasibility demonstrated

SCCA, squamous cell carcinoma; ACA, adenocarcinoma; OS, overall survival; DFS, disease free survival; QOL, quality of life.

**Figure 1** Possible algorithm for considering selective surgery after response to neoadjuvant chemoradiation.

reached on that question. What the RTOG 0246 study did show very nicely is that among the patients taken to selective resection, when the surgeon suspected that there would be persistent disease the results showed that 17/18 patients had disease in the pathologic specimen. The only patient in the study that was resected to a pathologic complete response had insisted on surgical therapy. These results underscore the positive predictive value of surgeons who are experienced in multi-modality therapy to predict when viable tumor will be present in the specimen. Several patients in that series also presented for later salvage resection, indicating that accuracy is not complete.

Based on the literature, it is reasonable to conclude that patients with locally advanced esophageal adenocarcinoma have better outcomes with planned resection compared to observation, as long as they are candidates for trimodality therapy (CXRT + surgery) (34).

As well, when considering selective surgery after successful chemoradiation, one should stratify patients by risk of surgery balanced with risk of recurrence (*Figure 1*). High-risk tumor, low-risk patients should prompt a planned resection. Lower-risk tumor (based on initial stage and

response) in a high-risk patient will encourage me to consider selective surgery—observation (35).

Summary pearls

- (I) Patients who have received dCXRT should have active surveillance for early detection of recurrence.
- (II) All medically fit patients with local regional recurrence after dCXRT should be referred to a surgeon to consider resection.
- (III) Patient selection for salvage is essential. Staging for metastatic disease and physiologic work up should be complete.
- (IV) Patients should be referred to centers experienced in multi-modality treatment of esophageal cancer and salvage resection.
- (V) Reviewing the previous radiation treatment plan is essential.
- (VI) Anastomoses should be placed above of the esophageal radiation field.
- (VII) Alternative conduits may be appropriate.

In conclusion, salvage resection is a reasonable option to treat patients with local regional recurrence after failed definitive therapy.

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Extent of lymph node dissection: common hepatic artery lymph node dissection can be omitted for esophageal squamous cell carcinoma

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Objective: Controversy persists regarding the adequate extent of lymph node (LN) dissection in thoracic esophageal cancer (EC) surgery. Oncologic efficacy should be balanced with the increased risk of postoperative complications after aggressive radical LN dissection. Here, we evaluate the effectiveness of common hepatic artery LN dissection in surgery for thoracic esophageal squamous cell carcinoma.

Patients and methods: Among a total of 1,563 EC patients who underwent surgery from May 2005 to December 2012 at the Fudan University Shanghai Cancer Center, 1,248 thoracic esophageal squamous cell carcinoma were selected for this study, including 682 patients who underwent esophagectomy with common hepatic artery LN dissection and 566 patients who underwent esophagectomy without common hepatic artery LN dissection. The clinical data of patients were retrospectively analyzed. In addition, the locoregional LN metastasis, relationship between metastatic rates of common hepatic artery LN and clinicopathological factors were analyzed. A propensity score match analysis were performed to control for potential differences in the characteristics of patients with EC cell carcinoma, and postoperative complications were analyzed after propensity score-matching.

Results: The metastatic rate of common hepatic LN was 3.5%. Logistic regression analysis revealed tumor diameter, N classification and pTNM stage were risk factors for common hepatic LN metastasis. Matching based on propensity scores produced 361 patients in each group. The overall incidence of postoperative complications was 32.70% and 35.45%, respectively, no significant difference was found (P=0.432).

Conclusions: The metastatic rate of common hepatic artery LN is low. For patients who undergo resection for Stage I thoracic esophageal squamous cell carcinoma, the dissection of common hepatic artery LN may be safely omitted.

Keywords: Esophageal squamous cell carcinoma; common hepatic artery lymph node (common hepatic artery LN); lymph node dissection (LN dissection); propensity score match

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Introduction

The outcomes for patients with esophageal cancer (EC) remain suboptimal and the incidence of EC has been increasing in recent years. To improve the outcomes of EC,

multidisciplinary treatment has been developed and the survival rates have been improving, however, they are still far from satisfactory (1,2). One reason is its high frequency of lymph node (LN) metastasis. In addition, lymphatic

metastasis of EC does not follow a standard pattern (3,4). The latest version of the UICC/AJCC TNM classification (7th edition) emphasizes the importance of LN metastasis for prognosis. However, the Japanese Classification of EC (10th edition) has not incorporated the number of LN metastases into the N factor for its staging system (5,6). Given its frequency and extent of LN metastasis, controlling LN metastasis is a rational therapeutic strategy, and an extended LN dissection may be logical in selected patients. But recent arguments have supported a reduction of unnecessary LN dissection in esophagectomy, which may be associated with increased operative time and postoperative complication (7). Here, we aimed to evaluate the effectiveness of common hepatic artery LN dissection in surgery for thoracic esophageal squamous cell carcinoma.

Methods

Patients

Between 2005 and 2012, 1,563 patients underwent curative intent surgery for EC at the Fudan University Shanghai Cancer Center. The records of all patients with esophageal squamous cell carcinoma were reviewed for the present study. Of these patients, 1,248 patients with esophageal squamous cell carcinoma were enrolled in this study, 682 patients were underwent esophagectomy with common hepatic artery LN dissection and 566 patients were underwent esophagectomy without common hepatic artery LN dissection. The exclusion criteria were as follows: (I) nonsquamous esophageal carcinoma; (II) double primary cancer involving another organ; (III) definite distant metastasis; and (IV) receive neoadjuvant chemotherapy and radiotherapy. All patients were staged according to the TNM classification of the 7th edition of the American Joint Committee for cancer staging manuals (8). The institutional review board of Fudan University Shanghai Cancer Center approved the database of esophageal carcinoma used for the present study.

Preoperative evaluation

Preoperative evaluation at Fudan University Cancer Center included chest and abdomen computed tomography (CT), barium esophagography, electronic gastroscopy, cervical and abdomen ultrasound, and endoscopic ultrasound (EUS). Through preoperative evaluation, patients with tumors that were confined to the mucosa without nodal metastasis

were referred to the endoscopic intervention department for endoscopic mucosal resection (EMR). However, for tumors that were invading the submucosa or for which adequate resection margins were not achieved, EMR was performed at our institution. If a patient had already undergone endoscopy at another hospital, pathology consultation was performed at our institution. If adequate resection margins were not achieved at another hospital, endoscopy was performed a second time. Integrated positron emission tomography and CT (PET-CT) has not been routinely performed to evaluate nodal metastasis and distant extrathoracic metastasis because of the high price that people cannot afford it. On the basis of the results from those examinations, the patients who were medically suitable, with stage T1-T3 tumors without distant metastases would undergo Surgery.

Surgical approach and lymphadenectomy

Patients was either Ivor Lewis, transhiatal esophagectomy or tri-incisional esophagectomy according to their bodies situation and tumor location, however, the choice of surgical approach also depend on surgeon preference. Middle and lower mediastinal nodes and upper abdominal nodes were routinely removed through a left thoracotomy, however, through a right thoracotomy (Ivor-Lewis procedures), usually the total mediastinal lymphadenectomy was performed. And cervical lymphadenectomy was performed through cervical incision when lymphatic involvement in the neck was indicated by CT scan or ultrasonography.

In our present study, the cervical LNs included the LNs in the supraclavicular and cervical paraesophageal regions. The upper mediastinal nodes included the upper paraesophageal LNs and recurrent laryngeal nerve LNs. The middle mediastinal nodes included the subcarinal, middle paraesophageal, and bilateral hilar LNs. The lower mediastinal nodes included the lower paraesophageal, and diaphragmatic LNs. The upper abdominal nodes included the paracardial LNs, lesser curvature LNs, left gastric artery LNs, common hepatic artery LNs, splenic artery LNs, and celiac artery LNs.

Statistical analysis

Descriptive statistics were used to compare variables between the unmatched groups, using the χ^2 test for categorical variables. Logistic regression analysis was conducted to evaluate the effects of clinical factors. To

Table 1 Distribution of baseline characteristics of the cohorts before and after propensity score matching

	Before matching		P value	After matching		P value
	Cohort one	Cohort two		Cohort one	Cohort two	
Total	682	566		361	361	
Age (years)						
Age >60	308	312	0.92	176	168	0.551
Age ≤60	374	254		185	193	
Sex						
Male	364	477	<0.01	272	277	0.663
Female	318	89		89	84	
Type of surgery						
Ivor Lewis	355	278	<0.01	172	177	0.955
Left transthoracic esophagectomy	22	82		14	14	
Tri-incisional esophagectomy	305	206		175	172	
Tumor location						
Upper	43	37	0.152	27	33	0.482
Middle	425	323		302	303	
Lower	214	206		32	25	
Tumor invasion degree						
T1	85	79	0.442	44	49	0.849
T2	183	163		101	101	
T3	414	324		216	211	
Tumor length (cm)						
≤5	595	488	0.283	314	312	0.826
>5	87	78		47	49	
N classification						
N0	300	285	0.017	160	184	0.106
N1	197	169		104	107	
N2	125	80		68	50	
N3	60	32		29	20	
Tumor differentiation						
Well	63	53	0.938	31	36	0.813
Moderate	457	374		241	238	
Lower	162	139		89	87	
Pathological TNM stage						
I	61	63	0.061	31	39	0.242
II	310	281		165	178	
III	311	222		165	144	

Cohort one, esophagectomy with common hepatic artery lymph node dissection; Cohort two, esophagectomy without common hepatic artery lymph node dissection.

control for potential differences in the characteristics of patients treated with common hepatic artery LN dissection or without common hepatic artery LN dissection, propensity score methods were used. By using logistic regression model, which included variables such as age, sex, type of surgery, tumor location, tumor invasion degree, tumor length, pathological N stage, tumor differentiation and pathological TNM stage, propensity scores were computed as the conditional probability of receiving either esophagectomy with common hepatic artery LN dissection or esophagectomy without common hepatic artery LN

dissection. Using the nearest neighbor match algorithm, we created propensity score-matched pairs without replacement (a 1:1 match). And the caliper definition was set 0.02. The paired patients were extracted from the database. Using this method, 361 of 682 patients who underwent esophagectomy with common hepatic artery LN dissection were matched with 361 of 566 patients who underwent esophagectomy without common hepatic artery LN dissection with similar propensity scores (*Table 1*). A P value of <0.05 was considered statistically significant. All statistical analyses were performed with SPSS package (version 19.0).

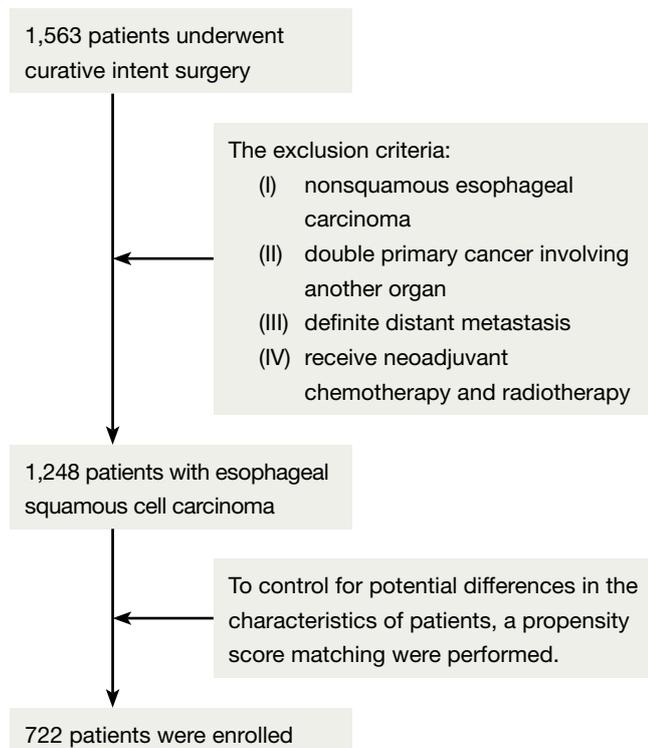


Figure 1 Reliable patients for inclusion.

Results

Patients characteristics

A total of 1,563 EC patients who underwent esophagectomy were enrolled onto the research at the Fudan University Cancer Center from May 2005 to December 2012. The results of the procedure are summarized in *Figure 1*. The enrolled study patients were divided into two cohorts: patients (n=682) who underwent esophagectomy with common hepatic artery LN dissection and patients (n=566) who underwent esophagectomy without common hepatic artery LN dissection. In the first cohort, 364 patients (53.37%) were male and 318 female (46.63%); in the second cohort, 477 patients (84.27%) were male and 89 female (15.73%), all the patients were stage I to III. The baseline characteristics of 1,563 patients are summarized in *Table 2*. Matching based on propensity scores produced 361 patients in each cohort, and the paired cohorts were well balanced (*Table 1*).

Lymph node metastasis (LNMs) before propensity score-matching

A total of 18,277 LNs were dissected (27 LNs per patient),

Table 2 The basic clinical characteristics of patients in two study cohorts

Characteristics	Cohort one	Cohort two	Total
Age (years)	Cases [n]	Cases [n]	
Median [Range]	59 [27-78]	59 [33-80]	59 [27-80]
Sex			
Male	364	477	841 (67.4%)
Female	318	89	407 (32.6%)
Type of surgery			
Ivor Lewis	355	278	633 (50.7%)
Left transthoracic esophagectomy	22	82	104 (8.3%)
Tri-incisional esophagectomy	305	206	511 (41%)
Tumor location			
Upper	43	37	80 (6.4%)
Middle	425	323	748 (60%)
Lower	214	206	420 (33.6%)
Tumor invasion degree			
T1	85	79	164 (13.2%)
T2	183	163	346 (27.7%)
T3	414	324	738 (59.1%)
Tumor length (cm)			
≤5	595	488	1,083 (86.78%)
>5	87	78	165 (13.22%)
N classification			
N0	300	285	585 (46.9%)
N1	197	169	366 (29.3%)
N2	125	80	205 (16.4%)
N3	60	32	92 (7.4%)
Tumor differentiation			
Well	63	53	116 (9.3%)
Moderate	457	374	831 (66.6%)
Lower	162	139	301 (24.1%)
Pathological TNM stage			
I	61	63	124 (9.9%)
II	310	281	591 (47.4%)
III	311	222	533 (42.7%)

Cohort one, esophagectomy with common hepatic artery lymph node dissection; Cohort two, esophagectomy without common hepatic artery lymph node dissection.

Table 3 The locoregional LN metastatic rates before propensity score-matching

LN metastasis	Cohort one (n=682)		Cohort two (n=566)		P value	
	Cases	Metastatic rates (%)	Cases	Metastatic rates (%)		
Neck	Cervical paraesophageal LNs	14	29.79% (14/47)	17	39.53% (17/43)	0.498
	Right supraclavicular LNs	34	16.59% (34/205)	22	22% (22/100)	0.345
	Left supraclavicular LNs	37	21.14% (37/175)	22	22% (22/100)	0.894
Upper mediastinum	Upper esophageal LNs	22	12.22% (22/180)	13	9.29% (13/140)	0.454
	Recurrent laryngeal nerve LNs	125	30.27% (125/413)	73	24.66% (73/296)	0.216
Middle mediastinum	Subcarinal LNs	52	11.71% (52/444)	35	10.12% (35/346)	0.524
	Mid-esophageal LNs	97	23.1% (97/420)	76	24.28% (76/313)	0.769
	Right hilar LNs	12	7.06% (12/170)	11	6.63% (11/166)	0.884
	Left hilar LNs	7	5.26% (7/133)	4	4.71% (4/85)	0.862
Lower mediastinum	Lower-esophageal LNs	79	21.29% (79/371)	66	21.15% (66/312)	0.971
	Diaphragmatic LNs	10	7.94% (10/126)	8	7.41% (8/108)	0.888
Upper abdomen	Lesser curvature LNs	69	28.51% (69/242)	43	23.37% (43/184)	0.360
	Paracardia LNs	84	37.5% (84/224)	59	28.64% (59/206)	0.167
	Left gastric artery LNs	68	27.42% (68/248)	37	27.41% (37/135)	0.998
	Celiac artery LNs	6	22.22% (6/27)	3	27.27% (3/11)	0.796
	Splenic artery LNs	5	9.26% (5/54)	2	11.76% (2/17)	0.786
	Common hepatic artery LNs	24	3.5% (24/682)	0	0	

Cohort one, esophagectomy with common hepatic artery lymph node dissection; Cohort two, esophagectomy without common hepatic artery lymph node dissection. LN, lymph node.

the LN metastatic rate was 55.87%. Of all the LNMs, the paracardial LNs were the most frequently involved (37.5%), followed by recurrent laryngeal nerve LNs (30.27%) in cohort one. Whatever, only 24 patients had common hepatic artery LN metastasis, with the metastatic rate of 3.5% in cohort one (Table 3). Compared with other LNMs, the metastatic rate of common hepatic artery LN is the lowest. In addition, all the common hepatic artery LN metastasis was accompanied with locoregional metastasis.

Risk factors for common hepatic LNMs

In our study, the relationship between metastatic rates of common hepatic artery LN and clinicopathological factors were also analyzed (Table 4). Logistic regression analysis identified that tumor length ($P=0.014$), N classification ($P<0.01$) and pathological TNM stage ($P<0.01$) correlated with the occurrence of common hepatic artery LNMs. The common hepatic artery LN metastatic rates of patients with diameter of tumor under or equal 5 cm and 5 cm were 2.86% and 8.05%, with significant difference ($P=0.014$). The common hepatic artery LN metastatic rates of patients in N0, N1, N2 and N3 stage were 0%, 1.02%, 7.2% and

21.67%, with significant difference ($P<0.01$). The common hepatic artery LN metastatic rates of patients with stage I, II, III were 0%, 0.65% and 7.07%, significant difference was found ($P<0.01$).

Postoperative complications after propensity score-matching

After propensity score-matching, the postoperative complications were analyzed in Table 5. The percentage of overall complications were 118 patients (32.70%) in cohort one and 128 patients (35.45%) in cohort two (Table 5): including anastomotic leakage, infection of incision, gastrointestinal dysfunction, cardiovascular and cerebrovascular disease, chylothorax, pulmonary complication, injury of recurrent laryngeal nerve and atrial fibrillation, no significant difference was found ($P=0.432$). The overall incidence of anastomotic leakage in the cohort one was lower than that in the cohort two, although this difference was not statistically significant ($P=0.054$).

Discussion

In EC, the overall 5-year survival rate after surgical

Table 4 clinicopathological factors are associated with common hepatic artery LN metastasis in cohort one before propensity score-matching

Clinical pathologic factor	Cases (n)	Common hepatic artery LN metastasis case (%)	P value
Tumor location			
Upper	43	2.33	0.427
Middle	425	4.24	
Lower	214	2.34	
Tumor invasion degree			
T1a	1	0	0.413
T1b	84	2.38	
T2	183	5.46	
T3	414	2.89	
N classification			
N0	300	0	P<0.01
N1	197	1.02	
N2	125	7.2	
N3	60	21.67	
Tumor length (cm)			
≤5	595	2.86	0.014
>5	87	8.05	
Tumor differentiation			
Well	63	0	0.265
Moderate	457	3.72	
Lower	162	4.32	
pTNM stage			
I	61	0	P<0.01
II	310	0.65	
III	311	7.07	

LN, lymph node.

resection is between 70% and 92% for patients without nodal involvement, but only 18-47% for patients with LN metastasis (9-11). However, aggressive radical LN dissection may increase postoperative morbidity and mortality. The latest version of the UICC/AJCC TNM classification (7th edition) emphasizes the importance of LN metastasis for prognosis (12). Therefore, the extent of adequate LN dissection has again become a matter of debate recently (13,14). LN dissection in EC is an old topic, but still requiring discussions.

Chen and colleagues suggested that abdominal LN

metastasis is not rare and is associated with poor survival (15). Abdominal LN dissection is a standard surgical procedure in thoracic EC, Shim *et al.* showed that for suitable people after preoperative evaluation, common hepatic artery LN dissection may be safely omitted (16).

In our retrospective study, the metastatic rate of celiac axis node involvement in thoracic EC is 22.2%. Seto *et al.* suggested that celiac axis nodes should be reclassified as regional LNs before the proposal of the new staging system (17). However, common hepatic artery LNs are located more distantly from the esophagus, and the metastatic rate of common hepatic artery LN was less frequent metastasis compared with celiac axis LNs and left gastric artery LNs (18), only 3.5% in our study and the left gastric artery LN metastatic rate is 27.42%. Furthermore, the celiac axis LNs can be dissected together with the left gastric artery LNs during gastric graft preparation. While the dissection of common hepatic artery node requires exposure of an additional surgical plane near the cisterna chyli and can result in complications such as chylous ascites (19,20). However, no case of chylous ascites was experienced in our institute among curative thoracic EC surgeries.

Among the 682 patients with esophageal thoracic squamous cell carcinoma, a total of 18,277 LNs were dissected, 24 had common hepatic artery LN metastasis, and the metastatic rate is the lowest compared with others (Table 3). Logistic regression analysis identified that tumor diameter (P=0.014), N classification (P<0.01) and pathological TNM stage (P<0.01) correlated with the occurrence of common hepatic artery LNMs. Rice *et al.* suggested that the depth of tumor invasion was associated with LNMs (21), but no significance difference was found between the tumor invasion and common hepatic artery LN metastasis in our study. For stage T1 tumors, common hepatic artery LN metastasis occurred in 2 (2.38%) of 84 patients with tumor infiltrating the submucosa (stage T1b), only one patient with tumor limited to the mucosa (stage T1a) was found, and no common hepatic artery LN metastasis was occurred (Table 4). When it comes to the tumor diameter, more studies are required. In our study, no common hepatic artery LN metastasis was found at stage I, while 2 patients and 22 patients was found at stage II and stage III. What about the postoperative complications between the cohorts? To control for potential differences in the characteristics of patients treated with common hepatic artery LN dissection or without common hepatic artery LN dissection, propensity score methods were used to compare the postoperative complications between the cohorts. The

Table 5 The postoperative complications of patients after propensity score-matching

Postoperative complications	Cohort one (n=361)		Cohort two (n=361)		P value
	Cases (n)	Percentage (%)	Cases (n)	Percentage (%)	
Overall complication	118	32.70	128	35.45	0.432
Anastomotic leakage	36	10.00	53	14.68	0.054
Infection of incision	13	3.60	18	4.98	0.359
Gastrointestinal dysfunction	13	3.60	19	5.26	0.278
Cardiovascular and cerebrovascular disease	12	3.32	10	2.77	0.665
Chylothorax	12	3.32	7	1.94	0.245
Pulmonary complication	19	5.26	15	4.16	0.482
Atelectasis or sputum retention	2	0.55	2	0.55	1
ARDS	5	1.39	4	1.11	0.737
Pneumonitis	10	2.77	6	1.66	0.312
COPD aggravation	2	0.55	3	0.83	0.654
Injury of recurrent laryngeal nerve	3	0.83	1	0.28	0.316
Atrial fibrillation	10	2.77	5	1.39	0.192

Cohort one, esophagectomy with common hepatic artery lymph node dissection; Cohort two, esophagectomy without common hepatic artery lymph node dissection.

overall incidence of anastomotic leakage in the cohort one was lower than that in the cohort two, however, this difference was not statistically significant ($P=0.054$).

A number of limitations apply to the present study and interpretations should be made with caution. Firstly, this is a retrospective study at our institute; therefore, selection bias was unavoidable. However, propensity score-matching gives the present study the power to represent; Secondly, there were some variability in the experience and skill of individual surgeons.

In conclusion, the metastatic rate of common hepatic artery LN is low. Common hepatic artery LN may be safely omitted in esophagectomy for thoracic esophageal squamous cell carcinoma at stage I. Though LN dissection is an old topic, curtail unnecessary LN dissection is still the most important issues to be resolved for EC, and further accumulation of data and prospective studies are warranted in the future.

Acknowledgments

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Jejunal graft conduits after esophagectomy

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Background: The jejunum is uniquely suitable for esophageal reconstruction because it is relatively abundant, does not require a formal preparation, is typically free of disease, has similar luminal size compared to the esophagus, has intrinsic peristalsis, and may not undergo senescent lengthening to the extent that colon does.

Methods: To obtain data to determine the outcomes of jejunal interposition for esophageal replacement, electronic databases were searched, including MEDLINE (Ovid SP), Scopus, EMBASE (Ovid SP), Science Direct's full-text database, and the Cochrane Library from January 1990 to September 2013.

Results: Two-hundred and forty-six abstracts were reviewed and an article search was performed on selected abstracts. Additional references from article bibliographies were included as appropriate. A thorough search of the literature demonstrates the widespread use of jejunum, either as a free, pedicled, or free- and pedicled-graft with acceptable results.

Conclusions: Any region of the esophagus can be replaced by jejunum, whether it is distal esophagus as a Merendino procedure for a vagal-sparing esophagectomy and segmental jejunal reconstruction connected to stomach, mid-thoracic esophagus as a pedicled jejunal interposition or free flap, cervical esophagus as a free segmental interposition, or the entire length as a long-segment super-charged pedicled jejunal interposition. When used, the jejunum is either pedicled, augmented ("super-charged"), a free segment (requiring microvascular anastomosis of artery and vein), or a combination of the above.

Keywords: Jejunum; esophagus; conduit; esophagectomy

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Introduction

The jejunum is uniquely suitable for esophageal reconstruction because it is relatively abundant, does not require a formal preparation, is typically free of disease, has similar luminal size compared to the esophagus, has intrinsic peristalsis, and may not undergo senescent lengthening to the extent that colon does. The mesenteric vasculature can easily be dissected and mobilized with adequate length to be used as a pedicled or free graft replacing virtually any or all segments of the esophagus. Any region of the esophagus can be replaced by jejunum, whether it is distal esophagus as a Merendino procedure for a vagal-sparing esophagectomy and segmental jejunal reconstruction connected to stomach

(*Figure 1*), mid-thoracic esophagus as a pedicled jejunal interposition or free flap (*Figure 2*), cervical esophagus as a free segmental interposition (*Figure 3*), or the entire length as a long-segment super-charged pedicled jejunal interposition (*Figure 4*). When used, the jejunum is either pedicled, augmented ("super-charged"), a free segment (requiring microvascular anastomosis of artery and vein), or a combination of the above.

History

Decades of surgical evolution are represented by the history of the development of full-length esophageal reconstruction using a pedicled jejunal flap augmented by cervical or

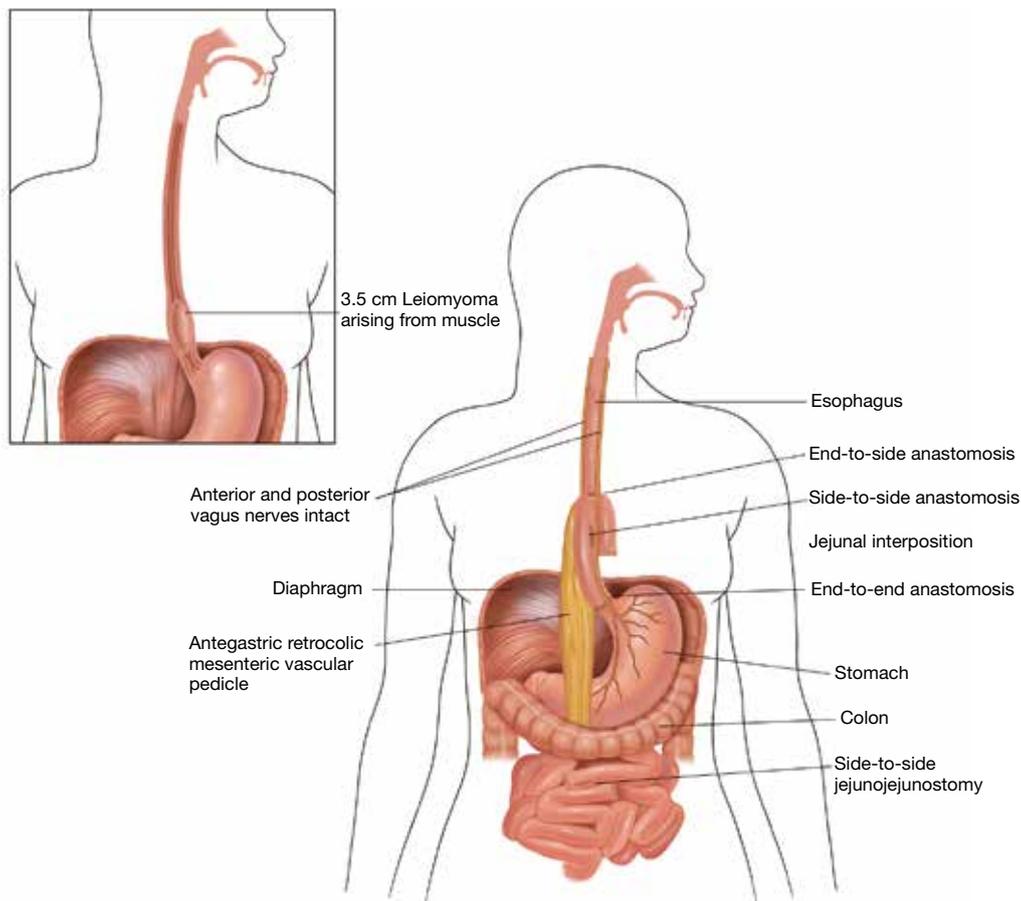


Figure 1 Merendino vagal-sparing esophageal replacement with jejunum.

thoracic vascular micro-anastomosis (super-charged pedicled jejunum, SPJ) to recreate esophageal continuity after resection. Although Roux was the first surgeon to replace the esophagus with jejunum in 1907 (1), Longmire was the first to describe a long-segment jejunal interposition with microvascular augmentation (2). Androsov used Longmire's vascular augmentation technique in 11 patients in 1956 (3). The complexity of the operation precluded widespread use in spite of these early reports demonstrating the technical feasibility of the augmented blood supply to the long-segment pedicled jejunal interposition. The utility of small bowel conduit for esophageal reconstruction was confirmed by Allison *et al.* (4), who in 1957 reported a 3-year follow-up of most patients having normal nutritive intake and work capacity. Ascoti *et al.* reported the first large series of pedicled jejunal interposition to replace the entire esophagus in cancer patients by using the "super-charging" technique (5), and this series was updated by Blackmon *et al.* in 2012 (6). This most recent series of 60 patients represents the largest

collection of cases of long segment super-charged pedicled jejunal interposition reported to date, however.

Review of the literature

To obtain data to determine the outcomes of jejunal interposition for esophageal replacement, electronic databases were searched, including MEDLINE (Ovid SP), Scopus, EMBASE (Ovid SP), Science Direct's full-text database, and the Cochrane Library from January 1990 to September 2013. The search strategies were developed using keywords, adjacency searching, and medical subject headings under existing database organizational schemes. Searches were restricted to English-language articles only. Terms used for the search included jejunum, esophageal neoplasms/surgery, esophagus/surgery, esophagectomy, and conduit. The search was limited to humans. British spelling variations were also included. Additionally, PubMed was keyword searched for newly published articles. Two-hundred and

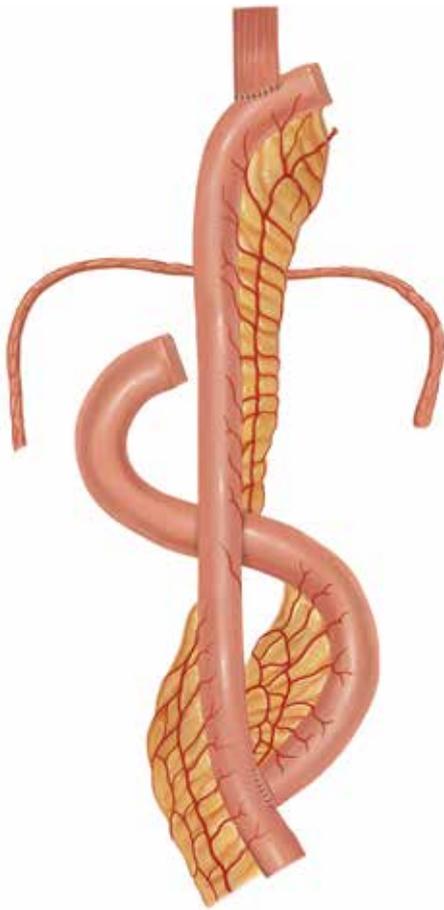


Figure 2 Mid-thoracic esophageal replacement options.

forty-six abstracts were reviewed and an article search was performed on selected abstracts. Additional references from article bibliographies were included as appropriate.

Ten articles were excluded because the English version and/or PDF version was not available for review. Five additional articles were excluded because they did not actually include jejunal conduits for esophageal replacement. In articles in which the authors appeared to re-publish data from the same series, the largest series was used and the smaller, earlier series from the same patient population were either excluded or not included in the tabulated results. Nine review articles were also excluded from inclusion into the summary chart. Case reports or series of three patients or less were excluded. Careful review revealed no randomized controlled trials or meta-analyses in adult literature studying esophageal replacement. A similar technique was used to review the literature for colon

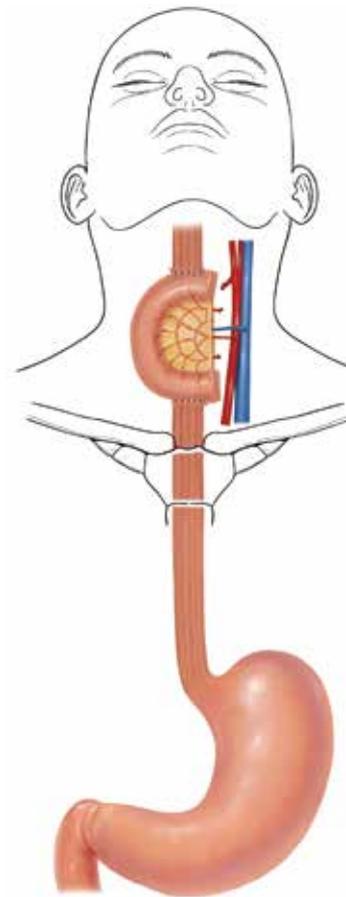


Figure 3 Cervical free flap replacement of esophagus with jejunum interposition.

interpositions to compare outcomes.

Jejunal interposition

Published articles about jejunal interposition to replace the esophagus are listed in *Table 1*. A total of 14 studies were selected for final analysis and review. One of the major studies was excluded as it reported results on 760 patients but did not specify the choice of conduit used within the body of the paper (17). The route of reconstruction (retrosternal or posterior mediastinal) selected is noted if discussed within the study. Additionally, peri-operative mortality as reported in the paper, anastomotic leak rate, and graft loss frequency are also reported in *Table 1*. Overall, retrosternal was the most common route utilized by surgeons with a reported 0-10% mortality, 0-36% anastomotic leak rate, and 5-11% graft loss frequency.

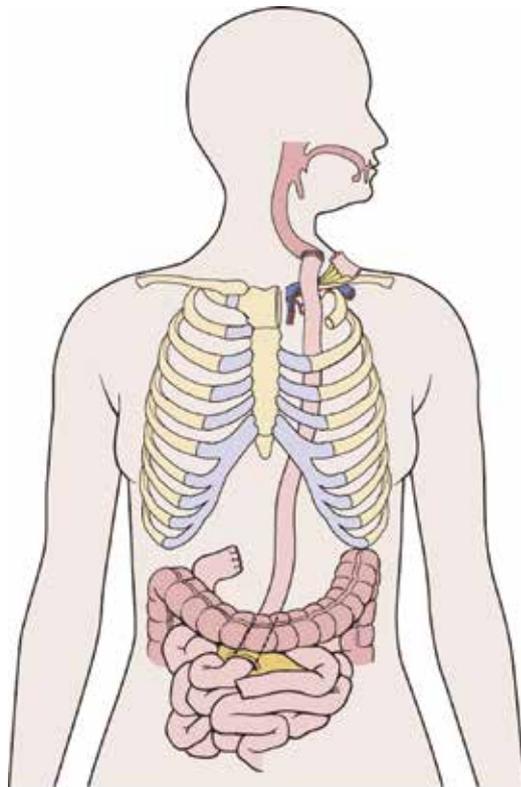


Figure 4 Long segment pedicled supercharged jejunal interposition.

The route of reconstruction and what the conduit is distally anastomosed to (either jejunum or stomach) may determine the functional outcome. While one strategy may produce more dumping and hypoglycemia, another may result in delayed mixing of food with digestive enzymes and therefore a poorer absorption of nutrients (when connected to jejunum). Pouch reconstruction to create a reservoir for food has shown some promise when the stomach has to be removed as well (19), but this is atypical when a long segment of esophageal replacement is included. Additionally, an intrapleural route, as compared to an extrapleural retrosternal route, may subject the conduit to negative intra-thoracic pressure resulting in both pushing and pulling food in a direction that either enhances digestion or causes aspiration.

Physiology of a jejunal conduit compared to stomach and colon

The physiology of a jejunal conduit is unique in comparison to other conduit options of colon and stomach. Manometric evaluation of the jejunal conduit indicates that the jejunum continues to exhibit antegrade segmental contraction as is typical for *in situ* jejunum (6). This segmental contraction

Table 1 Literature search of jejunal conduit studies

1 st Author last name (Ref)	Year of publication	n, Jej conduits	Route (major)	Mortality (%)	Leak (%)	Graft loss (%)
Iwata (7)	2012	27	AT	0	7	0
Blackmon (6)	2012	60	RS (65%)	10	32	8.3
Poh (8)	2011	51	RS (61%)	0	19.6	5.9
Barzin (9)	2011	5	RS	0	20	0
Doki (10)	2008	25	SC	NR	24	NR
Ueda (11)	2007	27	SC	NR	11	NR
Ascioti (5) [§]	2005	26 [§]	RS (50%)	0	19	7.7
Chana (12)	2002	11	SC	0	36.4	0
Mansour (13)*	1997	133*	NR	NR	NR	NR
Picchio (14)	1997	21	NR	4.8	NR	NR
Hirabayashi (15)	1993	14	NR	0	14.3	0
Gaissert (16)	1993	19	NR	10.5	0	5.3
Moorehead (17)*	1990	760*	NR	3.8	NR	11.3
Wright (18)	1987	30	NR	3.5	10	0
Total	1987-2012	290	RS	0-10.5	0-36.4	0-11.3

*, did not state how many of these were jejunal grafts and appeared to be mixed grafts, therefore not included in total of series.

§, earlier series of later reported data therefore not included in tabulated totals of chart. Abbreviations: AT, antethoracic route for conduit; RS, retrosternal route; SC, subcutaneous route; NR, not reported in the paper.

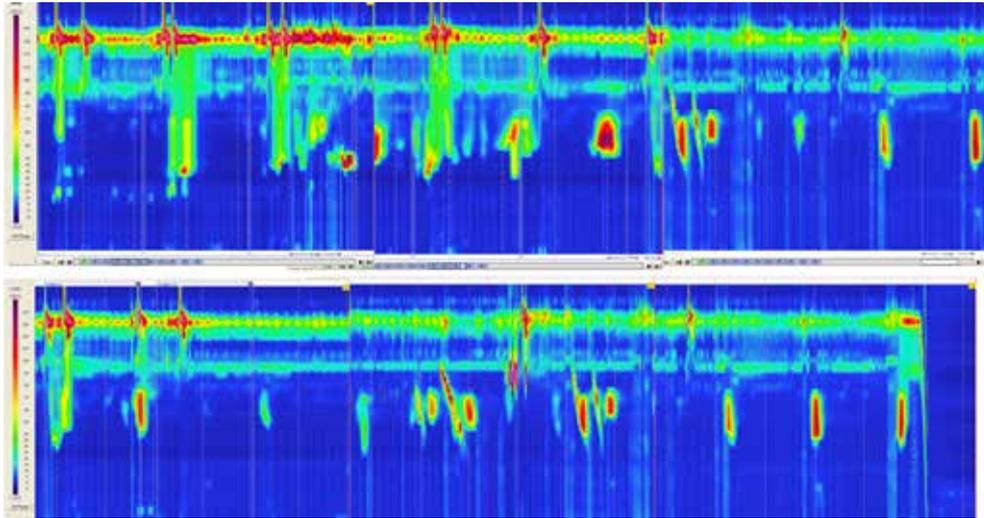


Figure 5 Manometry of a jejunal long segment interposition.

seen with jejunal conduits (*Figure 5*) does not seem to be coordinated, but appear to assist in evacuation of the conduit. Colon interpositions, on the other hand, have also been used as a part of a prospective evaluation and demonstrate poor to no motility (*Figure 6*) (20). The ability of the colon to stretch over time leads to redundancy in a negative pressure cavity while the jejunal conduit has lesser propensity to do so when noted in rhetorical studies. Additionally, studies have proposed higher anastomotic leakage rate with colonic interpositions possibly because of the intestinal flora compared to the relative sterile environment of the jejunum (10). For a comparison of colon conduits and review of the literature, please refer to *Table 2*.

Post-operative outcomes of jejunal interposition

Postoperative complications are common, including pneumonia, recurrent laryngeal nerve injury, non-occlusive mesenteric ischemia (NOMI), stricture, and graft loss requiring diversion (6,18). Up to 21% of patients suffer from anastomotic stenosis and stricture, as reported by Gaissert *et al.* (16). Delayed revisional surgery must be performed in many patients for intra-thoracic redundancy resulting in symptomatic partial obstruction, pyloric drainage, and compression of the conduit at the hiatus (6,12,16,18). Peri-operative mortality can be as high as 10.5% (16).

Multivariable analysis for graft loss and leak

Limited number of studies exist that performed logistic

regression analysis of those patients who underwent SPJ interpositions and subsequently suffered from conduit loss or leak (6); however, no particular variables have ever been shown to be independent predictors of failure of the SPJ conduit.

Discussion

Patients who have acquired long segment esophageal discontinuity and lack stomach as a viable replacement conduit primarily have two options for reconstruction: jejunum and colon. On the contrary, shorter esophageal segmental replacement has many other options, such as free pedicled forearm skin tubes and folded myocutaneous flaps in addition to the conventional choices. The future may hold many other options, as tissue-engineered 3-dimensional scaffolds repopulated with stem cells have already been used to replace the trachea (38). Esophageal stents have now given us the ability to bridge a disconnected segment of bowel and allow for regrowth of tissue and establish new continuity. Our group has successfully reconnected a distal esophagus to jejunum with a 2 cm separation with the use of stenting alone (39). The addition of antibiotics, stem cells, chemo-attractants, and other materials may enhance healing and re-growth of healthy tissue over the stent matrix. For the purpose of this paper, we focused on those patients where the stomach is not available to create an esophageal conduit, thus rendering the patient to either undergo jejunal or colon interposition to re-establish continuity.

A thorough search of the literature demonstrates the

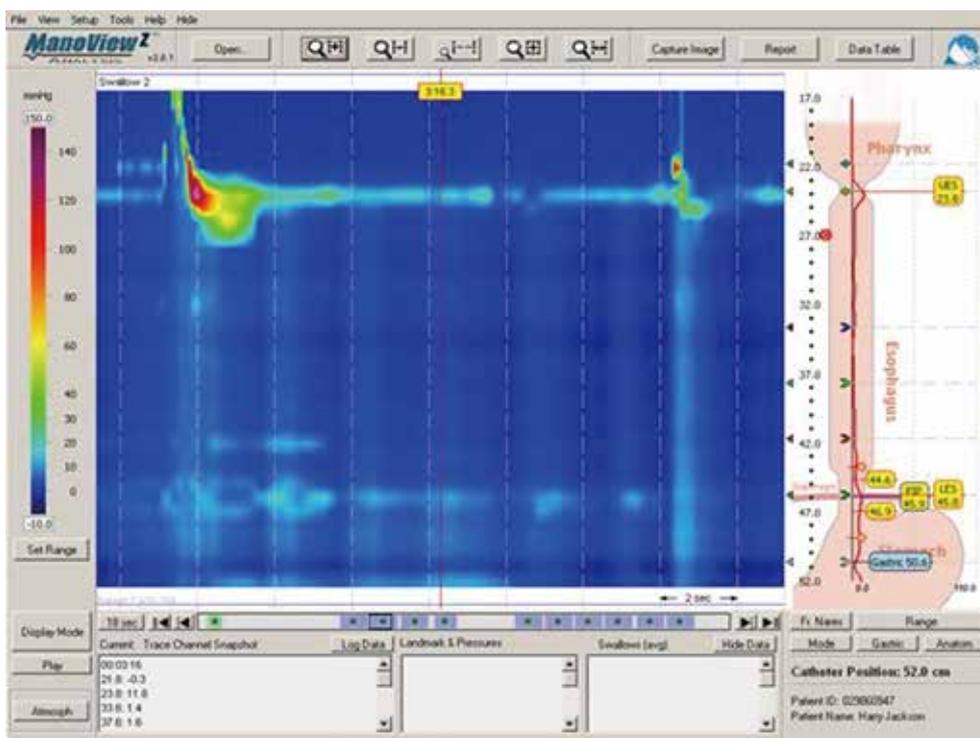


Figure 6 Manometry of a colon long segment interposition.

Table 2 Colon interposition for long-segment replacement of the esophagus

1 st Author last name (Ref)	Year of publication	n, Colon conduits	Route (major)	Mortality (%)	Leak (%)	Graft loss (%)
Kesler (21)	2013	11	AM	9	9	NR
Klink (22)	2010	43	PM (79%)	16	13	9
Mine (23)	2009	95	RS (97%)	5.3	13	0
Doki (10)	2008	28	AS	NR	46	0
Knezevic (24)	2007	336	RS	4.1	9.2	2.4
Renzulli (25)	2004	19	NR	15.8	NR	0
Briel (26)	2004	163	NR	NR	6.1	7.4
Davis (27)	2003	42	PM (71%)	16.7	14	2.4
Popovici (28)	2003	347	RS (84%)	4.6	6.9	1.4
Hagen (29)	2001	72	NR	5.6	13	5.6
Furst (30)	2001	53	NR	9.4	12	3.8
Kolh (31)	2000	38	PM	2.5	0	0
Wain (32)	1999	52	RS (88%)	3.8	5.7	9.6
Thomas (33)	1997	60	PM (63%)	8.3	10	5
Fujita (34)	1997	53	SC (81%)	17	28	5.7
Cerfolio (35)	1995	32	NR	9.4	3.3	6.2
Gaissert (16)	1993	22	NR	4.5	4.5	0
DeMeester (36)	1988	92	PM (52%)	5	4.3	7.6
Isolauri (37)	1987	248	RS	16	4	3
Total	1987-2013	1,806	RS	2.5-17	0-28	0-9

Abbreviations: AM, anterior mediastinal route for conduit; PM, posterior mediastinal route; RS, retrosternal route; AS, antesternal route; SC, subcutaneous route; NR, not reported in the paper.

widespread use of jejunum, either as a free, pedicled, or free- and pedicled-graft with acceptable results. Our institutional 10-year experience with SPJ demonstrates the re-establishment or maintenance of GI continuity with acceptable results with a 10% combined 90-day mortality. Closer analysis of the available studies and the circumstances and events that lead to graft loss and leak are multi-factorial and unpredictable. Nonetheless, the technique is replicable and transferable, as evidenced by the successful duplication of an SPJ program at The Houston Methodist Hospital (6). And, although this complex operation can be performed by any thoracic surgeon, the limitations of a jejunal interposition are worth mentioning. Early post-operative course is often associated with significant aspiration and pneumonia secondary to recurrent laryngeal nerve injury which is common with re-operative and/or complex cervical surgery. NOMI is a well-recognized but infrequently encountered complication in under-resuscitated patients who have advancement of tube feeds too early. Additionally, compromise of vascular inflow is highly likely and devastating to the conduit thus requiring frequent monitoring of the indicator flap using dopplers. The management of these patients, close follow up of the grafts (indicator flaps), and nutritional advancement requires a huge inter-disciplinary team of a tertiary care hospital. Therefore, we recommend that such major surgeries be reserved for large volume medical centers where established team of vascular and plastic surgeons as well as nurses, speech therapists, physical therapist, nutritionists, and case managers work together to help the patient recover.

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A video demonstration of the Li's anastomosis—the key part of the “non-tube no fasting” fast track program for resectable esophageal carcinoma

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Abstract: The main obstacle of fast track surgery for esophagectomy is early oral feeding. The main concern of early oral feeding is the possibility of increasing the incidence of anastomotic leakage. Dr. Yin Li used the Li's anastomosis to ensure oral feeding at will the first day after esophagectomy. This safe and efficient anastomosis method significantly reduced the anastomotic leak rate, the number of post-operative days and stricture. Importantly, the “non-tube no fasting” fast track program for esophageal cancer patients was conducted smoothly with Li's anastomosis. This article was focused on the surgical procedure of Li's anastomosis.

Keywords: Esophageal carcinoma; thoracolumbaroscopic esophagectomy; fast track surgery; Li's anastomosis; non-tube no fasting

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Introduction

The fast track (FT) surgical patient pathway, which aims to improve the perioperative treatment of surgery for cancer patients, has been well studied in colorectal (1), gynecological (2), and gastric cancer (3) patients and has significantly reduced the surgical stress and costs (4,5). However, this program for esophagectomy patients is rarely used. The main concern of allowing early oral feeding postoperatively in patients with esophagectomy is the possible increase in the incidence of anastomotic leakage. Based on retrospective studies and surgical technical experience, Dr. Yin Li used the Li's anastomosis to ensure first-day oral feeding at will after an esophagectomy (6), which made the early oral feeding fast track surgical program possible for esophageal cancer patients. More than two years have been passed since the Li's anastomosis together with “non-tube no fasting” fast track program. Until May 2015, about 260 cases have started oral nutrition on postoperative day (POD) 1 at will without a nutrition

tube and fasting, which represents the so-called “non-tube no fasting” fast track program.

Indications

This procedure is indicated in all operable esophageal carcinoma patients. We recommend to adopt the fast track surgery program “non-tube no fasting” followed by the Li's anastomosis.

Results

This procedure together with “non-tube no fasting” fast track program has been successfully conducted for more than 2 years by our group. We started a randomized control trial in February 2014, “early oral feeding following thoracolumbaroscopic oesophagectomy in patients with esophageal cancer”. In interim analyses, between February 2014 and September 2014, 148 continuous patients with

thoracoscopic esophagectomy were recruited. Seventy two patients were randomized in “non-tube no fasting” group and 76 patients in late oral feeding group. The anastomotic leakage rate was 2.8% for the “non-tube no feasting” group (6), which is significantly lower than that observed for mechanically stapled anastomosis and fasting for 7 days during the same period in other medical groups (n=92), (2.8% versus 10.9%, P=0.048). The post-operation hospital stay (7.6±2.2 versus 12.1±3.7, P<0.01) is quite short. In our cohort study, from June 2013 to August 2013 (n=30 in each group), the Health-related quality of life (HRQL) mean scores obtained 3 months post operation were significantly better, including those for reflux (14.07±14.86 versus 22.96±17.73, P=0.048) and dysphagia (15.56±15.33 versus 23.70±16.95, P=0.047) compared with the scores for conventional two-layer anastomosis and late oral feeding in other medical group. Additionally, the stricture rate is lower than that observed for conventional two-layer anastomosis at 6 months post operation (15.1±3.7 versus 13.2±3.4 mm, P=0.047). The simply summary of data for studies of Li’s anastomosis were shown in *Table 1*.

Conclusions

This safe and efficient anastomosis method significantly reduced the anastomotic leak, the number of post-operative days, reflux, dysphagia and stricture. Importantly, this method ensured at will oral feeding on first day after an esophagectomy. The “non-tube no fasting” fast track program for esophagectomy patients was thus conducted smoothly. A prospective randomized clinical trial (Clinical Trial Registration Number: NCT01998230) is ongoing in our cancer center, with a much larger sample size, to verify our findings and assess the additional potential benefits of early oral feeding after the Li’s anastomosis thoracoscopic esophagectomy for esophageal cancer.

Procedure

The operation is performed under general anesthesia. The thoracoscopic esophagectomy and a two-field lymph node dissection were adopted, with a left lateral decubitus position with 30° forerake. The thoracic esophagus was isolated, and the lymph nodes were harvested. Subsequently, the patient adopted a supine position. A 2-3 cm left cervical incision was made. The cervical esophagus was exposed and transected. Then, in the abdominal section, a 4-cm-wide gastric conduit was made by a linear cutting stapler (TLC,

Ethicon, USA). The gastric conduit was pulled up to the neck. Finally, the Li’s anastomosis was conducted to sew the gastric conduit and the distal esophagus (*Figure 1*).

The Li’s anastomosis procedures included the following (*Figure 2*):

- (I) We made a 2-3 cm skin incision on the left cervical. The muscle sparing method was utilized in the open tissue space. The distal esophagus and gastric conduit were explored.
- (II) The lesser curvature of the gastric conduit was faced forward, and the greater curvature was faced backward. The posterior esophageal wall and posterior wall of the stomach were put together. A row of 4-0 Vicryl (Ethicon) interrupted horizontal mattress sutures were used to sew the two walls. The muscularis layer of the esophagus and the seromuscular layer of the stomach were sewn by four interrupted sutures, including two sutures at each peak and using mosquito forceps as hang lines to define the corners of the layers and obtain an optimal view (sutures were placed at the A1, A2, A3 and A4 positions). These spots were near to the greater curvature of stomach in order to get enough blood perfusion and named as anastomosis initial spots, short for A, A1-A6. Shown in *Figure 2A*.
- (III) A three-leaf clamp was used to fix the gastric conduit and esophageal stump to facilitate the suture procedure. Then, the muscularis layer of the esophagus was cut at the anastomotic side, and the seromuscular layer of the stomach was opened at the anastomotic side. The two layers were sewn with seven to eight stitches of interrupted 4-0 silk suture. Shown in *Figure 2B*.
- (IV) The other side of the muscularis layer of the esophagus was opened, the muscular and mucous layers of the esophagus were dissociated by approximately 1.5 cm and the redundant esophagus was removed. Shown in *Figure 2C*.
- (V) The gastric mucosa layer was opened, and continuous sutures were used to carry out the mucosa anastomosis for the mucosal layers of esophagus and stomach using 4-0 Vicryl (Ethicon). Shown in *Figure 2D,E*.
- (VI) The three-leaf clamp was released, and the anterior muscular layer of the esophagus and the seromuscular layer of the stomach were sewn using 4-0 silk sutures. Shown in *Figure 2F*.

Table 1 Simply summary of data for studies of Li's anastomosis

Study type	Study design	Anastomosis methods	Tube	Oral intake	Patient number	Interval	Inclusion criteria	Anastomotic fistula rate (%)	First flatus	Length of postoperative stay
Prospective study	Single-arm trial (7)	Li's anastomosis	Nasogastric tube	POD1	68	01.2013-08.2013	ESCC, thoracoscopic esophagectomy, age <80 years, adequate organ function, no history of preoperative chemotherapy or radiotherapy	1.5	2.1±0.9	9.2±2.6
Retrospective study	Cohort study	mechanically stapled anastomosis (other group)	Nasogastric tube; naso-intestinal feeding tube	POD7	92	02.2014-09.2014	Adults subject to esophagectomy	10.9 P=0.048	NA	12.1±3.7 P<0.01
		Li's anastomosis	Non-tube	No fasting POD1	72		Adults subject to thoracoscopic esophagectomy for esophageal cancer	2.8	2.4±0.8	7.6±2.2
Prospective study	RCT interim analyses (6)	Li's anastomosis	Non-tube	No fasting POD1	72	02.2014-09.2014	Adults subject to thoracoscopic esophagectomy for esophageal cancer	2.8 P=0.612	2.4±0.8 P<0.001	7.6±2.2 P<0.001
		Li's anastomosis	Nasogastric Tube; naso-intestinal feeding tube	POD7	76		esophagectomy for esophageal cancer	1.5	3.3±0.7	11.7±3.9

POD, postoperative day; ESCC, esophageal squamous cell carcinoma; RCT, randomized controlled trials; NA, not available.

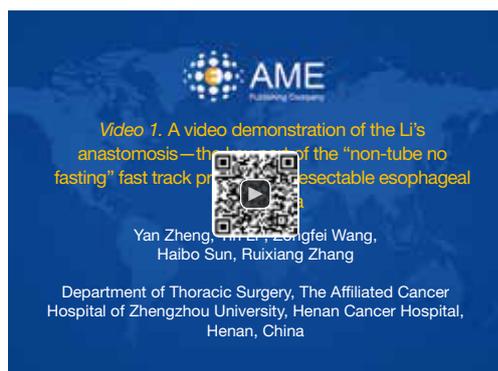


Figure 1 A video demonstration of the Li's anastomosis—the key part of the “non-tube no fasting” fast track program for resectable esophageal carcinoma (8).

Available online: <http://www.asvide.com/articles/611>

- (VII) A linear stapler was used to cut the redundant gastric conduit 1.5-2.5 cm above the anastomosis, shown in *Figure 2G*. Continuous 4-0 Vicryl (Ethicon) sutures were used to enhance the cutting edge. Then, the redundant gastric conduit was embedded into the gastric conduit cavity using forceps and fingers, shown in *Figure 2H,I*. This gastric folding was designed as a valve for anti-acid reflux. The valve was labeled in the *Figure 2H,I* as “V”. Finally, the gastric seromuscular layer and the anterior aspect of the esophageal muscle were sewn by intermittent 4-0 Vicryl (Ethicon) sutures together with fundoplication, shown in *Figure 2J*.
- (VIII) The mediastinal drainage tube was placed near the anastomosis. The incision was closed with an absorbable suture.

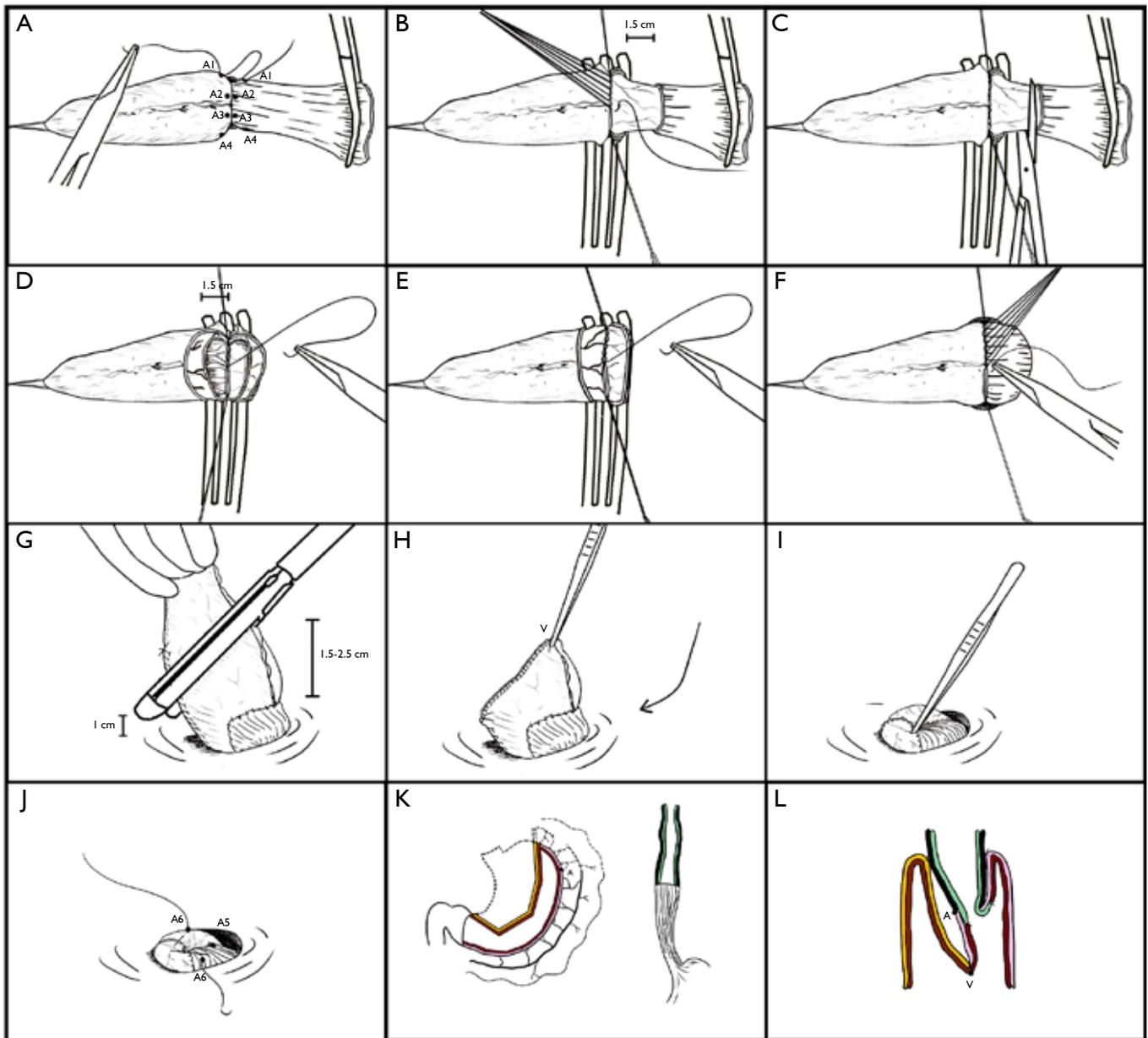


Figure 2 (A) Four interrupted sutures between the muscularis layer of the esophagus and the seromuscular layer of the stomach; (B) three-leaf clamp to fix the gastric conduit and esophageal stump. Open the muscularis layer of the esophagus. Seven to eight interrupted stitches between the muscularis layer of the esophagus and the seromuscular layer of the stomach; (C) esophageal stump was cut off; (D and E) continuous sutures between the mucosal layers of esophagus and gastric mucosa layer; (F) release three-leaf clamp. The anterior muscular layer of the esophagus and the seromuscular layer of the stomach were sewn using interrupted sutures; (G) the redundant gastric conduit was cut by a linear stapler; (H and I) embed the redundant gastric conduit into the gastric conduit cavity by forceps; (J) the gastric seromuscular layer and the anterior aspect of the esophageal muscle were sewn by intermittent two sutures together with fundoplication; (K and L) the simplified profile of Li's anastomosis. A1, A2, A3, A4, A5, A6 (Figure 2A), anastomosis site; V, valve.

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Footnote

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

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Cervical triangulating stapled anastomosis: technique and initial experience

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Objective: To explore the safety and efficacy of modified cervical triangulating stapled anastomosis (TSA) for gastroesophageal anastomosis (GEA) in minimally invasive esophagectomy (MIE).

Methods: From January 2013 to November 2013, eighty-four patients who underwent three-stage MIE was enrolled. During the cervical stage, either circular stapled (CS) or triangulating stapled (TS) anastomosis was applied for GEA. Clinical features were collected and compared to identify the differences between the two groups.

Results: A total of 84 patients were included in this study. The clinical characteristics were close between the two groups. Intra-operatively, the duration of GEA was close between the two groups (18 ± 3.4 vs. 17 ± 2.7 min, $P=0.139$). Post-operatively, Cervical anastomotic leakage occurred in one (3.0%) of the 33 TS patients, but in six (11.8%) of the 51 CS patients ($P=0.312$). The incidence of anastomotic stenosis was 0.0% and 13.7% in the TS and CS groups, respectively ($P=0.069$). The overall incidence of postoperative complications was significantly lower in TS than that in CS (15.2% vs. 35.3%, $P=0.043$). There was no difference in the median length of hospital stay or perioperative mortality rate between the two groups.

Conclusions: TSA is a safe and effective alternative for GEA, which would probably lower the incidence of leakage and stenosis following MIE. Further studies based on larger volumes are required to confirm these findings.

Keywords: Esophageal cancer (EC); minimally invasive esophagectomy (MIE); gastroesophageal anastomosis (GEA); triangulating stapled anastomosis (TSA)

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Introduction

Despite the technical advances in gastric conduit formation or anastomotic methods, the anastomotic complications following the surgical resection of esophageal cancer (EC) have continued to perplex thoracic surgeons (1-6).

Triangulating stapled (TS) anastomosis for GEA has been shown to be associated with lower incidence of anastomotic complications (7-10). However, there was only one previous report comparing the results of TS with circular stapled (CS) anastomoses, and partially due to the limited number of patients, the incidence of anastomotic leak of both TS and CS was undesirable (TS, 2/8, 25.0% vs.

CS, 1/12, 8.3%) (7).

In this report, we describe our surgical technique of TSA in the cervical part and examine its efficacy in compared with circular staplings.

Patients and methods

Patients

From January 2013 to November 2013, a total of 84 EC patients underwent minimally invasive esophagectomy (MIE) at Zhongshan Hospital of Fudan University were included in this retrospective study. The study was approved

Table 1 Clinical characteristics

Characteristics	TS (n=33)	CS (n=51)	P
Age [range], years	61 [46-79]	61 [45-75]	0.862
Sex (male/female)	27/6	41/10	0.871
Comorbidity, n (%)	7 (21.2)	9 (17.6)	0.684
Neoadjuvant therapy, n (%)	5 (15.2)	3 (5.9)	0.158
Location (U/M/L)	2/21/10	7/36/8	0.198
Pathological stage, n (%)			0.919
0-I	14 (42.4)	20 (39.2)	
II	10 (30.3)	15 (29.4)	
III-IV	9 (27.3)	16 (31.4)	

TS, triangulating stapled; CS, circular stapled.



Figure 1 The distal esophagus and proximal gastric conduit were cut open, and the first stapling was applied to the posterior wall of the remnant esophagus and the gastric conduit in an inverted fashion by the linear cutter.



Figure 2 The second and third stapling was applied to the anterior wall of the remnant esophagus and the gastric conduit in an extroverted fashion by the linear cutter with stay sutures.

by the hospital ethics committee, and a waiver for individual patient consent for this retrospective study was also obtained from the ethics committee. All patients were diagnosed as EC by endoscopic biopsy. Physical examination, standard



Figure 3 Completion of end to end triangulating anastomosis.



Figure 4 Cervical triangulating anastomosis for minimally invasive esophagectomy (MIE).

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laboratory tests, electrocardiogram, and lung function test were performed in all patients. Preoperative staging was determined by enhanced thoracic and abdominal CT. According to the clinical findings, T1-3N0M0 EC patients were selected as candidates for MIE. The clinic characteristics of patients were shown in *Table 1*.

Surgical techniques

All operations were three-stage MIE, which was described in previous publications (11,12). The operation was performed by the same surgeon (L.T). A 3.0 cm wide gastric tube formed by linear staplers (TLC75, Ethicon Endosurgery, Cincinnati, OH, USA) was used for alimentary reconstruction. GEA was performed by cervical end to side CS anastomosis until July 2013 or a more proximal anastomosis which was difficult for TS (CS group, n=51) and by the cervical TSA after August 2013 (TS group, n=33).

For the cervical TS, our surgical technique was basically similar to previous reports (7-9), in which an end-to-end GEA was performed using three linear staplers (*Figures 1-4*).

Table 2 Postoperative event

Characteristics	TS (n=33)	CS (n=51)	P
Time for GEA, min	18±3.4	17±2.7	0.139
Length of stay [range], days	10 [7-28]	10 [7-62]	0.799
Complications, n (%)	5 (15.2)	18 (35.3)	0.043
Mortality, n (%)	0 (0.0)	1 (2.0)	0.825
Gastrointestinal complication, n (%)	1 (3.0)	13 (25.5)	0.006
Anastomotic leakage	1 (3.0)	6 (11.8)	0.312
Anastomotic stricture	0 (0.0)	7 (13.7)	0.069
Pulmonary complication, n (%)	3 (9.1)	8 (15.7)	0.586

TS, triangulating stapled; CS, circular stapled; GEA, gastroesophageal anastomosis.

The formed gastric tube was pulled up to the left neck through posterior mediastinal route. After two-thirds of the superior end of gastric tube was cut off by tissue scissor, three suspension sutures through the whole layer were added to secure the first anastomosis which was applied to posterior wall of the remnant esophagus and the gastric tube in an inverted fashion (*Figure 1*). Then these sutures were pulled up and completely removed with a linear stapler (ATB 45, Ethicon Endosurgery, Cincinnati, OH, USA). After two-thirds of the superior end of gastric tube was cut off by tissue scissor, three suspension sutures through the whole layer were added to secure the first anastomosis which was applied to posterior wall of the remnant esophagus and the gastric tube in an inverted fashion. Then these sutures were pulled up and completely removed with a linear stapler (ATB 45, Ethicon Endosurgery, Cincinnati, OH, USA). The second and the third anastomosis were performed in the same manner using the second and third linear staples; however, these were done in an everted instead of in an inverted fashion. At last, interrupted sutures of the serosa were performed between the anastomosis which was covered with the attached omenta. Then the triangulating shaped end-to-end anastomosis was completed between the remnant esophagus and the gastric tube in the cervical region. A closed suction drain was placed in the anastomotic region (13).

Statistical analysis

Differences between the TS and CS were assessed using the Wilcoxon rank sum test for continuous variables, the chi-square or Fisher exact tests for categorical variables. For all calculations, a P value of <0.05 was considered to be significant. Statistical computations were all performed by

SPSS software, version 19.0 (SPSS, Inc, Chicago, IL, USA).

Results

In this study, eighty-four patients were enrolled, including 68 men (81%) and 16 women (19%). The median age was 61 years (range, 45-79 years). Sixteen patients presented with significant comorbidity and eight patients received neoadjuvant therapy. There were no significant differences in clinical characteristics between two groups (*Table 1*).

None of the procedures were converted to thoracotomy. Postoperative pathology reported that all cases were squamous cell carcinoma. The overall incidence of postoperative complications was significantly lower in TS than that in CS (15.2% vs. 35.3%, P=0.043). There was no significant difference in length of hospital stay, and mortality rate between two groups (*Table 2*).

No difference was found for the mean time of GEA. In TS, there was only one minor leakage, which healed after 16 days of drainage. Of the six cases of leakage in the CS group, five (83.3%) were minor or moderate, and resolved after inserted drainage from a cervical drain. However, One of these six patients in CS died of severe anastomotic leak during the perioperative period. Anastomotic leakage tended to occur less frequently in TS than in CS, although the difference was not significant (3.0% vs. 11.8%, P=0.312).

Patients who suffered swallowing dysfunction following the operation would receive endoscopic examination, and the stenosis was defined to the cases when endoscopic dilation at the anastomotic portion was required. Post-operative stenosis was found in 0.0% and 13.7% for the TS and CS anastomosis, respectively (*Table 2*).

Discussion

In this study, modified TS anastomosis was introduced to the gastroesophageal anastomosis (GEA) during MIE, and it was found to be superior to CS anastomosis in the incidence of postoperative complications. The overall gastrointestinal complication was significantly lower in TS following the surgery, which suggested TSA as a safe and effective alternative for GEA.

The gastric tube is the most commonly used conduit for the GEA. The major complications after GEA, including anastomotic leakage and anastomotic stricture, are frequently encountered, which would prolong patients' hospital stay, compromise quality of life, and even be life-threatening (1,2,14,15). However, previous studies, either



Figure 5 Esophageal Barium swallows examination in a patient three months after triangulating stapled anastomosis (TSA).

on gastric formation or anastomotic methods, were based on improvements of blood supply in the reconstruction of gastric conduits and the outcome was less promising (2,4-6).

There are encouraging results of TS anastomosis in both colo-colonic (16,17) and GEA (8,9). Theoretically, this end to end anastomosis preserves the integrity of vascular network of the gastric wall, which provides more blood supply to the anastomotic site. Furthermore, it allows reserving longer gastric tube and bringing less tension to the anastomotic site and it would be ideal for the passage of food. Finally, our modification that only two-thirds of the proximal gastric conduit was cut open for the GEA, which may ease the procedure of the first stapling for the anastomosis, and it would be convenient for further adjustment before the first linear stapler was fired. As in our study, anastomotic leak in TS had the tendency of reduction compared with CS.

Conventionally, anastomotic stenosis after CS anastomosis occurs in 12.3-20% (18,19), which remains considerable concerns for this technique. The cause may include that all the layers of alimentary tract are punched out, which led to unexpected exposure to the inner lumen of the alimentary tract for the muscular layer (7). It is easily understood that this would increase the incidence of stenosis. For TSA, however, only one third of the anastomotic site is inverted, which theoretically may greatly eliminate the adverse effect caused by CS anastomosis. As a result, there was no anastomotic stenosis in TS (*Figure 5*), compared with 13.7% in CS (*Table 2*).

Additionally, other series reported reducing the time

to perform GEA by using the TSA (7). Since this was our initial experience, the recorded time for GEA had no significant difference between two groups.

However, the limitations of our study include its nonrandomized retrospective study design and its lack of exploration of the long-term effects of TSA, especially on quality of life analysis. To minimize technical bias, all operations were performed under the guidance of one single experienced surgeon. We chose to include patients only in whom the esophageal bed was used as the route for the conduit pull-up, since the retrosternal route has been reported to be longer in length than the posterior route (20).

In conclusion, the TSA is a safely and effectively alternative method for cervical GEA. Further randomized controlled trials are needed to confirm this conclusion.

Conclusions

TSA is a safe and effective alternative for GEA, which would probably lower the incidence of leakage and stenosis following MIE. Further studies based on larger volumes are required to confirm these findings.

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Managing complications I: leaks, strictures, emptying, reflux, chylothorax

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Abstract: Esophagectomy can be used to treat several esophageal diseases; it is most commonly used for treatment of esophageal cancer. Esophagectomy is a major procedure that may result in various complications. This article reviews only the important complications resulting from esophageal resection, which are anastomotic complications after esophageal reconstruction (leakage and stricture), delayed emptying or dumping syndrome, reflux, and chylothorax.

Keywords: Complications; leaks; strictures emptying; reflux; chylothorax

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Introduction

Esophagectomy can be used to treat several esophageal diseases; it is most commonly used for treatment of esophageal cancer. Esophagectomy is a major procedure that may result in various complications. This article reviews only the important complications resulting from esophageal resection, which are anastomotic complications after esophageal reconstruction (leakage and stricture), delayed emptying or dumping syndrome, reflux, and chylothorax.

Anastomotic leaks

Overview

The incidence of anastomotic complications, clinical manifestations, and treatment are all related to the methods of esophageal resection and reconstruction; therefore, we first briefly introduce esophagectomy. The history of esophagectomy is less than 100 years, and esophageal reconstruction after resection was first documented in 1942 (1,2). To date, the common surgical approaches are the Ivor-Lewis esophagectomy (3); McKeown esophagectomy (4); Sweet procedure (single

left-sided thoractomy), left thoracoabdominal approach, and transhiatal esophagectomy (THE) (5). The most common substitute organs are the stomach (>90% of the cases) (6), colon (when the stomach is resected or diseased), small intestine (microvascular surgery is required) (7), and pedicled skin-muscle flaps. Anastomosis methods include hand-sewn anastomoses (continuous and interrupted sutures, single or double layer sutures, absorbable or non-absorbable stitches), stapling (circular and linear), and combined hand-sewn and stapled anastomoses (8,9).

Since the advent of esophagectomy, anastomotic complications—especially for the prevention and treatment of anastomotic leaks—have been an important issue involving many factors. In general, thoracic surgeons should have the following three qualities in order to avoid fatal anastomotic leaks: “flexibility” between different surgical techniques; “knowledge” of the esophageal anatomy, physiology, and esophageal diseases; and “skill” in the esophageal surgical techniques. That is, the surgeon should have a personalized “flexible” selection of methods for esophageal resection and mode of reconstruction based on the characteristics of specific patients and tumors. Familiarity with every type and flexibility between different types of surgical approaches are important for good clinical

outcomes. Considering esophagectomy, no specific surgical approach is suitable for all patients at present. Experienced surgeons in large centers for esophagectomy play an important role in the success of the surgery. Mastering the knowledge about various complications is not only essential for the prevention of anastomotic complications, but it also plays a significant role in selecting the appropriate treatment. Recognizing early signs of complications and initiating appropriate treatments are important components in reducing the serious consequences of complications. Since the advent of esophagectomy 60 years ago, there has been a significant progress in the prevention and treatment of anastomotic leaks; however, continuous effort for long-term improvement is necessary. The emphasis on the details of the appropriate treatment has always been important among the various factors in the prevention and treatment of anastomotic leaks.

The importance of and susceptibility to esophagogastric anastomotic leaks

Esophageal reconstruction mostly involves the stomach (>90% of cases); therefore, we focus on esophagogastric anastomotic leaks. The esophagus is connected to the hypopharynx at the top, descends from the posterior mediastinum to the abdominal cavity, and connects to the stomach. It traverses three anatomical sites—the neck, thorax, and abdomen—and is mostly located within the thorax. Esophagogastric anastomotic leaks often involve pleural contamination, infection, and obstructions that affect the negative intrathoracic pressure, leading to respiratory problems and unstable hemodynamics, which are different from the characteristics of systemic inflammatory response syndrome caused by other gastrointestinal leaks. The clinical presentations are quite serious, and often fatal; therefore, esophagogastric anastomotic leaks are more important than other types of gastrointestinal leaks.

Compared with other digestive organs, the esophagus does not have a serosa and mainly comprises longitudinal muscle; therefore, it has insufficient suture strength and demonstrates poor healing. The blood supply to the esophagus is segmental with communicating branches that extend over long distances, which can easily lead to ischemic necrosis around the esophageal anastomotic site. The anastomosis is directly located in or in close proximity to the thorax that has a negative pressure, which causes gastric fluid to be easily drawn through anastomotic sutures or staples lines, resulting in leaks after surgery. When

the stomach is elevated from the abdominal region to the thoracic cavity, the blood supply to the stomach depends completely on the right gastroepiploic artery; this easily leads to ischemia of the stomach around the anastomosis after surgery. The aforementioned reasons can lead to the incidence of anastomotic leaks after surgery.

Diagnosis of anastomotic leaks

For a long time, the definition of anastomotic leaks has not been very clear. The definition of anastomotic leaks included the outflow of gastric fluid from chest tubes, pleural or mediastinal infections, or outflow of saliva from the neck, which are obvious “leaks”, as well as leaks without the presence of any clinical symptoms but with only occult leaks observed with esophagography (10,11). The concept of anastomotic leaks has become clearer after Lerut graded it in 2002 (12). However, we believe that conduit necrosis (Lerut Grade IV) should not be classified as an anastomotic leak, but should be considered a separate terminology because this condition, in order to save lives, requires emergency debridement, exteriorization of the cervical esophagus, and repositioning of the residual vital gastric conduit back to the peritoneal cavity. After the condition improves, colon interposition may be performed via retrosternal approach. Owing to the different definitions and grading systems, the comparability between studies on anastomotic leaks is poor. Therefore, clear diagnostic criteria are the bases for the comparisons between studies, as well as the guidelines for treatments. Obvious clinical presentations, such as gastric fluid drawn from the thorax or saliva drawn from the neck, can help to provide a clear diagnosis and treatment. In addition, esophageal imaging by using orally administered Gastrografin is the gold standard for the diagnosis of anastomotic leaks.

Prevention of anastomotic leaks

The prevention and treatment of anastomotic leaks are closely related, where prevention is more important than cure. The esophagus does not have a serosa, is mainly composed of longitudinal muscle, and has a segmental blood supply from a few anastomotic branches. Therefore, both hand-sewn and staple sutures require gentle maneuvers during operation to avoid tears and damage. It is easier for anastomosis when the length of the free esophagus is more; however, a longer isolated esophagus is more prone to ischemia, and therefore, the good blood supply and the

ease of operation need to be balanced. The gastric conduit is supplied blood only via the right gastroepiploic artery, which provides blood to the 60% of the stomach that is proximal to the pyloric end, whereas the remaining 40% of the stomach that is distal to the pyloric end depends on the supply from the submucosal network of small vessels. The stomach is tailored along the greater curvature, forming a 4 cm-wide neo-esophagus, therefore, the gastric conduit should be extended to obtain a “tubular shape stomach”, and the distal fundus that has poor circulation should be removed, which allows the anastomosis to be moved closer to the start of the right gastroepiploic artery.

The more area that is responsible for acid secretion is removed, the lower risk of anastomotic leakage will be encountered. The degree of pathophysiologic changes in consequence of intrathoracic anastomotic leaks is positively correlated with the amount of gastric fluid entering the thorax through anastomosis. The “tubular shape stomach” has only half of the gastric tissue, and the rest has been removed; therefore, it has less area for secreting acid. The decrease in the secretion of acidic gastric fluid is another factor that may reduce the extent of clinical damage after the occurrence of anastomotic leaks.

A “tubular shape stomach” results in the same length of both lesser curvature and greater curvature of the reconstructed stomach; this allows the positioning of the anastomosis and pylorus in a straight line, which solves the anatomical and mechanical problems of gastric retention and emptying, and thus also reduces the risk of anastomotic leaks.

Our usual practice is to simultaneously elevate the gastric conduit and the drainage tube from the abdominal cavity to the location of the anastomosis. The drainage tube starts from the abdominal wall to fully achieve mediastinal drainage and reduce the risk of infection caused by mediastinal exudate; this positioning helps to decrease the risk of anastomotic leaks from the thoracic stomach.

After surgery for esophageal cancer, jejunostomy is performed or a nasoduodenal feeding tube is routinely placed to ensure enteral nutrition. Studies have shown that small intestinal function recovers within 12 hours post-operation; therefore, enteral nutrition administration may start within 24 hours post-operation. The advantages of early enteral nutrition are as follows: promote the recovery of gastrointestinal function and downward movement of intestinal contents, protect the mucosal barrier, prevent the translocation of bacteria, balance metabolic stress, and promote anastomotic healing.

Gentle maneuvers should be performed always when the stomach is being mobilized, and excessive kneading of the fundus should be avoided to prevent direct damage and venous thrombosis. Pulling up the gastric conduit should be carefully performed while paying careful attention to the direction of movement for preventing intrathoracic gastric volvulus or twisting of the blood vessels. The presence of tightness in the thoracic inlet should be assessed. If it is very tight, the sternum ligaments should be cut, and the clavicular head or sternoclavicular joint should be resected when necessary.

Although it is debatable, some surgeons insist on routinely performing pyloroplasty or pyloric myotomy. Of course, the patient’s comorbidities such as diabetes mellitus, malnutrition, and atherosclerosis should also be noted before the operation. Additionally, strengthening perioperative management and performing early postoperative lung expansion, as well as preventing hypoxemia and hypotension, are all important measures to reduce the risk of anastomotic leak.

Treatment for anastomotic leaks

The aforementioned preventive measures can largely reduce the incidence of severe anastomotic leaks. No special treatments are necessary for occult anastomotic leaks that occur in patients who do not show any clinical symptoms and that are only discovered by using upper gastrointestinal contrast radiography; these occult anastomotic leaks can be cured by delaying the time to oral food intake. For small leaks in stable patients, food and water intake should be restricted, and enteral or/and parenteral nutrition support should be strengthened. In addition, if there are signs of infection, a broad-spectrum antibiotic therapy should be administered, as well as somatostatin treatment to reduce the secretion of gastric acid, and proton pump inhibitors to reduce the production of gastric acid. When thoracic fistula occurs and the encapsulated fluid exhibits empyema around the intrathoracic anastomosis, adequate drainage can be achieved by using a CT-guided thoracocentesis.

For treating abscesses formed around the wound in the neck, adequate drainage can be achieved by opening the incision, if necessary, at the bedside. Further treatment measures depend on the location of the anastomosis and the surrounding fluid. For example, patients with severe intrathoracic anastomotic leakage (Lerut Grade III) and gastric tube necrosis (Lerut Grade IV) have perioperative mortality rates of approximately 60% and 90%,

respectively; patients with gastric tube necrosis often require a second surgery for removing the necrotic tissues and retracting the distal stomach back to the abdominal cavity after excluding the proximal esophagus to the neck. Adequate surgical drainage from the mediastinum and sincere collaborations in the multidisciplinary supported treatment post-operation are important for success. Crestanello *et al.* (13) reported the experience of early surgical intervention for postoperative anastomotic leaks after treatment for esophageal cancer at the Mayo Clinic for a span of ten years. Approximately 70% of the patients who required a second surgical treatment underwent direct fistula repair, whereas the remaining patients underwent traditional esophageal diversion. The mortality rate for the patients who underwent direct fistula repair was approximately 15%.

Anastomotic stricture

Anastomotic stricture causes dysphagia; however, postoperative dysphagia may not necessarily result from anastomotic stricture. Theoretically, dysphagia can be classified into anastomotic stricture-induced dysphagia and functional dysphagia. In addition, anastomotic stricture can be classified into scar contracture and anastomotic leakage-induced stricture. Functional dysphagia may be explained as described below. Firstly, subtotal esophageal resection, especially cervical anastomosis where the remnant esophagus is extremely short at the location of the esophagogastric anastomosis, can result in insufficient muscle strength during swallowing. Neck incisions can cause damage to the muscles in the neck, which leads to weakening of the accessory swallowing muscles. Age and malnutrition can lead to weakness of muscles in the tongue. Denervation and devascularization of the substituted esophagus can cause delayed gastric emptying. All of the above can lead to functional dysphagia.

The use of endoscopy and upper gastrointestinal radiography at this point will not reveal any objective evidence of anastomotic stricture. Results of our prospective database survey showed that >10% of the patients exhibited various degrees of dysphagia within one year after the surgery; however, examination findings confirming the presence of anastomotic stricture that requiring dilatation only accounted for <1% (unpublished data). Dysphagia in the rest of the patients either reduced or disappeared over time. Several studies have suggested that anastomotic stricture spontaneously disappears in a few years without

the need for dilatation (14). Early benign stricture can be classified into scar contracture and fistula induced stricture. The former can be easily cured by dilatation, whereas dilatation for the latter in serious conditions is sometime counterproductive. The stricture is often exacerbated by dilatation related injuries. Therefore, careful acquisition of the patient's medical information, especially through UGI endoscopy and radiography, is required to distinguish between functional dysphagia, scar contracture, and a true case of fistula induced stricture. The treatment for functional stricture should mainly focus on enhancing enteral nutrition and swallowing training, and not on rash offer a dilatation.

Early anastomotic stricture after the operation is mostly benign, whereas attention should be paid to late anastomotic stricture, which may be related to tumor recurrence. Endoscopy and PET/CT examinations are effective approaches to identify the benign and malignant stricture. The esophagus is a muscular tube with elastic walls. In the resting state, the esophageal lumen is in a collapsed state, whereas during the swallowing process, the muscles of the esophagus relax to accommodate the food bolus (anterior-posterior diameter, up to 2 cm; lateral diameter, up to 3 cm) (15). However, esophagogastric anastomotic healing is a scar-healing process resulting in an inelastic anastomosis and a fixed-size scar around the anastomosis; the size of the anastomosis varies depending on the diameter of the stapler, the anastomotic method, and an individual's degree of scar retraction, but remains fixed and inelastic. Therefore, patients who consume food that forms a bolus exceeding the diameter of the anastomosis or who do not have the strength to swallow may exhibit symptoms of dysphagia. Thus, either hand-sewn anastomosis (continuous or interrupted, single or multiple layers), staple anastomosis (circular or linear), or combined hand-sewn and staple anastomosis—either end-to-end, end-to-side, or side-to-side anastomosis—may cause dysphagia or even true anastomotic stricture owing to anastomotic scar formation, which requires detailed examination to distinguish between them.

Most anastomotic stricture results from anastomotic leaks; therefore, they have similar factors which cause. At present, the clinical definition and classification of anastomotic stricture are not clear. Additionally, a diagnosis of anastomotic stricture is often based on the symptoms of subjective dysphagia; therefore, the reported incidence rates greatly vary between 10-40% (9). However, the majority of scholars believe that the incidence rate for anastomotic

stricture is high, which renders it as one of the most common complications after esophagectomy.

Delayed gastric emptying, dumping syndrome, and reflux

Long-term survival, operative mortality rate, and complication incidence are generally quality indicators for esophagectomy. In recent years, postoperative long-term quality of life has received increasing attention, and has become an important component in assessing esophagectomy. The stomach is the first choice substitution of esophagus for most surgeons. However, compared to the normal stomach, the stomach elevated into the thorax induces many anatomical and physiological changes, which results in a series of clinical manifestations. Meanwhile, the shape and size of the remodeled stomach, its pulling up pathway, and its status in the thorax greatly affect the incidence and severity of the symptoms, which manifests as abnormal motility of the thoracic stomach as well as common pathophysiological changes including delayed gastric emptying, dumping syndrome, and reflux.

Anatomical and physiological bases for motility defects of the substituted esophagus

Blood supply to the stomach is provided by six vessels, which are the left gastric, right gastric, left gastroepiploic, right gastroepiploic, short gastric, and posterior gastric arteries. These blood vessels not only provide nutrients to the stomach but also fix the stomach in the upper abdomen, in order to allow the stomach to perform its normal function. However, the free thoracic stomach has only the right gastroepiploic artery for blood supply (15).

Esophageal resection typically involves the complete removal of the vagus nerve for malignant lesions; therefore, innervation of the thoracic stomach solely depends on autonomic innervation by the gastric myenteric plexus, which greatly affects the regular relaxation function of the pyloric sphincter. In addition since the stomach is elevated from the positively pressured abdomen to the negatively pressured thorax, which can further impede gastric emptying. During gastric mobilization and pulling up, the angle of His disappears and the spring action of the diaphragm on the lower esophagus is lost, which causes the loss of the anti-reflux mechanism at the gastroesophageal junction. Thus, compared with normal esophagus, the emptying and acid clearance rates after esophagectomy are

impaired. Owing to the extremely shortened esophagus that remains, the weakened swallowing ability, and the loss of the anti-reflux mechanism, the acid clearance capacity of the remnant esophagus is reduced.

Resection of the fundus results in changes in the receptive expansion and volume of the stomach when shaping the new esophagus; the pressure inside the thoracic stomach is very easily affected by the amount of stomach content.

Gastric secretion changes affect pyloric opening and closure as well as gastric emptying when shaping the new esophagus.

As mentioned above, changes in the physiological function ultimately lead to abnormal motility of the substituted esophagus. The clinical presentations are delayed emptying, dumping syndrome, and reflux, of which delayed emptying and reflux are most prevalent (16-18).

Prevention and treatment

Delayed gastric emptying

Delayed gastric emptying is the most common problem in patients with motility dysfunction of the thoracic stomach, with an incidence of 50% after esophagectomy reported in the literature. The basis of gastric emptying is that the pylorus opens to empty food when the pressure in the stomach exceeds pyloric pressure. Reduced stomach volume, weakened receptive expansion, and vagotomy cause pylorus dysfunction, which leads to delayed emptying that manifests as early satiety or vomiting. Results of earlier studies suggest that the thoracic stomach does not exhibit contractility (16,17), and the food passes relying solely on gravity. However, recent studies have revealed that the myenteric plexus and the remnant of the vagus nerve in the antrum of the lesser curvature can gradually become the center of gastric motility (18). Through muscle and topical hormone coordination, the contractility of the thoracic stomach can be restored to some extent. Therefore, some people do not favor excessive removal of the tissues near the antrum of the lesser curvature, and hope that the remnant nerve can exert its function. When early emptying is delayed, enteral nutrition supply should be administered, and most patients recover over time.

Pyloric drainage procedures such as myotomy, pyloroplasty, or pyloric balloon dilatation can be performed during the resection. This operation is inspired by vagotomy for ulcers; however, esophagectomy is different, which leads to controversy. However, some surgeons would

argue that these pyloric drainage procedures may pose the risks of fistula, bile reflux and dumping syndrome. However, it is currently believed that regardless of the pyloric draining procedure, pyloric balloon angioplasty is still effective once delayed emptying occurs.

The whole stomach pulled up as a neo-esophagus includes three types, i.e., full stomach, subtotal stomach, and narrow gastric tubes. Each has its own advantages and disadvantages. As of now, narrow gastric tubes have demonstrated more advantages. The use of the whole stomach as a substitute helps to recover gastric motility; however, because of large gastric volume and receptive expansion, the pressure inside the stomach does not easily reach above that of the pylorus, which results in gastric dilatation, as well as retention, reflux, and delayed emptying. In addition, owing to the excessive length and lack of innervation, the low-tension greater curvature of the stomach is prone to gastropnoxis, causing the pyloric opening to be higher than the lowest point of the stomach. The presence of the pyloric opening at a higher point or even the presence of an acute angle between the axis of the stomach and the pylorus, both lead to delayed thoracic stomach emptying. The shaping of a narrow gastric tube results in the lesser and greater curvatures to be of the same length, the anastomosis and pylorus to be positioned along a straight line, and limited gastric expansion; all of these can cause an increase in the pressure in the stomach, which is easier than that of the pylorus, thus triggering gastric emptying. The pathways for gastric pulling up include those along the posterior mediastinum, retrosternal as well as anterior sterna subcutaneously. Studies have shown that the pathway along the posterior mediastinum has a minimal impact on emptying. Meanwhile, compared to narrow gastric tubes, whole stomach pulling up can easily cause axial torsion or even folds, resulting in delayed emptying. Strengthening postoperative management and keeping the stomach empty will benefit the positioning of the tubular stomach at the posterior mediastinum, thus ensuring good emptying.

Delayed gastric emptying might be treated with the appropriate medication. Currently used drugs for gastric motility include metoclopramide, cisapride, bethanechol, and domperidone, all of which have been shown to alleviate symptoms of delayed gastric emptying. However, they cause significant adverse effects. Erythromycin is a motilin receptor agonist, which induces migrating motor complexes by stimulating the motilin receptors enriched in the gastric antrum and duodenal smooth muscle, thus

promoting pyloric motility and gastric emptying. In addition, erythromycin is more suitable for the treatment of endogenous paralysis or paralysis caused by vagotomy, with rare or minimal adverse effects. Erythromycin is routinely used after esophageal resection to improve gastric emptying.

Dumping syndrome

Dumping syndrome is a common clinical complication of abnormal motility of the thoracic stomach. However, only 5% of patients show symptoms with moderate severity, and 1% show very severe symptoms. The causes of dumping syndrome are the same as that of delayed gastric emptying; the causes include devascularization, denervation, abnormal pyloric function, and decreased gastric capacity, all of which results in rapid emptying. It is currently believed that rapid entry of hypertonic food into the intestine results in the movement of parenteral fluid into the intestine. However, the detailed mechanism is not fully understood, but may be related to gastrointestinal hormones. The clinical manifestations are gastrointestinal symptoms (diarrhea, bloating, etc.) and/or hypovolemic symptoms.

Most symptoms of dumping syndrome can be alleviated by modifying eating habits and styles; these modifications include eating multiple small meals (at least 6 meals/24 h), avoiding drinking more fluid immediately after a meal, avoiding eating foods containing monosaccharides (sugar, cookies, sweets), replacing foods containing monosaccharides with those containing polysaccharide (such as fruits, pasta, potatoes and other grains), avoiding dairy products, and appropriately increasing the proportions of fat and protein. In severe cases, drugs including propranolol, verapamil, prednisolone, methysergide maleate, acarbose, and octreotide can be administered. Avoiding damage to the vagus nerve has been proposed as a preventive measure; however, it is only possible during the treatment for early-stage cancer of the gastroesophageal junction or Barrett esophagus, and is not suitable during surgery for locoregional advanced squamous cell carcinoma.

Reflux

Damage to the anti-reflux mechanism at the gastroesophageal junction, diaphragm, and angle of His is the cause of reflux. In addition, partial localization of the stomach in the positively pressured abdominal cavity, delayed gastric emptying, and denervation can all aggravate reflux. Clinical manifestations include bile- and gastric acid-induced laryngitis, vomiting, repeated coughing, pneumonia, and inability to lie in a supine position. The affecting

factors include low anastomosis (below the aortic arch), substitution of the whole stomach, and partial localization of the stomach in the abdomen. Preventive methods that help alleviate reflux include sufficient mobilization of the stomach (allowing it to be localized in the thorax during pulling up), placement of the anastomosis at a high position, adequate shaping of the tubular stomach, resection of most of the area secreting acid, performing operations that enhance emptying, changing eating habits (including having multiple small meals), and avoiding lying in the supine position immediately after meals and walking. Many researchers have performed experimental operations on patients with anastomosis to imitate anti-reflux function, such as fundoplication; however, the expected results have not been achieved, and therefore, these operations have not been widely accepted.

Chylothorax after surgery for esophageal cancer

Chylothorax after surgery for esophageal cancer is a rare complication with an incidence rate of approximately 2.7-3.8% (19,20). However, improper handling can lead to fatality, which is caused by the damage to thoracic ducts and/or its branches. Chylothorax is defined as the leakage of lymphatic fluid (containing lymphocytes, immunoglobulins, and various biological enzymes) that is enriched with chylomicrons and lipids (including lipid-soluble vitamins, chylomicrons, and triglycerides) into the thorax (21). Chyle does not contain fibrinogen; therefore, unlike blood, the damaged thoracic tube cannot heal on its own. Persistent loss of chyle causes decrease in the lymphocyte numbers, nutritional deficiencies, reduced immunity, and eventually leads to systemic infections. If large amounts of chyle leakage (daily chylous drainage >1,000 mL) persists, a decrease in the lymphocyte number should be expected.

Diagnosing a case of chylothorax requires a combination of clinical presentations and the results of laboratory tests and imaging examinations. The clinical presentations include early, postoperative, and unexplained drainage of large amounts of a brownish or beige fluid into the thorax; rapid emergence of contralateral pleural effusion; or drainage of a white milky fluid in the pleura of patients with restored enteral nutrition (22). Drainage of a fluid with triglyceride concentrations >110 mg/dL into the thorax can be diagnosed as a case of chylothorax. In addition, the lymphocyte concentration in the chyle is significantly higher than that in the peripheral blood (the percentage of lymphocytes amongst total white blood cells usually exceeds

90%) (23). Lymphaticangiography can help to diagnose thoracic duct injury and its severity (24), with a diagnostic accuracy of up to 81% (25).

Conservative treatment is often used as the first-line treatment for chylothorax, although the success rate is relatively low. Adequate surgical drainage and promoting lung re-expansion can help in the adhesion and final closure of the trauma in the thoracic duct. Nutritional modification may improve the resolution of chylothorax: medium-chain fatty acids may be administered, or enteral nutrition may be temporarily replaced with parenteral nutrition support. Somatostatin inhibits the secretion of intestinal fluid and the activity of various enzymes; therefore, it can reduce chylous drainage to some extent (26). Etilerfrine is a sympathomimetic drug, which helps to treat postoperative chylous leakage by stimulating smooth muscle contraction in the thoracic duct (27). After conservative treatment, if the daily volume of chest drainage is <200-300 mL, then it suggests that the condition has been effectively controlled, and normal enteral nutrition supply or a high-fat diet can be considered. If no further increase in the daily volume of chest drainage (<450 mL) is observed, closed thoracic drainage may be stopped (23).

If chylothorax persists after conservative treatment, a secondary surgery is required; these include video-assisted thoracoscopic surgery and traditional thoracotomy, as well as laparotomy and horizontal ligation of the thoracic duct at the crura of the diaphragm. The principles for the secondary surgery are as follows: (I) confirm the location of the damage to the thoracic tube and ligated; (II) use methods similar to pleurodesis to cause the lung to adhere to the parietal pleura for obliterating residual pleural space; and (III) address the problems of co-existing morbidities, such as empyema and anastomotic leakage (25). Tube feeding of high-fat enteral nutrients 30 minutes before surgery can help to determine the sites of intraoperative injury in the thoracic duct. Treatments for damage include ligation with a vascular clip, or use of ultrasonic scalpel and ligation after solidification, suture with hemostatic gauze, ligation with fibrin glue, use of tetracycline or talc pleurodesis, and postoperative radiotherapy. The thoracic duct is one of the main branches of the lymphatic system. It originates in the abdominal cavity (behind the second and third lumbar vertebrae) and the cisterna chyli (between the aorta and right crura of the diaphragm), travels along the right side of the vertebral body, enters the thorax through the aortic hiatus in the diaphragm, moves horizontally to the left at the fifth thoracic vertebra, continues up to

the neck, and finally reaches the junction where the left internal jugular vein and subclavian vein converge. Clinical data show that the aforementioned route occurs only in 55% of cases, whereas other abnormal routes occur in the remaining 45%.

Summary

Since the beginning, esophageal resection and reconstruction has always been a thoracic surgery with complex operations and various postoperative complications. Mastering the causes of postoperative complications and principles for treatment is the cornerstone for improving the efficacy of surgery for esophageal cancer. These concepts should not be limited to thoracic surgeons, but should include anesthetists, intensive care physicians, and nurses who are also involved in the treatment. The goals of prolonging lives and improving the postoperative quality of life cannot be reached without sincere cooperation and elimination of the various associated dangers.

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Managing complications II: conduit failure and conduit airway fistulas

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Abstract: Conduit failure and conduit airway fistula are rare complications after esophagectomy, however they can be catastrophic resulting in high mortality. Survivors can expect a prolonged hospital course with multiple interventions and an extended period of time prior to being able to resume oral nutrition. High index of suspicion can aid in early diagnosis. Conduit failure usually requires a period of proximal esophageal diversion and staged reconstruction. Conduit airway fistulas may be amenable to endoscopic repair but this has a high failure rate and many patients will require surgical repair with closure of the fistula and interposition of vascularized tissue to minimize recurrence.

Keywords: Esophageal cancer; complications; fistula

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Introduction

Although decidedly uncommon, conduit necrosis and conduit airway fistula are two of the most feared complications after esophagectomy. Both are associated with high mortality and may result in loss of the conduit and need for additional operations to reestablish continuity of the gastrointestinal tract. The treatment course of survivors generally includes prolonged ICU and hospital stay as well as multiple additional interventions and procedures.

Conduit failure

Multiple systems exist to classify anastomotic leak. One commonly used example is the system developed by Lerut, *et al.* shown in *Table 1* (1). The most severe category of leak in this and other systems includes those due to necrosis of a portion of the gastric conduit. The incidence of gastric conduit necrosis is reported between 0.5-3.2% (2-4). Orringer and colleagues reviewed 1,085 patients who underwent transhiatal esophagectomy with gastric tube conduit with a reported incidence of graft ischemia of 2.6% (5). Ramage and colleagues reviewed 155 patients who

underwent minimally invasive esophagectomy and found a similar 2.6% incidence of conduit necrosis (6).

Risk factors

Risk factors for gastric conduit necrosis can be divided into patient-related factors, technical factors and postoperative care. Anatomic factors such as the lack of a serosal layer on the esophagus and the longitudinal orientation of the muscular layer have been implicated in anastomotic leak in general but not specifically related to conduit necrosis (7). It is important to understand the blood supply of the conduit. The majority of the gastric conduit is supplied directly by the right gastroepiploic artery with the remainder of the conduit supplied by a network of microvascular submucosal collaterals (8). The anastomosis is necessarily created within the most ischemic portion of the conduit. Therefore it is important when mobilizing the conduit to not only preserve the macroscopic blood supply but also avoid trauma to the submucosal vascular plexus.

Patient-related factors include peptic ulcer disease, history of external beam irradiation, and severe malnutrition (9). Peptic ulcer disease can cause local inflammation in the area

Table 1 Classification of esophageal anastomotic leaks, based on nomenclature developed by Lerut *et al.* (1)

Leak class	Definition
Radiological	No clinical signs, identified on radiologic study only, requires no intervention
Clinical minor	Local inflammation of cervical wound, fever, elevated WBC, managed by local drainage
Clinical major	Severe disruption of anastomosis with sepsis, managed by percutaneous drainage or reoperation
Conduit necrosis	Endoscopic evidence of necrosis, mandates reoperation

of the conduit which will be used for anastomosis. External beam radiation leads to localized fibrosis and decreased microvascular network in the stomach and may affect the vascularity of the conduit. Severe malnutrition is not uncommon in patients with esophageal cancer as most have a variable period of time during which they will attempt to adjust their diet and adapt to the progressive dysphagia prior to seeking diagnosis and treatment. Patients with severe malnutrition may benefit from feeding jejunostomy tube placement with a period of nutritional support prior to proceeding with esophagectomy. Interestingly, both diabetes and perioperative steroid use have not been shown to correlate with anastomotic breakdown despite their well-known association with poor wound healing (10,11). Although age is commonly implicated as a risk factor for morbidity and mortality in complex operations, it has not been shown to be associated with conduit necrosis or other anastomotic complications (12).

Technical factors include mobilization of the stomach, creation and placement of the conduit, and anastomotic technique. The stomach is the most commonly used conduit for benign and malignant disease for several reasons: it is relatively easy to mobilize, it only requires one bowel anastomosis, and it has a fairly consistent right gastroepiploic arterial supply. The stomach must be mobilized with careful attention to the vascular supply on which the entire conduit depends. It is important to minimize trauma to the conduit, especially the most proximal portion, during mobilization. In a series of over 1,000 patients, Orringer and colleagues reported failure to adequately mobilize the gastric conduit (as opposed to improper anastomosis creation) as the most likely cause of gastric tube necrosis (5). The width of the conduit is also important. Pierie and associates demonstrated that creating a gastric tube which is too narrow can lead to fundal tip necrosis as a result of decreased mucosal blood flow (13). On the other hand a conduit which is too wide may become redundant within the chest or compressed as it passes through the thoracic inlet. Liebermann-Meffert and colleagues reported an ideal width of 4-5 cm in creating a

gastric tube conduit (8).

Although several routes exist for placement of the neo-esophagus, the posterior mediastinal route allows for the best alignment and least tension on the conduit (14). Placement of the conduit in the substernal position may be used for patients with a hostile right thorax or mediastinum, but this route risks compression by the clavicular head. The subcutaneous position, used in only extreme conditions, is disadvantageous due to the longer length required and increased risk of conduit trauma (15). If the posterior mediastinal route is not available, then substernal should be the second choice with removal of the clavicular head and a portion of the manubrium to prevent compression.

Tension is also a key factor in preventing anastomotic complications. The length of the conduit available should be taken into account when choosing the level of the anastomosis. For example, in the case of a bulky gastroesophageal junction tumor requiring resection of a portion of the proximal stomach with the specimen, anastomosis in the neck may be under significant tension and a decreased chance of leak may be obtained by instead choosing an anastomosis within the chest. Some surgeons have attempted to reduce the tension on the anastomosis by tacking the conduit to the prevertebral fascia with sutures; however, this may increase the risk of anastomotic leak and gastric tube tip necrosis and should be avoided (16).

A variety of anastomotic techniques have been proposed to prevent leak and necrosis. Law *et al.* compared 1-layer hand sewn anastomoses to circular end-to-end stapled anastomoses and found no difference in leak rate (17). Heitmiller and colleagues describe using a two-layer hand sewn cervical anastomosis with an anastomotic leak rate of 0.8% (18). Orringer and colleagues favor a semi-mechanical anastomosis. An endoscopic linear stapler is used to create the back wall of a side-to-side esophagogastric anastomosis and the anterior wall is hand sewn in a single layer (19). Using this technique, they reported a significant decrease in their incidence of anastomotic leaks from 13% to 3%. Completely stapled anastomoses may be created using several techniques, including end-side on the anterior aspect

of the stomach, end-side on the posterior aspect of the stomach, end-side with a circular stapler, and end-end with triangulated linear stapling. A recent retrospective study of the anastomotic strategies showed the highest leak rate with single layer hand sewn and the lowest stricture rate with the linear stapled technique (20). Despite the lack of consensus, an important technical aspect of all esophagogastric anastomoses is the incorporation of mucosa in order to provide adequate blood supply to the anastomosis.

The same risk factors which lead to the development of gastric conduit necrosis can generally be applied to the use of colon and jejunum with a few differences. Colon interposition requires the creation of at least three anastomoses instead of one, although the majority of ischemic complications are related to the esophagogastric anastomosis as is seen with the gastric conduit. Colon interpositions have an incidence of conduit necrosis reported as 2.4-18% which is much higher than that reported for gastric conduits (3,21,22). Similarly, jejunal conduits have necrosis rates reported up to 14.1% (23). Further differences particular to surgical technique in using colon and jejunum conduits are described below.

Postoperative management can also contribute to conduit ischemia. Postoperative hypotension has been reported to increase the risk of ischemia and ultimately necrosis (16). This may be exacerbated by some of the commonly used vasopressor agents which will cause splanchnic vasoconstriction. Conduit distention can also lead to decreased perfusion by increasing wall tension above the capillary perfusion pressure. Many surgeons routinely leave a nasogastric tube in the conduit at the completion of the procedure in an attempt to prevent this.

Diagnosis

The clinical presentation of conduit necrosis usually reflects mediastinitis and severe sepsis as sequelae of anastomotic leak and ischemic bowel. Signs and symptoms include fever, chest pain, tachycardia, tachypnea, oliguria, hypotension, acidosis and "coffee-grounds" nasogastric tube drainage. Conduit necrosis is usually an early postoperative event and rarely presents after the seventh postoperative day (24). As with any anastomotic leak, the key to diagnosis is having a high index of suspicion with any change in clinical status. What starts as simple tachycardia and fever can rapidly progress to hemodynamic instability and multi-organ system failure. Initial diagnostic maneuvers with any concern for anastomotic leak should include drainage which for a

cervical esophageal anastomosis means opening the neck incision. If this does not resolve the fevers and systemic symptoms, endoscopy or operative exploration is indicated to confirm and manage conduit necrosis. Rapidly developing sepsis in combination with diffuse leakage on a contrast radiologic study mandates further investigation for conduit necrosis. If there is clinical suspicion with an intrathoracic anastomosis, a contrast esophagogram should be obtained to establish the presence of anastomotic leak. This may also demonstrate a mucosal cobblestone appearance characteristic of ischemia. Endoscopic evaluation of the conduit is the next step to evaluate the anastomosis and extent of graft necrosis. Evidence of mucosal ischemia or necrosis on endoscopy should prompt immediate surgical exploration. Endoscopy is a safe procedure with little risk of injury to the gastric conduit. Page and colleagues demonstrated that routine endoscopy in 100 patients within one week of esophagectomy posed no risk of injury to the gastric conduit or anastomosis (25). Computed tomography is a less useful test which can delineate a large anastomotic leak but often demonstrates only fluid and air within the mediastinum which may be normal postoperative findings and do not confirm a diagnosis of leak (26).

Management

With small anastomotic leaks, non-operative management is the strategy of choice. As long as there is adequate drainage and nutrition, the leak will likely heal. Conduit necrosis on the other hand mandates urgent surgical exploration. The conduit and anastomosis are examined, necrotic tissue including the conduit and surrounding mediastinum are debrided, and the area is widely drained. If the defect is not profound, consideration may be given to placing a t-tube to create a controlled fistula. If the defect is large with significant necrosis of the conduit, non-viable esophageal and gastric conduit tissue is resected and the remaining conduit is returned to the abdomen. The majority of patients will have signs of sepsis including hemodynamic instability and the conservative and most commonly used approach includes proximal diversion. Reconstruction with a new conduit in the same setting is not recommended (27). Proximal diversion by creation of a temporary cervical esophagostomy and feeding jejunostomy allows sepsis to resolve prior to future esophageal reconstruction. The longest possible length of remaining esophagus should be preserved in creating a temporary esophagostomy to allow for an easier future reconstruction of gastrointestinal continuity.

The most common options for esophageal reconstruction following necrosis of a gastric conduit include colon interposition or jejunal transfer as a free or “supercharged” conduit. Advantages to using a colon interposition include its fairly consistent arterial supply, and the ability to replace long segments of necrotic esophageal conduit. Disadvantages include the possibility of intrinsic vascular disease and the need for three anastomoses. Advantages to using jejunum as conduit include its similar width size match to the esophagus, arterial supply largely spared of intrinsic vascular disease, and active peristalsis to assist in food bolus transit. The use of jejunum conduit is less popular than colon, however, because its vascular anatomy limits its use to short-segment esophageal replacement. A jejunum conduit which has been “supercharged” by microvascular augmentation has been shown to reduce incidence of ischemic complications and achieve long-segment esophageal reconstruction, however this more technically demanding operation has not gained favor among most surgeons (28).

Outcomes

Although conduit necrosis is rare, it can be a disastrous complication. Hospital mortality has been reported approaching 90% especially if the necrosis is not diagnosed promptly (4). Iannettoni and colleagues reported a series of six patients with gastric tip necrosis. Two of the six (33%) died during that hospital stay (16). Schuchert *et al.* reported a similar rate with one of three patients with gastric tip necrosis dying in the perioperative period (29). Although they were able to preserve the conduit, both of their survivors ended up with strictures requiring multiple dilations.

Conduit airway fistula

A benign fistula between the trachea and the neo-esophagus following esophagectomy is a rare but potentially fatal complication. Conduit airway fistula has a reported incidence of 0.04-0.3% and, like conduit necrosis, tends to present relatively early in the postoperative course (30). Fistula formation is possible due to the close anatomic relationship of the conduit and the airway. If the esophagectomy is done using the Ivor Lewis technique, the anastomosis lies just cephalad to the azygous vein directly posterior to the membranous airway. A fistula at this level will potentially involve the distal trachea, carina, right main bronchus or left

main bronchus. With a transhiatal or McKeown approach, the anastomosis is in the cervical esophagus which lies behind and slightly to the left of the membranous airway. Fistulas can also occur at levels other than the anastomosis. Fistulas can originate from the gastric staple line which runs the length of the conduit, from old feeding tube sites or from a penetrating gastric ulcer (31-34).

Etiology

Conduit airway fistula generally occurs in the setting of anastomotic leak. The local inflammation of the leaking enteric contents and saliva cause necrosis of the surrounding tissue which can erode into the airway. There may or may not be an underlying airway injury as well which creates a weak point susceptible to fistula creation. The trachea is most commonly injured during mobilization of the esophagus within the chest, either by direct trauma or injudicious use of an energy source (such as electrocautery). This is particularly likely when the tumor is at or above the level of the carina (35). Unsuspected airway injuries can also occur during intubation. Extensive dissection around the trachea at the level of the carina can interrupt the local blood supply and lead to ischemia. Fistulization has been reported to be particularly related to devascularization of the membranous trachea overlying the esophagus as a result of radical upper mediastinal lymph node dissection (36). Maruyama and colleagues demonstrated a relationship between conduit-airway fistula and three field lymph node dissection or a total lymph node count of greater than 60 nodes (37). Airway injury has also been reported due to chronic irritation from the gastric staple line running the length of the conduit. Neoadjuvant therapy can lead to preexisting tissue injury/ischemia. Heitmiller and colleagues identified a correlation between neoadjuvant chemotherapy and increased risk of neo-esophageal fistula development (18). Bartels and colleagues found an even stronger association with neoadjuvant radiation (35).

Even without an underlying airway injury, an inadequately drained anastomotic leak will cause inflammation with local release of gastric enzymes and may fistulize into the airway. Another more chronic issue which may lead to fistulas is pressure created by the cuff of an endotracheal or tracheostomy tube in a patient requiring mechanical ventilation for a prolonged period postoperatively (38,39). Patients who successfully heal an anastomotic leak may require long term treatment for a resulting stricture. The more liberal use of stents to treat anastomotic

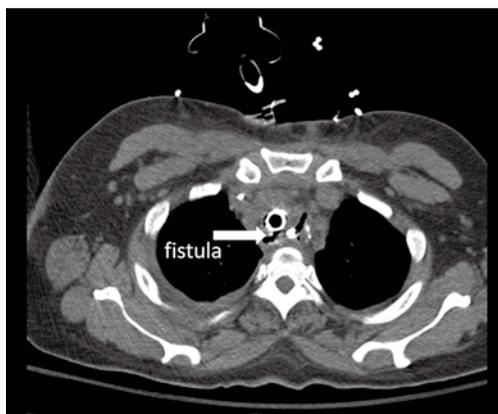


Figure 1 CT scan demonstrating a posterior fistula from the membranous trachea to the cervical anastomosis after transhiatal esophagectomy.

stricture after leak has led to case reports of stent erosion into the airway with resulting fistula (40). Fistula has also been reported after endoscopic dilation of anastomotic stricture (30).

Diagnosis

The clinical presentation spectrum varies from mild disease to life-threatening sepsis. The most common early symptom of fistula is cough with oral intake and shortness of breath due to aspiration of gastric contents. This can progress to recurrent aspiration pneumonias and sepsis. Some patients will present early in the development with relatively few symptoms while others present with acute decompensation related to chemical with or without superimposed bacterial pneumonitis and pneumonia. An esophagram may demonstrate oral contrast entering the airway although if the fistula is small the study may be nondiagnostic. If the clinical suspicion is high or the esophagram shows a fistula endoscopic confirmation is necessary. This should include endoscopic inspection of the upper esophagus, anastomosis, conduit and airway. The anastomosis and gastric staple line are common sites of leak and should be inspected carefully but it is often difficult to identify a small fistula from the esophageal side. The folded mucosa of the conduit may hide a small opening. The fistula is often better identified from the airway side where the size and location should be noted. Unless the patient is in the early postoperative period, it is important to biopsy the fistula to determine if it is due to recurrent cancer or is truly a benign lesion. If it is still in the early postoperative period, a CT scan may be useful to

identify surrounding fluid collections which will need to be drained. The fistula itself can occasionally be identified on a CT scan (*Figure 1*) but this should not be relied upon for diagnosis as it is neither sensitive nor specific.

Management

Optimal management of conduit airway fistulas should be dictated by the location and size of the fistula in conjunction with the severity of the patient's symptoms. In a patient presenting with minimal symptoms, endoscopic approaches to repair are a reasonable first choice. Many endoscopic techniques have been tried to directly close the fistula including application of fibrin glue with or without a vicryl mesh plug and metallic clip placement (41). These approaches are more likely to work with a long narrow fistula tract and good results have been reported (42,43). Unfortunately, even in the ideal fistula, this approach may be unsuccessful at obliterating the leak or lead to early recurrence (44). Another endoscopic approach is to cover the fistula with a self-expanding stent which may allow the surrounding tissue to remodel and scar over the opening. Boyd and Rubio reviewed the published experience with this technique and concluded that covered metallic stents may be more successful at occluding the fistula initially and preventing further airway soilage but there was no difference in long term success (45). Initial closure was successful in 75% of the cases they reviewed. Most failures were due to leakage around the stent related to an imperfect seal. It is often difficult to stent from the conduit side because of the large diameter of the conduit, which leads to both stent migration as well as reflux around the distal end of the stent. This is a more significant issue if the fistula is with the body of the conduit rather than at the anastomosis. The airway side of the fistula is often a more feasible diameter to allow good contact with the wall circumferentially. Stenting has a high recurrence rate (39%) and the patients must be monitored carefully for recurrence and extension. There is a concern that the radial force of an oversized stent will create local tissue ischemia and actually enlarge the fistula rather than allowing it to heal. More recently, several studies have demonstrated the feasibility of using dual self-expandable stents placed by endoscopy and tracheoscopy in the alimentary and respiratory tracts for benign and malignant fistulas following esophagectomy (46). Although this approach may improve initial closure rates, the tissue between the stents then becomes even more susceptible to pressure ischemia and necrosis. While this stent-based

strategy has had variable success in fistula closure, it is a useful tool for temporizing the patient who presents acutely ill. Occlusion of the fistula allows treatment of associated pneumonia and nutritional optimization as needed and facilitates a safer, elective reconstruction with single-stage repair instead of an urgent surgical intervention. A final experimental endoscopic approach which has been reported for use in fistulas recurrent after both endoscopic and surgical closure is placement of a cardiac septal occluder (47). This device is delivered over a wire using the gastroscope and consists of two self-expanding nitinol discs joined at their centers. The link between the two sides sits across the fistula with a disc providing occlusion from either side.

Surgical intervention requires an individualized approach based on the location of the fistula and quality of the surrounding tissue. Successful repair can be achieved with adherence to the following principles: drainage and debridement of non-viable tissue, primary repair of the tracheal and conduit defects, and interposition of well vascularized tissue between the trachea and esophagus to prevent recurrent fistulization. Many sources of vascularized tissue have been successfully used including omentum, pericardium, pleura, pericardial fat pad, and intercostal muscle. The tracheal defect can be closed primarily if small enough not to compromise the lumen. If it is too large the membranous portion of the airway can be reconstructed with either autologous tissue or biologic mesh and then reinforced with vascularized tissue. Bakhos and colleagues were successful with primary repair of a fistula buttressed with an intercostal muscle flap (31). Kron and colleagues describe using pericardial patch to replace membranous trachea followed by interposition of a latissimus dorsi flap to isolate the gastric conduit from the trachea (32). If inadequate local tissue is available, the use of biologic mesh with a reinforced interposition flap may be helpful as described by Reames and colleagues (48). Since the conduit has more flexibility and redundancy than the airway it can most often be closed primarily. In rare circumstances the gastric conduit may be deemed nonviable, in which case it should be excised and managed as for gastric conduit necrosis. In their series of six patients with benign trachea-neo-esophageal fistulas following esophagectomy, Buskens and colleagues report two patients who were treated conservatively, one patient who had a fistula partly excised via a right sided cervical incision, and three patients who underwent partial exclusion or excision of the gastric conduit followed by colonic interposition reconstruction with good results (30). A staged reconstruction with

proximal esophageal diversion followed by delayed re-establishment with the colon should be used if esophageal continuity is disrupted.

Summary

Prevention of ischemic complications can be best achieved by early identification of potential patient risk factors, careful conduit mobilization during surgery, and diligent postoperative care. Diagnosis relies on a high index of suspicion in patients with unusual findings in their postoperative course such as unexplained sepsis and recurrent pneumonias or cough with oral intake. Conduit necrosis mandates surgical intervention with aggressive debridement of nonviable tissue and will often require esophageal diversion with staged reconstruction after controlling mediastinal sepsis. Conduit airway fistulas are more variable in their clinical presentation making diagnosis challenging. The size and location of the defect in conjunction with the severity of symptoms should dictate the appropriate management. Despite optimal identification and management of these complications, mortality rates are high and survivors can expect a prolonged course with multiple reinterventions.

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Current strategies in chemoradiation for esophageal cancer

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Abstract: Chemoradiotherapy (CRT) has an important role in the treatment of esophageal cancer in both the inoperable and the pre-operative settings. Pre-operative chemoradiation therapy is generally given to 41.4-50.4 Gy with platinum or paclitaxel based chemotherapy. The most common definitive dose in the U.S. is 50-50.4 Gy. New advances in CRT for esophageal cancer have come from looking for ways to minimize toxicity and maximize efficacy. Recent investigations for minimizing toxicity have focused advanced radiation techniques such as IMRT and proton therapy, have sought to further define normal tissue tolerances, and have examined the use of tighter fields with less elective clinical target volume coverage. Efforts to maximize efficacy have included the use of early positron emission tomography (PET) response directed therapy, molecularly targeted therapies, and the use of tumor markers that predict response.

Keywords: Esophageal cancer; radiotherapy; positron emission tomography (PET)

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Esophageal cancer overview

Incidence and epidemiology

Approximately 17,990 new cases of esophageal cancer are estimated to be diagnosed in the U.S. in 2013, with 15,210 deaths (1). Adenocarcinoma has increased in incidence among Caucasians in the United States over the last 25 years (2) and is now the most common histological subtype. Risk factors for esophageal adenocarcinoma include columnar metaplasia (Barrett's esophagus) (3), obesity (4), and smoking (5). Globally, squamous cell carcinoma (SCC) is the more common histology and the incidence of esophageal cancer is ten times higher than the U.S. in certain geographic areas including northern China, Iran, Russia, South Africa, Hong Kong, and Brazil. Part of this discrepancy may be due to ingestion of alcoholic beverages and nitrate-rich foods including pickled vegetables, cured meats, and fish. Esophageal cancer is about three times more common in men than in women. While 95% of esophageal tumors are histologically defined as SCC or adenocarcinoma, other types are occasionally seen including adenoid cystic carcinoma, mucoepidermoid tumors, small cell carcinoma, lymphoma, and melanoma.

Presentation and work-up

Dysphagia is the most common presenting symptom (90% of cases) followed by weight loss (40-70%), and odynophagia (50%), as well as pain, bleeding, hoarseness, and cough (6). Complete diagnostic investigation includes a thorough history and physical examination with special attention to cervical and supraclavicular lymph nodes and head and neck mucosal surfaces as second tumors of the head and neck are common. Laboratory investigations such as a basic metabolic panel, complete blood counts, and liver function tests should be obtained. While barium swallow is common for initial work-up of symptoms, endoscopy is essential to define the location and extent of the primary lesion. Imaging studies should include a computed tomography (CT) scan with IV and oral contrast of the chest and abdomen to identify sites of metastasis. Endoscopic ultrasonography has become a very common study to assess periesophageal and celiac lymph node involvement and the extension of disease through the esophageal wall. Positron emission tomography (PET) is also commonly used to detect nodal and distant metastases.

Management

Surgery remains a mainstay of treatment for operable patients. Transthoracic esophagectomy (Ivor-Lewis procedure) appears to provide a trend toward improved long-term survival compared to transhiatal approach for mid-to-distal or gastroesophageal junction adenocarcinomas (7). This approach allows for better visualization of the operative field and lymph node dissection. However, higher rates of perioperative morbidity were seen in patients receiving transthoracic esophagectomy in a randomized comparison (7).

Radiation therapy alone is not recommended as a curative strategy. Patients achieved a 0% cure rate at 5 years in the control arm of RTOG 8501 (8). Two trials have examined the omission of surgery [chemoradiotherapy (CRT) alone] compared to tri-modality therapy. The French FFCD 9102 trial randomized patients with operable T3N0-1 thoracic esophageal squamous (90%) or adenocarcinoma (10%) with a response after 46 Gy CRT with cisplatin/5-FU to further CRT to 66 Gy *vs.* surgery (9). Tri-modality therapy resulted in higher local control (65% *vs.* 57%, $P < 0.05$), and fewer stents required (5% *vs.* 32%, $P < 0.001$). There was no difference in overall survival. The German trial reported by Stahl and colleagues employed induction chemotherapy (5-FU, leucovorin, etoposide, cisplatin) followed by CRT to 40 Gy with cisplatin and etoposide followed by surgery versus CRT to 50 Gy in 2 Gy fractions followed by 1.5 Gy BID to 65 Gy for T4 or obstructive T3 tumors or 60 Gy followed by high dose rate (HDR) brachytherapy for non-obstructed T3 tumors (10). Again, no difference was seen in survival, but patients who received surgery had a higher rate of 2-year freedom from local progression (64% *vs.* 41%, $P = 0.003$). In both trials, differences in the rates of surgical complications were non-significant across the treatment arms.

The strategy of reserving surgical resection for those patients who experience a less than complete response after CRT has also been examined in the phase II trial, RTOG 0246 (11). Definitive chemoradiation included induction chemotherapy with 5-FU, cisplatin, and paclitaxel for two cycles, followed by concurrent CRT to 50.4 Gy with 5-FU and cisplatin. A total of 51% of patients (21/41) ultimately underwent surgery following CRT because of residual (17 patients, 41%) or recurrent (3 patients, 7%) disease, and 1 patient (2%) underwent surgery by choice. The study was not encouraging however, because the 1-year survival rate of 71% did not meet the study goal of 77.5%. Surgery is also withheld in favor of definitive CRT in the case of SCC of the cervical esophagus because adequate surgical

resection often leads to significant morbidity and loss of the entire larynx, thyroid gland, portions of the pharynx, and the proximal esophagus.

The standard strategy for the treatment of thoracic locally advanced esophageal cancer is now neoadjuvant chemoradiation followed by surgery (“tri-modality therapy”). This strategy has resulted in better outcomes than surgery alone in several randomized trials (12-15) including higher overall survival in a meta-analysis (16). Many U.S. centers now favor tri-modality therapy for all patients except non-surgical candidates for whom definitive chemoradiation is still a viable option (8). The remainder of this review will focus on promising avenues for the optimization these strategies including consideration of radiation dose and technique, chemotherapy, and patient selection. Ongoing and future research will be necessary to fully realize the benefits of therapy.

Minimizing toxicity

RT dose

A dose of 50.4 Gy in 28 fractions has generally been regarded as standard in the United States in tri-modality therapy (12) and is being employed in ongoing randomized trials (17,18). In contrast, the CROSS trial (14) utilized a dose of only 41.4 Gy in 23 fractions. The CROSS regimen yielded a pathological complete response rate of 29%, with an excellent locoregional recurrence (LRR) rate of only 14% and a median survival of 49.4 months. This is similar to results that have been seen in preoperative regimens utilizing 50.4 Gy or more (12), raising the possibility that clearly resectable patients could be spared the toxicity of an additional week of radiation therapy. Additional studies have also shown efficacy for preoperative doses of 45 Gy or less (13,19,20), although others have failed to do so (21). Caution must be used in interpreting these results due to the heterogeneity of patient populations, RT fields, chemotherapy, surgical approaches, and pathology techniques involved.

In the setting of definitive chemoradiation, dose-escalation has been a subject of investigation, spurred by the fact that local failure is common after therapy (22). The Intergroup 0123 trial was a randomized investigation of 236 patients with T1-4, N0-1, M0 disease receiving monthly cisplatin (75 mg/m²) and 5-fluorouracil (1,000 mg/m²) concurrent with radiation of 50.4 Gy plus or minus a 14.4 Gy boost to the tumor only with a 2 cm margin. There was no significant difference in the overall survival, or

locoregional failure between the two arms but there were an unexpected high number of deaths in the boost arm with 7/11 of them occurring before 50.4 Gy for unclear reasons. Brachytherapy boost has also been attempted in a phase II trial (23). In this investigation, 49 eligible patients received 50 Gy EBRT in 2 Gy fractions followed two weeks later by brachytherapy [either three weekly fractions of 5 Gy by HDR or low dose rate of 20 Gy]. All patients received concurrent monthly cisplatin (75 mg/m^2) and continuous infusion 5-fluorouracil ($1,000 \text{ mg/m}^2$) for four cycles. Because life-threatening toxicity occurred in 24%, including six tracheo-esophageal fistulas, and 10% died, the authors urged caution in employing this technique. Although many European and Asian groups still favor higher doses, the standard of care in the United States remains external beam radiation to 50-50.4 Gy in 1.8-2 Gy fractions.

Discouragingly, this standard of care is often unable to control local disease as patterns of failure studies show high rates of failure in the treated areas. After CRT alone to 50.4 Gy, 75% of patients in one institutional experience failed in the GTV and 85% failed in the PTV (24). Only three patients failed outside the treatment field as determined by fusion with the planning CT scan. This suggests that current doses are inadequate to sterilize local disease, and dose escalation could hold promise if increased surrounding tissue toxicity could be mitigated.

Normal tissue tolerances

Careful attention must be paid to normal tissue tolerances in esophageal chemoradiation therapy. Depending on the location of the primary tumor the spinal cord, lungs, larynx, brachial plexus, heart, pericardium, normal esophagus, normal stomach, liver, and/or kidneys may be at risk and should be dose constrained. Generally, the spinal cord should be limited to a max-dose of 45 Gy. Rates of lung toxicity after tri-modality therapy were predicted best by the volume of the lung receiving 5 Gy in recent analysis (25). Alternately, mean lung dose less than 20 Gy generally helps keep rates of radiation pneumonitis to acceptable levels. Minimizing dose to the lungs can be accomplished with AP/PA beam weighting but the spinal cord and heart present a competing risk. Keeping the volume of heart receiving 25 Gy less than 10% can limit long-term cardiac mortality (26). Even more common is the shorter-term complication of pericarditis. Pericarditis is found in 20-40% of patients after definitive esophageal chemoradiation therapy with a median time to onset of about 5 months.

Investigators at M.D. Anderson Cancer Center found that the rate of pericarditis is associated with the volume of pericardium receiving 30 Gy (V30) (27). They reported that when the relative V30 of the pericardium was less than 45%, the rate of PCE at 18 months after radiation was 13%, whereas it was 73% when this limit was surpassed.

IMRT

Several dosimetric analyses suggest that IMRT may have potential benefit for esophageal cancer. The theoretical advantages of IMRT include increased target homogeneity, the ability to shape dose to avoid organs at risk, and the possibility of dose escalation with tighter conformality. A dosimetric analysis of ten patients treated with 3D conformal therapy then replanned using four, seven, and nine beam IMRT plans showed a 10% decrease in the lung V10, a 5% decrease in the lung V20, and a 2.5 Gy decrease in the mean lung dose, with no clinically meaningful differences in the irradiated volumes of heart, liver, or spinal cord, or the total body integral dose (28). Another dosimetric analysis from Memorial Sloan-Kettering Cancer Center reviewing 19 patients treated with 5-field IMRT plans compared to theoretical 4-field 3D conformal plans, found a significant reduction in average mean heart dose (22.9 vs. 28.2 Gy) and heart V30 (24.8% vs. 61.0%) with significant sparing of the right coronary artery (average mean dose, 23.8 vs. 35.5 Gy), but no significant improvement in the left coronary artery (mean dose, 11.2 vs. 9.2 Gy) with IMRT (29). It is unclear to what extent this would impact the development of coronary artery disease. This analysis showed no significant difference in lung, liver, kidney, stomach or spinal cord parameters. Nutting and colleagues performed a dosimetric analysis on five patients and noted no advantages to a 9-field IMRT plan, but a reduced mean lung dose when a 4-field IMRT plan was used compared to 3D conformal therapy (30).

Volumetric modulated arc therapy (VMAT), which allows for treatment during gantry rotation with conformal and/or modulated fields, has also been shown to have the potential to reduce the heart V30 (31% vs. 55%, $P=0.02$) compared to 3D conformal therapy (31).

While there is a lack of strong comparative data, retrospective single arm experiences are forthcoming such as an institutional review of 30 patients (18 definitive, 12 preoperative) treated with IMRT at Stanford with chemotherapy for non-cervical esophageal cancer (32). The encouraging results of this study suggest IMRT was at least

safe and effective compared to the published experience with 3D conformal therapy.

Proton therapy

Proton therapy has theoretical advantages in the mediastinum where a sharp dose drop off may be able to limit dose to structures such as the heart and lungs, and may enable dose escalation in the target volume without a corresponding dose increase in surrounding tissues. In a dosimetric study, investigators at MD Anderson Cancer Center examined theoretical distal esophageal intensity modulated proton therapy (IMPT) plans using AP/PA, LPO/RPO, or AP/LPO/RPO beam arrangements compared actual IMRT plans with beam angles optimized for each patient (33). All three of the IMPT plan types were advantageous over IMRT. The AP/PA plans achieved optimal lung sparing, and LPO/RPO plans optimized sparing of cardiac tissue. IMPT plans with three beam angles (AP/LPO/RPO) were associated with lowered mean lung (4.3 *vs.* 8.3 Gy, $P=0.0002$), heart (17 *vs.* 21 Gy, $P=0.003$), and liver (14.9 *vs.* 5.4 Gy, $P<0.0001$) doses compared to IMRT. In these plans, the prescribed dose was 65.8 Gy to the GTV and 50.4 Gy to the PTV in 28 fractions using concomitant boost, suggesting the possibility for high dose delivery with this method. Proton therapy to thoracic targets must take into account respiratory motion however, especially when using a pencil beam scanning technique. Concurrent carboplatin/paclitaxel with proton beam therapy followed by surgery is being investigated in current phase II (34) and phase III trials (50.4 Gy *vs.* IMRT to same dose) (35).

Field size

Lymphatic drainage of the esophagus follows an extensive longitudinal network, and lymph can travel for a considerable length of the esophagus before draining into lymph nodes (36). The lymphatic system of the esophagus drains into nodes that generally follow arteries, including the gastric artery/celiac axis, which represents a dominant area of lymph node metastasis for all but cervical esophageal cancer (37). Patterns of lymphatic spread are influenced by the location of the primary tumor. Historically, large elective nodal fields were used to cover the area at risk. Modern treatment techniques generally omit elective lymph node irradiation. However, celiac and SCV nodes that are not easily dissected can be included electively depending

on the location of the primary tumor. Conversely, when the celiac station is dissected as in the CROSS trials, lower esophageal and gastroesophageal junction lesions can be treated without elective celiac nodal irradiation with a celiac recurrence rate of 3.8% in patients receiving tri-modality therapy (17). Local recurrences are more common after definitive CRT without surgery and most relapses after definitive CRT are in the region of the primary tumor. An analysis by Button and colleagues from Cardiff, UK analyzed the recurrence patterns of patients treated with chemotherapy followed by definitive CRT to 50 Gy in 25 fractions using an EUS defined GTV plus a 3 cm superior/inferior expansion and 1 cm radial CTV expansion from GTV plus 0.5 cm radial PTV expansion from the superior/inferior expanded volume (38). At a median follow-up of 18 months, 88 of 145 (61%) patients had evidence of relapse. A total of 49% failed locally as a part of their first site of relapse. While the field expansions used were minimal compared to the widely used 5 cm superior/inferior margins as required by Int-0123 (22), 96% of locoregional relapses occurred within the radiation field and thus would not have been prevented by larger fields, nor would the three locoregional relapses occurring outside the field been prevented by clinically acceptable larger fields. The percentage of infield relapse was not significantly associated with AJCC stage, disease length, and lymph node involvement.

An analysis of patterns of failure of patients on the CROSS trials showed that, in 213 evaluable patients treated with CRT followed by surgery, 14% experienced LRR (17), 5% experienced LRR in the radiation target volume, 2% at the margins, 6% outside of the target volume, and 1% experienced LRR with unclear relation to the radiation target volume. In these trials a total of 41.4 Gy was delivered in 23 fractions with a superior/inferior margin of 4 cm (3 cm distal margin if extending into gastric cardia) and a radial margin of 1.5 cm.

While some trials have used even more conformal fields, there is still not enough evidence to stray from the standard 3-5 cm superior/inferior expansion. Current RTOG protocol calls for a 4 cm superior/inferior CTV expansion and 1.0-1.5 cm radial CTV expansion plus a uniform 0.5-1.0 cm PTV expansion to 45 Gy followed by a uniform 0.5-1.0 cm uniform expansion around the GTV for the last three fractions to 50.4 Gy (39). In practice, the field expansions depend partially on the confidence of the radiation oncologist in the staging workup, motion management, and set-up accuracy of the treatment.

Along with the traditional workup consisting of CT and endoscopy, the incorporation of advanced staging procedures such as PET and EUS helps to better define the tumor and may justify a smaller CTV expansion. PET fusion to the CT simulation scan may help define the extent of disease (40). In practice, when multiple diagnostic modalities (Endoscopy, EUS, CT, PET) are obtained during diagnostic work-up, generally the greatest extent of disease found should determine the size of the GTV.

Maximizing efficacy

PET guided therapy

Improving upon standard chemoradiation strategies in esophageal cancer treatment involves selecting the patients who are most likely to benefit. One way of individualizing esophageal cancer treatment is to adapt therapy based on early PET response. Weber and colleagues showed that PET response after 14 days of chemotherapy predicted for higher rates of pCR (53% vs. 15%, $P < 0.01$), longer time to progression/recurrence ($P = 0.01$), and longer OS ($P = 0.04$) (41). This analysis established a decrease in SUVmax of 35% as the optimal cutoff for differentiation. Because of this study and others (42-44), prospective studies have now shown that tailoring therapy based on early PET response is feasible (45). In the prospective MUNICON study, locally advanced esophageal adenocarcinoma patients with a metabolic response (>35% decrease in SUVmax) after two weeks of neoadjuvant chemotherapy continued chemotherapy for up to 12 weeks followed by surgery (45). Those without a metabolic response discontinued chemotherapy and underwent resection. The 49% of patients achieving a metabolic response had a pCR rate of 58% (0% in non-metabolic responders), and had higher rates of OS ($P = 0.015$) and event-free survival ($P = 0.002$) than non-metabolic responders. Retrospective comparison of non-responders who received abbreviated neoadjuvant chemotherapy and previous patients treated by the MUNICON group suggested no detriment to discontinuation.

Early PET response during combined chemoradiation therapy is muddled by non-specific radiation induced inflammation causing SUV uptake. Using PET response has not been shown to be useful in selecting patients for early termination of CRT (46,47), but has been correlated with tumor response and patient survival (48). PET response after the completion of neoadjuvant or definitive CRT has been shown to be a significant prognostic factor

in some studies (49,50) and not prognostic in others (51). Overall, its value in guiding further treatment decisions is not definitely established (52). The MUNICON II trial examined PET response after induction chemotherapy (cisplatin, fluorouracil, and leucovorin as well as paclitaxel in some patients) followed by CRT in non-responders in an attempt to improve the rate of pathologic CR and thus survival (53). However, none of the initial non-responders achieved a pCR. This has been attributed to study design factors including a low radiation dose (32 Gy in 1.6 Gy BID fractionation) and the continuation of part of the same “failed” chemotherapy (cisplatin) during RT.

Current prospective trials are looking at a strategy of induction chemotherapy followed by PET evaluation and individualization of the chemotherapy to be used concurrent with radiation (18,54). CALGB 80803 is a multicenter phase II trial looking at PET response adapted neoadjuvant therapy for T1N+ or T2-4(N0/N+) esophageal cancer (18). Patients are randomized to modified FOLFOX 6 for three cycles or carboplatin/paclitaxel for two cycles after which they are evaluated by PET. Patients who achieve a greater than 35% decrease in SUVmax continue the same chemotherapy during RT, followed by surgery. If the SUVmax response is less than 35%, they cross over to the chemotherapy of the other arm during RT, followed by surgery. The primary endpoint is to induce a complete pathologic response in patients who cross over. In the IMAGE trial sponsored by the EORTC, early PET responders will continue with induction chemotherapy, whereas those who do not respond will be randomized to immediate surgery versus a change to taxane based chemoradiation therapy followed by surgery.

One final domain in which PET response may be instrumental in guiding treatment is the decision between tri-modality therapy and chemoradiation alone. A retrospective review of 272 patients treated at MDACC showed that OS and DFS were higher among patients receiving tri-modality therapy, yet among patients exhibiting a PET SUVmax ≤ 4.6 after CRT, the addition of surgery was not associated with improved OS ($P = 0.22$) or DFS ($P = 0.37$) (55).

Predictive tumor markers-ERCC1

The success of chemoradiation therapy in individual patients can be partially predicted by the expression of certain gene products. The excision repair cross-

complementing (ERCC-1) protein is a component of the ERCC1-XPR endonuclease complex that functions to repair platinum damaged DNA through the nucleotide excision repair pathway. When compared to patients who receive surgery alone, patients with ERCC-1 negative tumors tend to achieve longer event free survival (51 *vs.* 20 months, $P=0.042$) and overall survival (59 *vs.* 25 months, $P=0.057$) when treated with preoperative cisplatin-based chemoradiation therapy (56). However, the addition of pre-operative chemoradiation therapy made no difference in outcomes in patients with ERCC-1 positive tumors in this retrospective study. SWOG S0353 was a prospective phase II trial investigating the effect of mRNA levels of ERCC-1 as well as thymidylate synthase (TS) in the tri-modality treatment of clinically staged II or III esophageal cancer using oxaliplatin and 5-FU (57). Intra-tumor ERCC-1 expression with a cutoff of 1.7 was significantly inversely related to 2-year overall survival (16% *vs.* 62%) and progression free survival (39% *vs.* 72%). TS gene expression was not associated with survival.

Targeted agents

Because disease free survival is poor even in the best studies, further advances are still desperately needed. In the dawning age of cancer genomics, targeted agents including antibodies, tyrosine kinase inhibitors, and immune modulators are coming into the mainstream for many cancer types. In esophageal cancer, HER-2/neu gene amplification has been shown to correlate with shortened patient survival in Barrett's esophagus-associated adenocarcinoma (58). The monoclonal antibody trastuzumab is being investigated in patients with esophageal adenocarcinoma in RTOG 1010 (39). This ongoing trial tests the addition of concurrent and adjuvant trastuzumab to carboplatin, paclitaxel, and radiation (50.4 Gy) in patients with esophageal cancers that overexpress HER-2. Surgery follows 5-8 weeks after the completion of RT in both arms.

Attempts to use cetuximab in the treatment of esophageal cancer have not been encouraging however. RTOG 0436 randomized 344 unselected, inoperable esophageal cancer patients to cisplatin, paclitaxel, and radiation (50.4 Gy) versus the same therapy with concurrent weekly cetuximab (59). Cetuximab failed to improve overall survival (the primary endpoint), or clinical response, as evaluated by endoscopy 6-8 weeks after the completion of treatment. These results were consistent with those from previous studies of EGFR inhibitors in metastatic and locally advanced gastric and

esophageal adenocarcinoma where cetuximab (60) and panitumumab (61) have been shown to be ineffective in phase III trials.

Right chemotherapy

An essential task in maximizing the efficacy of chemoradiation therapy is selecting the best cytotoxic agents. Some earlier positive trials of pre-operative CRT *vs.* surgery alone used cisplatin-based chemotherapy (12,13). Most recently, the CROSS trial showed increased overall survival (49 *vs.* 24 months, $P=0.003$), and R0 resections (92% *vs.* 69%, $P<0.001$) when carboplatin and paclitaxel based CRT were used compared to surgery alone (14). The results of this trial and several promising phase II trials of two- and three-drug paclitaxel based CRT regimens (62,63) may result in their increasing use (64). Retrospective data has not produced a clear winner (65) while prospective head-to-head comparisons are in want.

Altered fractionation

Another way of intensifying treatment is through altered fractionation radiation therapy during pre-operative CRT. Hyperfractionation has been looked at in single armed studies, but has shown high toxicity in one paclitaxel based regimen (66), as well as high operative mortality, albeit with an impressive 56% pathological complete response (67).

Conclusions

Chemoradiation therapy followed by surgery is the standard strategy for the treatment of locally advanced esophageal cancer. However, optimization of radiation dose, technique, chemotherapy, and patient selection is necessary to maximize its benefits. In the future, newer radiation techniques such as IMRT and proton therapy may take hold as a way to reduce toxicity. Also, a better understanding of predictive tumor markers may dictate which patients benefit most from CRT and spare toxicity to those less likely to respond. PET response is also a promising area that can help individualize CRT strategy. This is a fast moving and exciting area of oncology in which much work remains to be done.

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The role of induction therapy

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Abstract: The incidence of esophageal cancer has been steadily increasing. The 5-year survival of esophageal cancer has minimally improved over the past 30 years. In this article, we review the management of esophageal cancer, focusing on the literature investigating the role of induction chemotherapy and radiation therapy.

Keywords: Esophageal cancer; chemotherapy; radiation therapy; trimodality therapy

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Introduction

An estimated 17,990 cases of esophageal cancer are estimated to be diagnosed in the United States annually, with greater than 15,000 deaths attributed to the disease. Over the past 30 years, esophageal cancer 5-year survival rates have improved only slightly and still remain low at 19 percent (1). Although esophageal cancer was traditionally thought of as a surgical disease, the poor cure rates prompted ongoing research into improved treatment modalities. The most promising results have been in induction chemoradiotherapy followed by surgical resection. In this review, we present the current data on induction and adjuvant therapy for locally advanced, resectable esophageal cancer. We illustrate the evolution of practice standards and describe the role of induction chemoradiotherapy in the management of this disease.

Treatment modalities

Surgery alone

In multiple series from the Japanese Oncology Group (JCOG), 5-year survival from monotherapy with surgery alone approached 40% (2,3). Recent Western series have failed to duplicate these results, with 5-year survival rates of 16% (1,4). As such, surgery only is reserved mainly for early

stage esophageal cancer (T1-T2) with no nodal involvement (N0) or in urgent circumstances, such as perforation or life-threatening bleeding. More recently, due to concerns over accurate staging of T2 lesions (5), there has been a trend toward treating T2 lesions with induction therapy prior to surgical resection as well.

Radiotherapy alone

Early attempts at single modality therapy resulted in low 5-year survival rates of 4% and 6% percent for surgery alone and radiotherapy alone, respectively (6). Later studies reported slightly improved survival in patients treated with radiotherapy alone. A series from 1985-1994 treated a subset of 101 patients with tumors determined to not be metastatic or locally advanced in patients who were not medically fit for surgery with definitive radiotherapy alone. Staging included endoscopy, barium swallow and occasionally computed tomography (CT). This period was prior to the availability of endoscopic ultrasound (EUS) or positron emission tomography (PET). The majority of patients were given 50 Gray (Gy) of radiation delivered over 15 fractions. The reported 3- and 5-year survival were 27% and 21%, respectively, with a median survival of 15 months (7). Despite these more promising results, treatment for esophageal cancer resulting in better survival rates was sought.

Chemotherapy versus surgery alone

While the standard therapy for thoracic esophageal cancer had been surgical resection, disease-free survival remained poor and adjunct therapies were evaluated. A Japanese phase II study found the combination of cisplatin and 5-fluorouracil (5-FU) offered an improved tumor response above the then standard of cisplatin and vindesine. JCOG 9204 randomized 242 patients with squamous cell carcinoma (SCC) of the thoracic esophagus to receive surgery alone or surgery followed by chemotherapy with cisplatin and 5-FU. The chemotherapy group demonstrated an improved 5-year disease-free survival rate over surgery alone (55% *vs.* 45%, $P=0.037$). Overall survival, too, was improved at 61% for dual therapy as compared to 52% for surgery alone ($P=0.13$) (2).

A recent French study evaluated a similar regimen in 224 patients diagnosed with resectable adenocarcinoma (AC) of the distal esophagus, gastroesophageal junction, or stomach. Patients were randomized to receive induction chemotherapy with cisplatin and 5-FU versus surgical resection alone. The chemotherapy plus surgery group had a disease-free survival of 34%, compared to 19% ($P=0.003$) in the surgery alone group (8). Five-year survival was 38% versus 24% ($P=0.02$) in the chemotherapy plus surgery cohort and surgery alone cohort, respectively. Moreover, post-operative morbidity was similar in the two groups.

Induction chemotherapy versus adjuvant chemotherapy

Following the results of JCOG 9204, the same clinical group from Japan randomized over 300 patients with clinical stage II or III SCC of the esophagus in JCOG 9907 (3). Conducted between 2000 and 2006, the cohorts of patients received either preoperative or postoperative cisplatin and 5-FU. The primary endpoint was survival free of disease progression. With a median follow-up of 61 months, the 5-year overall survival in the induction group exceeded the 5-year overall survival in the adjuvant group 55% versus 43% ($P=0.04$). However, rates of recurrence were equivalent and those in the induction group underwent more surgical procedures for recurrent disease. Of those with recurrence, approximately one third were locoregional in nature. The authors made three conclusions with regards to the improved success of the neoadjuvant administration of chemotherapy: there was more frequent tumor downstaging, R0 resection was more often achieved, and completion of treatment protocols was possible in patients receiving induction chemotherapy.

Induction chemotherapy versus induction chemoradiotherapy

A phase III German study randomized 119 patients with gastroesophageal AC to induction chemotherapy (CT) or chemoradiotherapy (CRT). While the study was closed early due to poor accrual rates, a trend toward improved 3-year survival (47% *vs.* 27%, $P=0.007$) was noted in the chemoradiotherapy group. Additionally, pathologic complete response (pCR) was significantly increased (2.0% *vs.* 15.6%, $P=0.03$), as was the rate of lymph nodes free of tumor burden (36.7% *vs.* 64.4%, $P=0.01$), in patients who received induction chemoradiotherapy (9). This study was criticized, however, for being underpowered.

A similarly underpowered phase II trial from Australia randomized 75 patients with gastroesophageal AC to preoperative chemotherapy or chemoradiotherapy. Akin to the German study the advantages of the chemoradiotherapy with regards to overall survival (32 *vs.* 29 months, $P=0.83$) and progression-free survival (26 *vs.* 14 months, $P=0.37$) did not reach statistical significance. However, there was significant improvement in pCR (CRT 31% *vs.* CT 8%, $P=0.01$) and R1 resection rates (CRT 0% *vs.* CT 11%, $P=0.04$) (10).

Chemoradiotherapy

Concurrent chemotherapy and radiation therapy have been used in gastroesophageal cancer as both a definitive treatment and an induction therapy. Radiotherapy is used to treat locoregional tumor growth while chemotherapy is known to both control micrometastatic disease and serve as a sensitization agent for radiotherapy.

Definitive chemoradiotherapy

Definitive chemoradiotherapy is the standard of care for unresectable gastroesophageal tumors and patients medically unfit for surgery as a result of two major trials. RTOG 85-01 demonstrated a 5-year overall survival of 26% versus zero percent in patients with locoregional malignancy. There was, however, a high rate of locally recurrent and persistent disease (11). In an effort to improve the rate of local control, a US Intergroup study (INT 0123) randomized 236 patients all to receive definitive chemoradiotherapy with either 50 Gy (same dose used in RTOG 85-01) or 64 Gy. The increased dose neither yielded improved survival nor locoregional control (12).

Table 1 Randomized trials of induction therapies in esophageal cancer

Author/year (Ref.), study	Dates	Techniques evaluated	Agents/dose given	Patients/histology	Overall survival	pCR	Disease free survival	Notes
Van Hagen <i>et al.</i> 2012 (13), CROSS Trial	2004-2008	Induction CRT vs. surgery	Carboplatin, paclitaxel, 41.4 Gy	366 (75% AC)	CRT 47%; surgery 34% (P=0.003)	29%	NR	
Ando <i>et al.</i> 2012 (3), JCOG9907	2000-2006	Induction vs. adjuvant CT	Cisplatin, 5-FU	330 SCC	Induction 55%; adjuvant 43% (P=0.04)	2%	Induction 44%; adjuvant 39% (P=0.22)	
Ychou <i>et al.</i> 2011 (8)	1995-2003	Induction CT vs. surgery	Cisplatin, 5-FU	224 AC	Chemo 38%; surgery 24% (P=0.02)	NR	CT 34%; surgery 19% (P=0.003)	Included gastric tumors
Burmeister <i>et al.</i> 2011 (10)	2000-2006	Induction CT vs. CRT	Cisplatin, 5-FU, 35 Gy	75 AC	CRT 32 months; CT 29 months (P=0.83)	CRT 31%; CT 8% (P=0.01)	CRT 26 months; CT 14 months (P=0.37)	CT more R1 resections
Stahlet <i>et al.</i> 2009 (9)	2000-2005	Induction CT vs. CRT	Cisplatin, 5-FU, leucovorin, 30 Gy	119 AC	CRT 47%; CT 23% (P=0.07)	CRT 15.6%; CT 2% (P=0.03)	NR	Only 3-yr survival reported
Tepper <i>et al.</i> 2008 (4), CALGB9781	1997-2000	Induction CRT vs. surgery	Cisplatin, 5-FU, 50.4 Gy	56 (75% AC)	CRT 39%; surgery 16% (P= NR)	40%	CRT 28%; surgery 15% (P= NR)	

pCR, pathologic complete response; Gy, Gray; AC, adenocarcinoma; SCC, squamous cell carcinoma; 5-FU, 5-fluorouracil; CT, chemotherapy; CRT, chemoradiotherapy; NR, not reported.

Induction chemoradiotherapy

There are five completed randomized trials comparing neoadjuvant CRT to surgery alone (*Table 1*). Two trials are described in this section in detail. The remaining three trials are included in the meta-analyses reported in the following section. CALGB 9781 was a US study that failed to meet accrual goals of 475 patients but enrolled 56 patients (75% AC, 25% SCC) between 1997 and 2000. The patients were assigned to trimodality therapy (cisplatin and 5-FU concurrent with 50.4 Gy of radiation therapy) or surgery alone with a median follow-up of 6 years. Trimodality demonstrated an improved median survival of 4.5 years compared to 1.8 years in patients undergoing surgery alone (P=0.02). Five-year survival was 39% versus 16% [95% CI of OS hazard ratio (HR) 1.46 to 5.69], in favor of trimodality therapy. Lastly, a pCR rate of 40% was noted (4). However, this study must be considered in the context of incomplete accrual (56 accrued/475 targeted patients) and the relatively low survival with surgery alone.

The Dutch CROSS trial, considered the best evidence regarding induction therapy, enrolled 366 patients (75% AC, 23% SCC) who were randomized to trimodality

therapy with carboplatin and paclitaxel plus 41.4 Gy of radiation versus surgery alone for stage II and III esophageal and GE junction tumors. The trimodality group demonstrated a significantly better median overall survival (49.4 *vs.* 24 months, P=0.003) and higher R0 resection rate (92% *vs.* 69%, P<0.001). pCR was seen in 29% of patients in the trimodality group. Toxicity was low with chemoradiotherapy (7% with grade 3 hematologic effects) and preoperative treatment did not result in higher postoperative morbidity or early mortality in this group as compared with the surgery alone group. Patients treated with induction chemoradiotherapy followed by surgery had a 34% lower risk of death during follow-up (HR 0.657; 95% CI, 0.495 to 0.871; P=0.003) (13).

Induction chemoradiotherapy meta-analyses

A recent meta-analysis reviewed six randomized studies (n=929) comparing definitive chemoradiotherapy to surgery either alone or with induction therapy. An overwhelming majority of patients included in this meta-analysis had SCC (810/929). Despite variability in the exact therapeutic

regimen (total 30-46 Gy of radiation in patients receiving induction therapy; total 45-71 Gy of radiation in patients receiving definitive therapy; infusion versus bolus injection of leucovorin, cisplatin or carboplatin, and paclitaxel), the results were relatively consistent. Overall survival was equivalent between definitive medical therapy and surgery (HR 0.98; 95% CI, 0.8-1.2; P=0.84). There was trend toward higher rate of local recurrence (HR 1.54; 95% CI, 1.2-1.98; P=0.0007) and cancer-related deaths (HR 1.19; 95% CI, 0.98-1.44; P=0.07) in the medical treatment arms. However, treatment related mortality was lower (HR 0.16; 95% CI, 0-0.89; P=0.001) and protocol compliance was better in the nonoperative arms (14).

The most recent meta-analysis on esophageal cancer therapy reviewed 24 trials from 1983-2004 including comparisons of neoadjuvant chemoradiotherapy versus surgery alone (n=1,854), neoadjuvant chemotherapy versus surgery alone (n=1,981), and neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy in patients undergoing resection (n=194). The hazard ratio for all-cause mortality for neoadjuvant chemotherapy (HR 0.87; 95% CI, 0.79-0.96; P=0.005) and neoadjuvant chemoradiotherapy (HR 0.78; 95% CI, 0.70-0.88; P<0.0001) demonstrated a survival benefit of induction therapy (either chemotherapy or chemoradiotherapy) over surgery alone. Chemoradiotherapy maintained its advantage across histologic subtypes (absolute 2-year survival benefit 8.7%), and AC was more sensitive to either treatment than SCC. The advantage of chemoradiotherapy over chemotherapy as a preoperative treatment was apparent (HR 0.88; 95% CI, 0.76-1.01) but not statistically significant (P=0.07). There was no significant increase in post-operative mortality in the neoadjuvant treatment groups (15).

Discussion

The diagnosis of esophageal cancer typically portends a poor prognosis, with 50-60% of patients presenting with incurable locally advanced or metastatic disease. The two main histologic tumor types are SCC and AC. While the incidence of AC is increasing in the United States, worldwide SCC is the predominant tumor type. SCC and AC behave quite dissimilarly and there is little doubt that they represent two different diseases with varying pathogenesis, epidemiology, tumor biology, and outcomes. This difference is reflected in the 2010 TNM staging system, which provides separate stage groupings for SCC and AC of the esophagus. A comprehensive statistical review

of the studies on induction chemoradiation for esophageal cancer from 1992-2009 by Bollschweiler *et al.* demonstrated that the rate of pCR is equivalent between the two histologies. However, AC required higher radiation doses to achieve pCR than did SCC (16). Until studies investigating the benefit of induction therapy randomize patients not only by treatment but also by histology, the current data on induction therapy will be applied to the management of esophageal cancer regardless of histology.

Poor outcomes of surgical treatment alone prompted investigations on the use of adjunct therapies with the goal of improving treatment success. Early studies on radiation therapy demonstrated mild improvement in survival. However, a more notable improvement in overall survival was noted with adjuvant chemotherapy following resection. Later studies comparing induction chemotherapy with adjuvant chemotherapy demonstrated a survival benefit to induction therapy, particularly in that patients were more likely to complete treatment protocols, were more likely to be downstaged, and were more likely to achieve a R0 resection. Efforts towards investigating the role of induction chemoradiotherapy then pursued. While several trials were closed early due to low accrual, several meta-analyses of the multiple existing data sets were possible. It was confirmed that any induction therapy (chemotherapy or chemoradiotherapy) resulted in improved 5-year survival over surgery alone. A trend toward improved survival in patients who had received chemoradiotherapy compared to patients who received induction chemotherapy was noted, but was not found to be statistically significant. The benefit of induction therapy was noted in both SCC and AC, although AC was more responsive than SCC.

Summary

Surgical resection remains the primary treatment for patients with early stage (T1N0) esophageal cancer. In patients with locally advanced disease (\geq T2 or node-positive disease), however, induction therapy plays a critical role towards improving 5-year survival over surgery alone. Patients who received induction chemoradiotherapy appear to have a benefit over those who received induction chemotherapy. However, a clear advantage for chemoradiotherapy has not been established.

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Overall survival analysis of neoadjuvant chemoradiotherapy and esophagectomy for esophageal cancer

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Background: Patients treated with neoadjuvant chemoradiotherapy (NAC) followed by esophagectomy are more likely to have negative margins at resection, be downstaged, and have improved overall survival (OS). The specific aim of this study was to analyze OS outcomes using NAC followed by esophagectomy at a single, tertiary care academic medical center.

Methods: We retrospectively analyzed 106 patients that underwent NAC with platinum-based chemotherapy plus 5-fluorouracil (5-FU) or capecitabine followed by esophagectomy from September 1996 to May 2011. OS was analyzed by the Kaplan Meier method.

Results: Initial staging determined that of 106 patients, 62% had stage III (n=66), 31% stage II (n=33), and 7% had stage I disease (n=7). Following NAC, 92.5% (n=98) were resected with negative (R0) margins and pathologic staging revealed 59% (n=62) were downstaged, 9% (n=10) were upstaged, and 32% (n=34) remained at the same stage. A pathologic complete response (pCR) was achieved in 29% (n=31) of the cohort. Median OS was 35.2 months for all patients, 42 months for downstaged patients, 13 months when upstaged, and 17 months for those who remained at the same stage (P=0.08). OS by histological type was 30 months for adenocarcinoma and 71 months for squamous cell carcinoma (P=0.06).

Conclusions: NAC was effective in downstaging 59% of patients and effectively increased the chance for an R0 resection. These patients, in turn, had improved OS compared to the median OS. Patients with squamous cell carcinoma showed a trend towards more favorable OS.

Keywords: Esophageal cancer; neoadjuvant chemoradiotherapy (NAC); esophagectomy

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Introduction

In the United States alone nearly 18,000 new esophageal cancers are diagnosed and more than 15,000 deaths occur each year, illustrating the high mortality of this disease and the ongoing need for improved treatment strategies (1). Randomized controlled trials comparing neoadjuvant chemoradiotherapy (NAC) with surgery alone have demonstrated statistically significant improvements in overall survival (OS) (2-5). More recently, the CROSS trial modified traditional chemotherapy protocols, introducing weekly administration of carboplatin and paclitaxel with

concomitant radiotherapy. This resulted in a clear OS benefit for NAC versus surgery alone, with a median OS of 49.3 versus 24 months, respectively (5). These studies are consistent with several meta-analyses, which demonstrate that NAC significantly increases OS compared to surgery alone (6-9). Taken together, these studies highlight the utility of NAC in the treatment of esophageal cancer.

In addition to providing a clear survival benefit, NAC increases the likelihood of an R0 resection (6), which is associated with significantly improved OS in patients with esophageal cancer (10). Importantly, the pathologic stage following esophagectomy in patients treated with NAC is

a strong predictor of OS, and in particular, downstaging by NAC is associated with improved disease-free survival (DFS) and OS (11). Additional studies have demonstrated that patients with a pathologic complete response (pCR) following NAC and esophagectomy have high long-term OS rates (12,13).

Based on these and other data, multimodality treatment including NAC followed by esophagectomy has been established as standard of care for early stage (II-III), resectable esophageal cancer and that patients treated with NAC are more likely to have an R0 resection and pCR, more likely to be downstaged, and have improved DFS and OS. Therefore, the specific aim of the current study was to analyze OS outcomes of NAC at a single, tertiary care academic medical center. Additional objectives were to quantify the downstaging secondary to NAC, analyze the impact of downstaging on OS, and determine to what extent histologic subtype affects OS.

Materials and methods

Eligibility

The study was approved by the Institutional Review Board at Oregon Health & Science University (OHSU) and patient informed consent was waived. Medical records from patients with esophageal malignancies treated with NAC followed by esophagectomy at OHSU from September 1996 to May 2011 were selected from a prospective esophageal registry and retrospectively reviewed. Eligible patients included those with stage I-III esophageal cancer deemed medically operable by an experienced general or thoracic surgeon or medically inoperable who went on to receive NAC and were subsequently deemed operable. Patients with recurrent or metastatic disease, a history of previous malignancy, and as those unable to undergo chemoradiotherapy were excluded from the study. A cohort of 106 consecutive patients formed the basis of this selection.

Treatment plans

Patients who underwent NAC were treated with platinum-based chemotherapy (including cisplatin, oxaliplatin, or carboplatin) together with 5-fluorouracil (5-FU) or capecitabine concurrently with radiation. Additionally, 17 patients received a mitotic inhibitor (paclitaxel or docetaxel) in their regimen. Notable exceptions include

six patients who received platinum-based therapy but did not receive 5-FU or capecitabine and a single patient who received paclitaxel and 5-FU but did not tolerate a platinum-based agent. The majority of patients received 50.4 Gy radiation by standard fractionation, although cumulative dose ranged from 36-63 Gy. Surgical resection was performed via a transhiatal, Ivor-Lewis, or 3-field approach as previously described (14,15). Eligible patients underwent chemoradiotherapy at OHSU as well as local community hospitals, however all surgical resections were performed at OHSU by experienced general, thoracic, and/or oncologic surgeons.

Staging and pathology

Prior to administering NAC, all patients were staged by endoscopic ultrasound (EUS), computed tomography (CT), or positron emission tomography (PET). Following NAC and esophagectomy, post-operative pathological staging was compared to initial staging to analyze the effect of NAC and subsequent down- or upstaging. In this study, an R0 resection is defined as a curative resection, with microscopic examination of margins demonstrating absence of tumor cells while a R1 resection demonstrates the presence of tumor cells at the margin of resection. A pCR is defined as the absence of any residual tumor cells during histologic examination.

Survival analysis and statistical methods

Clinical follow up and the Social Security Death Index were used to determine length of survival for each patient. OS was analyzed by the Kaplan Meier method and survival curves were generated using R statistical software (version 2.13.1, R Development Core Team, Vienna, Austria). Inter-group comparisons were analyzed using a log-rank test and statistical significance was determined by P value <0.05.

Results

Patient and tumor characteristics

We analyzed 106 patients with esophageal cancer that underwent NAC followed by esophagectomy from September 1996 to May 2011. Patient characteristics as well as tumor histology and staging are presented in *Table 1*. The vast majority of patients in this study were male (n=88, 83%) and the median age was 61 (range, 31-86) years at

Table 1 Patient characteristics, histology, and staging	
Characteristic	n [%]
Total patients	106 [100]
Gender	
Male	88 [83]
Female	18 [17]
Age (years)	
Median	61
Range	31-86
Follow-up (years)	
Median	6.7
Range	2.6-17.5
Tumor histology	
Adenocarcinoma	92 [87]
Squamous cell carcinoma	14 [13]
Pre-NAC stage	
I	7 [6.6]
II	33 [31.1]
III	66 [62.3]
Post-NAC stage	
NED	31 [29.2]
I	5 [4.7]
II	43 [40.6]
III	27 [25.5]
Change in stage	
Up	10 [9.4]
No change	34 [32.1]
Down	62 [58.5]

Abbreviations: NED, no evidence of disease; NAC, neoadjuvant chemoradiotherapy.

the time of diagnosis. The predominant histology was adenocarcinoma (n=92, 87%) while 13% were squamous cell carcinoma (n=14). Prior to treatment, nearly two-thirds of patients presented with stage III disease (n=66, 62%), with stage IIIA being the most frequent presenting stage (n=51, 48%), while one-third had stage II (n=33, 31%) and 7% had stage I (n=7) disease. Median follow up was 6.7 (range, 2.6-17.5) years.

Pathologic response and post-operative staging

Following NAC and esophagectomy, a pCR with no evidence of disease histologically was achieved in 31 patients (29%) of the cohort. Moreover, the majority of patients had an

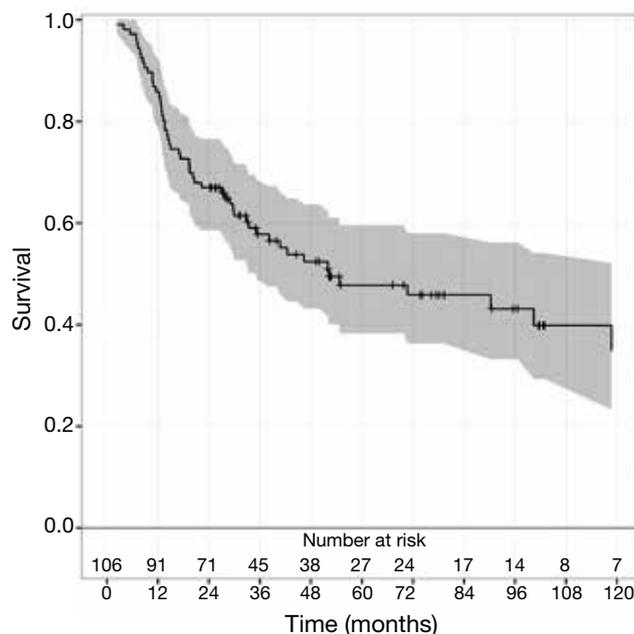


Figure 1 Overall survival for the 106 patients in our cohort.

R0 resection with negative margins microscopically (n=98, 92.5%). Grossly, 14 patients (13.2%) had an R1 resection with confirmed positive margins in 8 patients (7.5%). Expectedly, post-operative pathologic staging determined that 62 patients (59%) were downstaged following NAC while 9 patients (8%) were upstaged and 34 patients (32%) remained at the same stage (Table 1).

Survival analysis

The median OS was 31.2 months (range, 2 months -17 years) for all patients in this cohort (Figure 1). When analyzed by histologic subtype, there was a trend toward increased OS in patients with squamous cell carcinoma *vs.* adenocarcinoma (53 *vs.* 29 months, respectively; P=0.06, Figure 2). Interestingly there was a similar extent of downstaging between squamous cell carcinomas and adenocarcinomas (50% *vs.* 51.9%, respectively). However 35.7% (n=5 of 14) of squamous cell carcinomas had a pCR compared to only 24.5% (n=23 of 92) of adenocarcinomas. Moreover, there were a greater proportion of patients who had squamous cell carcinoma with stage III disease compared to those in the adenocarcinoma group (78.6% *vs.* 51.9%, respectively).

Importantly, there was also a trend toward increased OS for downstaged patients following NAC and esophagectomy (P=0.08, Figure 3). The OS for downstaged patients was

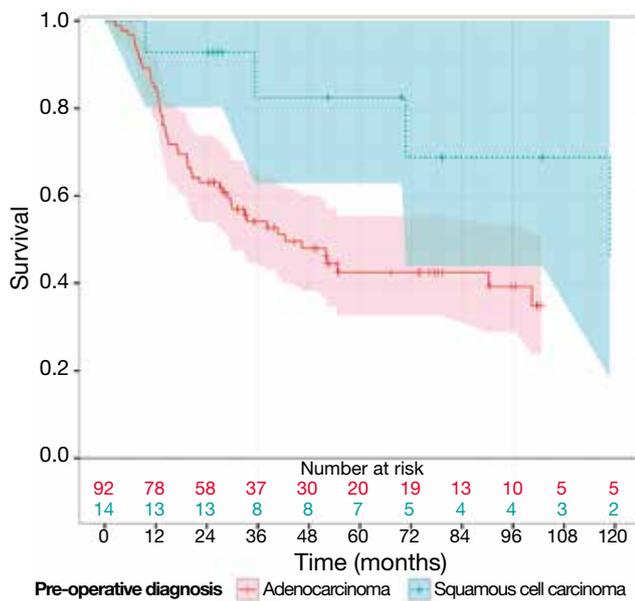


Figure 2 Overall survival (OS) by histological subtype in all 106 patients in our cohort (P=0.06).

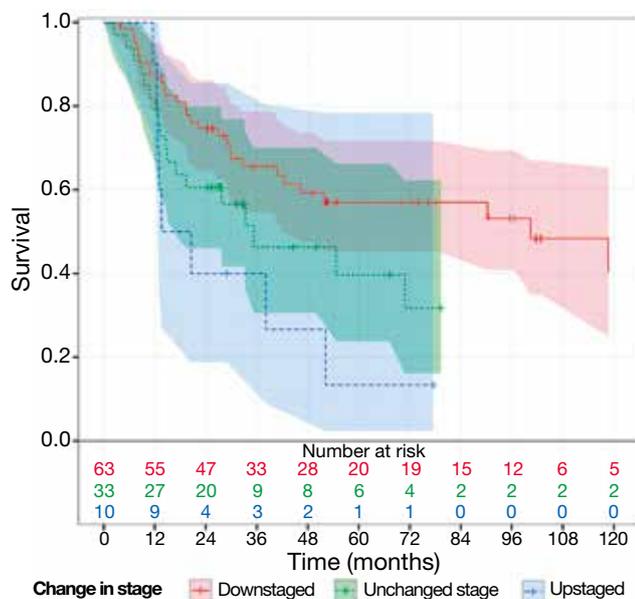


Figure 3 Overall survival as a function of post-operative tumor stage compared to initial stage following NAC and esophagectomy (P=0.08, n=106). NAC, neoadjuvant chemoradiotherapy.

40 months, upstaged patients was 20.6 months, and 27 months for those who remained at the same stage. Patients that had no evidence of disease on histological exam at surgery (pCR) had a median OS of 52 months.

Discussion

The results in this study demonstrate that NAC was effective in downstaging the majority of patients in this cohort and effectively increased the chance of an R0 resection. These findings are important, as pathologic stage following esophagectomy in patients treated with NAC is a strong predictor of OS. Consequently, downstaging by NAC is associated with improved DFS and OS (11). The patients in this study had improved OS survival compared to the median OS, suggesting patients from this tertiary care academic medical center treated with NAC and esophagectomy had similar outcomes compared to those in recent multi-center clinical trials (5,13). Additional studies have demonstrated that patients with a pCR following NAC and esophagectomy have high long-term OS rates (12,13). Our findings are consistent with these results and patients in our cohort that had a pathological complete response rate had a median OS of 52 months.

Interestingly, our patients with squamous cell carcinoma showed a trend toward more favorable OS compared to those with adenocarcinoma. The relationship between histologic subtype and OS in esophageal cancer is multifactorial and not completely understood at the present time. Indeed, studies in early stage esophageal cancer suggest squamous cell carcinomas are more susceptible to distant lymphatic spread and confer reduced 5-year OS rates (16). Conversely, analysis of patients with esophageal cancer and non-regional nodal metastasis revealed squamous cell histology was an independent positive predictor of long-term survival following esophagectomy (17). Given that the majority of patients in our cohort presented with stage III disease, our results are consistent with those studies in more advanced disease and suggest squamous cell histology confers a more favorable OS. However, as only 13% of patients in our study had squamous cell carcinoma, further characterization of the factors contributing to this observation is not possible within this current study.

While these results have contributed to the understanding of the effectiveness of NAC followed by esophagectomy for esophageal cancer at a single academic medical center, there are particular limitations of this study. Once such limitation was the variation in chemotherapy and radiation regimens used throughout the 15 years for which patients were analyzed in this cohort. These treatment alterations introduced additional variables difficult to account for given the heterogeneity of treatment plans and

improvement of surgical techniques over such a lengthy time period. Additionally, while this study identified a trend in improved OS compared to the median OS for downstaged patients following NAC and esophagectomy, this study was underpowered to detect a statistically significant difference.

In conclusion, this study analyzed OS outcomes for patients with esophageal cancer who underwent NAC followed by esophagectomy at a single, tertiary care academic medical center. This study determined that NAC was effective in downstaging the majority of patients and effectively increased the chance for an R0 resection. These patients, in turn, had improved OS compared to the median OS. Together, the results of this study support the rationale for NAC followed by esophagectomy in effectively downstaging patients and increasing the likelihood of an R0 resection and improved OS.

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Safety and efficacy of esophageal stents preceding or during neoadjuvant chemotherapy for esophageal cancer: a systematic review and meta-analysis

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Background: Patients with locally advanced esophageal cancer who require neoadjuvant therapy have significant dysphagia and may severely impair nutritional status. We conducted a meta-analysis to assess the efficacy of self-expandable metal stents prior to neoadjuvant therapy.

Methods: A systematic search was conducted using MEDLINE, PubMed, EMBASE, Current Contents Connect, Cochrane library, Google Scholar, Science Direct, and Web of Science. Original data was abstracted from each study and used to calculate a pooled odd ratio (OR) and 95% confidence interval (95% CI).

Results: Only nine studies comprising of 180 patients were included for analysis. The overall procedural success rate was 95% (95% CI, 0.895-0.977). There was a substantial decrease in the dysphagia scores standard difference in means (SDM) -0.81 [standard error (SE) 0.15, 95% CI, -1.1 to -0.51], similar increase in weight SDM 0.591 (SE 0.434, 95% CI, -0.261 to 1.442) and serum albumin SDM 0.35 (SE 0.271, 95% CI, -0.181 to 0.881). The incidence of major adverse events included stent migration 32% (95% CI, 0.258-0.395) and chest discomfort 51.4% (95% CI, 0.206-0.812).

Conclusions: Placement of stents in patients with locally advanced esophageal cancer significantly improves dysphagia and allows for oral nutrition during neoadjuvant therapy. Stents appear to be effective for palliating dysphagia. Stent migration was a common occurrence; however, migration may be a sign of tumor response to neoadjuvant therapy.

Keywords: Neoadjuvant therapy; self-expandable metal stents; esophageal cancer

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Introduction

The incidence and mortality from cancer of all types in the United States has decreased during the 1991-2006 timeframe (1). However, the opposite is true for esophageal cancer. Its incidence and mortality continue to rise. In 2010, estimated new cases of esophageal cancer number 16,640 in the United States, while deaths total 14,500 (1). The United States has seen an average increase of 20.6% per year in the incidence of adenocarcinoma of the esophagus since that time (2). Esophageal cancer is a highly lethal disease in which only one-third of patients present with resectable disease. Of this select group, the average 5-year survival is

only 35-45% (3). The overwhelming majority of patients have a fatal outcome, but advances in multimodality therapy appear to be improving the long term survival outcome for patients with locally advanced disease.

Most patients with advanced esophageal cancer have significant dysphagia, which contributes to weight loss and malnourishment. The majority of patients with esophageal cancer present with signs of malnutrition at the time of diagnosis as a result of both dysphagia and tumor-induced cachexia (4). Additionally, patients undergoing multimodal therapy have been shown to have significantly worse nutritional parameters than those only undergoing

resection (5). Radiation-induced esophagitis develops in 15-28% of treated patients' further aggravating dysphagia (6,7). Also, the side effects of 5-fluorouracil and cisplatin, the most common chemotherapy regimen employed to treat esophageal cancer, include nausea, vomiting, and diarrhea. Malnutrition reduces the potential response of the malignancy to chemoradiotherapy and impairs the patient's ability to tolerate the full course of treatment (8). In addition, the importance of adequate nutritional status prior to a major operation is well recognized (9).

Evidence clearly indicates that malnourished patients who undergo major operations are predisposed to infectious complications and worse postoperative outcomes (9-11). Nutritional deficiencies may also contribute to the trend of amplified perioperative morbidity and mortality among esophageal cancer patients receiving multimodal therapy compared with patients undergoing resection alone (12,13).

We hypothesized that patients treated with neoadjuvant therapy and who received removable stents would have better nutrition-related outcomes compared with those who were not stented. The objective of this study was to evaluate of the effectiveness of stents for improving the nutritional status of patients undergoing neoadjuvant therapy for esophageal cancer.

Methods

Study protocol

We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses PRISMA guidelines where possible in performing our systematic review (14). We performed a systematic search through MEDLINE (from 1950), PubMed (from 1946), EMBASE (from 1949), Current Contents Connect (from 1998), Cochrane library, Google scholar, Science Direct, and Web of Science to May 2013. The search terms included "esophageal cancer", "neoadjuvant therapy" and "stents", which were searched as text word and as exploded medical subject headings where possible. No language restrictions were used in either the search or study selection. The reference lists of relevant articles were also searched for appropriate studies. A search for unpublished literature was not performed.

Study selection

We included studies that met the following inclusion criteria:

- Studies identifying the population of patients with esophageal cancer undergoing stent implantation prior or during neoadjuvant therapy.

Data extraction

We performed the data extraction using a standardized data extraction form, collecting information on the publication year, study design, number of cases, total sample size, population type, country, continent, mean age and clinical data. The event rate and confidence intervals (CIs) were calculated.

Statistical analysis

Pooled event rate and 95% CI were using a random effects model (15). We tested heterogeneity with Cochran's Q statistic, with $P < 0.10$ indicating heterogeneity, and quantified the degree of heterogeneity using the I^2 statistic, which represents the percentage of the total variability across studies which is due to heterogeneity. I^2 values of 25%, 50% and 75% corresponded to low, moderate and high degrees of heterogeneity respectively (16). The quantified publication bias using the Egger's regression model (17), with the effect of bias assessed using the fail-safe number method. The fail-safe number was the number of studies that we would need to have missed for our observed result to be nullified to statistical non-significance at the $P < 0.05$ level. Publication bias is generally regarded as a concern if the fail-safe number is less than $5n + 10$, with n being the number of studies included in the meta-analysis (18). All analyses were performed with Comprehensive Meta-analysis (version 2.0), Biostat, Englewood, NJ, USA [2005].

Results

The original search strategy 418 retrieved studies (*Figure 1*). The abstracts were reviewed and after applying the inclusion and exclusion criteria, articles were selected for full-text evaluation. Of the articles selected, only nine studies (180 patients) met full criteria for analysis and are summarised in *Table 1*. The years of publication ranged from 2007 to 2012.

The overall procedural success rate was 95% (95% CI, 0.895-0.977). There was a substantial decrease in the dysphagia scores standard difference in means (SDM) -0.81 [standard error (SE) 0.15, 95% CI, -1.1 to -0.51] (*Figure 2*), similar

increase in weight SDM 0.591 (SE 0.434, 95% CI, -0.261 to 1.442) and serum albumin SDM 0.35 (SE 0.271, 95% CI, -0.181 to 0.881). The incidence of major adverse events included stent migration 32% (95% CI, 0.258-0.395) and chest discomfort 51.4% (95% CI, 0.206-0.812) (Figure 3).

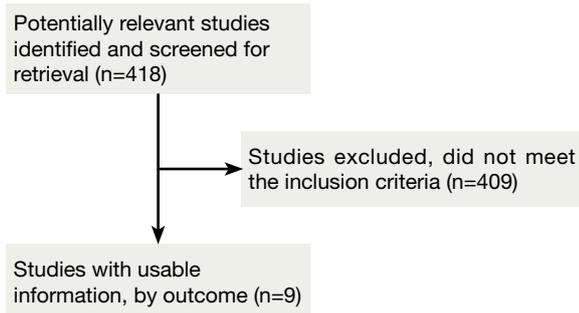


Figure 1 Flow of included studies.

Heterogeneity and publication bias

The heterogeneity of outcomes has been summarized in Tables 2 and 3. The reason for significant heterogeneity may be attributed to different population groups. No publication bias was detected using the Egger's regression model.

Discussion

The current standard of care is to offer neoadjuvant therapy to patients with locally advanced esophageal cancer (28). These patients receive three to six weeks of therapy before surgery (29,30). During oncologic therapy, dysphagia often increases due to mucositis and esophagitis induced by chemotherapy and radiotherapy. Others factors contributing to this include obstruction to sufficient dietary intake by luminal narrowing, anorexia and tumor cachexia. Improved baseline

Table 1 Characteristics of the studies included in the systematic review and meta-analysis

Author	Country	Year	Patients	Stent
Siddiqui <i>et al.</i> (19)	USA	2009	12	Polyflex stent
Adler <i>et al.</i> (20)	USA	2009	13	Polyflex stent
Siddiqui <i>et al.</i> (21)	USA	2007	6	Polyflex stent
Bower <i>et al.</i> (22)	USA	2009	25	Polyflex stent
Langer <i>et al.</i> (23)	Austria	2010	38	Self-expanding, plastic stents, covered metal stents
Pellen <i>et al.</i> (24)	UK	2012	16	Self-expanding removable metal stents
Siddiqui <i>et al.</i> (25)	USA	2012	55	ALIMAXX-E stent, WallFlex stent
Lopes <i>et al.</i> (26)	USA	2010	11	ALIMAXX-E, stent
Martin <i>et al.</i> (27)	USA	2009	5	Polyflex stent

Table 2 Overall odds ratio and 95% CI for patient outcomes

Outcome	Event rate	95% CI	I ²	P value
Successful placement	0.95	0.895-0.977	0	0.76
Stent migration	0.32	0.258-0.395	0	0.82
Chest discomfort	0.514	0.206-0.812	82.16	<0.0001

CI, confidence interval.

Table 3 Standard difference in means and 95% CI for patient outcomes

Outcome	Standard difference in means	Standard error	95% CI	I ²	P value
Dysphagia scores	-0.81	0.15	-1.1 to -0.51	59.72	0.01
Increase in weight	0.591	0.434	-0.261 to 1.442	86.98	<0.001
Increase in serum albumin	0.35	0.271	-0.181 to 0.881	70.68	0.01

CI, confidence interval.

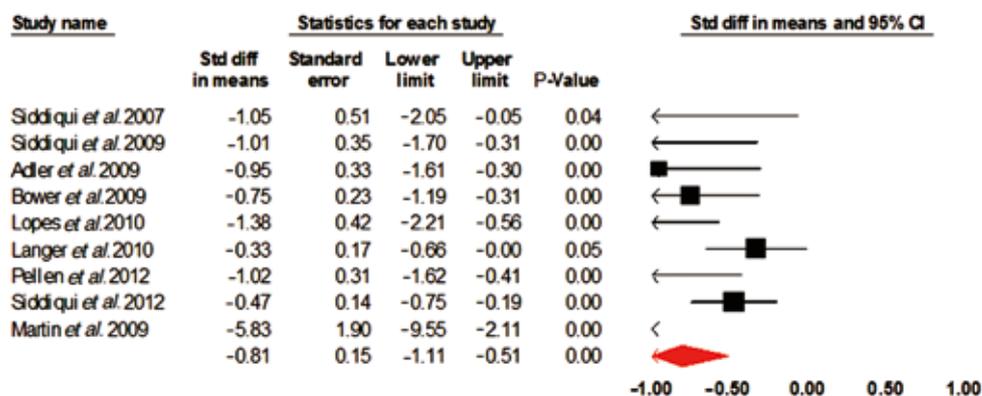


Figure 2 Dysphagia scores. CI, confidence interval.

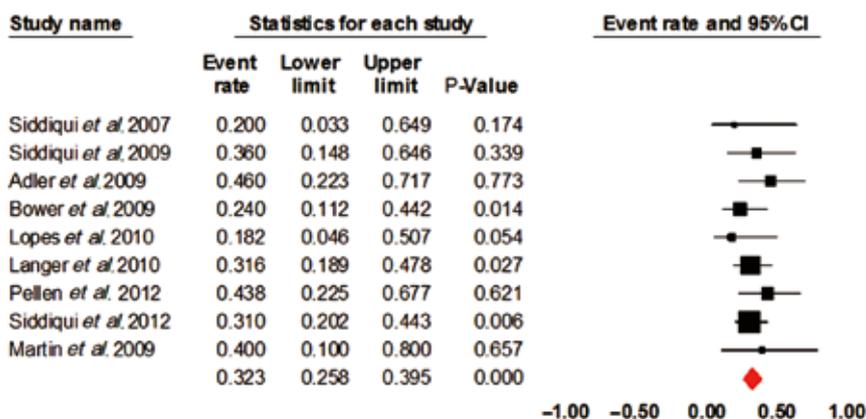


Figure 3 Stent migration. CI, confidence interval.

nutritional status independently predicts superior response to definitive chemoradiotherapy (albumin >35 g/L) and survival (BMI >18 kg/m²) in locally advanced esophageal cancer receiving nonsurgical treatment with curative intent (31). Therefore, the need for nutritional support is increased.

Options for nutritional supplementation during neoadjuvant therapy include parenteral nutrition or enteral nutrition given via a feeding tube. Parenteral nutrition is generally avoided because of increased costs, higher rates of infectious complications, and less efficacious reversal of malnutrition (32-36). Enteral supplementation requires feeding tube placement by either an open, laparoscopic or percutaneous technique. In fact, some centers advocate routine feeding tube placement in all patients undergoing multimodal therapy (37,38). Nasogastric feeding can be poorly tolerated and unsightly for the patient. It is associated with blockage, displacement, reflux and aspiration risks, and do not palliate dysphagia.

Percutaneous endoscopic gastrostomy (PEG) mandates that the tumor be negotiable with an endoscope and even if traversable, the pull-through technique may traumatize or transfer disease from the primary tumor. In the case of PEG tube placement, the potential exists for injury to the gastroepiploic artery rendering the stomach unusable as a replacement conduit for the esophagus (39). Besides procedure-related morbidity, tube placement delays chemotherapy by 1-2 weeks to allow for resolution of local inflammation and contamination that develops at the insertion site.

Jejunostomies arguably represent the mainstay of perioperative nutritional supplementation in esophagectomy patients and may be performed radiologically or surgically. However, both pre- and postoperative jejunostomies are associated with morbidity including displacement, obstruction, tube-site infection and peritonitis (40,41).

Preoperative esophageal stenting provides a possible

alternative to address the nutritional status of patients receiving multimodal therapy. Removable self-expanding silicone stents can be placed prior to neoadjuvant therapy and later removed endoscopically or at the time of surgery (27). The overall procedural success rate was good according to our analysis.

Complications

The overall incidence of stent migration was 32%. However, the majority of them did not require stent replacement because the stent migration probably was a result of tumor shrinkage from neoadjuvant therapy (25). Additionally, all the migrations were of stents that were deployed across the gastroesophageal junction and hence were at increased risk for migration. Stent migration correlated with restoration of an esophageal lumen that allowed for adequate oral nutritional intake (25). Another advantage of preoperative esophageal stenting not all patients with locally advanced esophageal cancer will have a curative resection. Patients who do not proceed to surgery can have their stents left in place as a palliative measure.

Quality of life (QoL)

The primary aim of treatment in patients with inoperable EC is to relieve dysphagia with minimal morbidity and mortality, and thus improve their QoL. Implantation of a SEMS has become established as a treatment modality for the palliation of malignant dysphagia. SEMS relieves dysphagia rapidly and improves the nutritional status. However, in most studies, relief of dysphagia is the only aspect of health-related quality of life (HRQoL) being measured, although physical, mental and social functioning and other EC-specific aspects of HRQoL are additional important outcome measures.

A randomized clinical trial comparing SEMS with plastic endoprotheses published in 2002 by University of Glasgow and Edinburgh (42) included 50 patients suffering from dysphagia due to an inoperable EC, and measured QoL using EORTC QLQ-30, a multi-dimensional cancer-specific QoL questionnaire and an EC specific questionnaire (EORTC OES-24), allowing QoL to be measured over 26 components relating to cancer in general and EC in particular. Although the authors found no statistical significance in any of the 26 components, 21 of the 26 components showed a trend towards the metal group, five were neutral and none favored plastic stents.

Shenfine *et al.* (43) in a randomized controlled trial

regarding the cost-effectiveness of palliative therapies for patients with inoperable EC studied QoL in detail using four different questionnaires including Spitzer QoL index, Karnofsky performance scale, Euroqol EQ-5D and EORTC QLQ-30. They also used proxy and self-administered questionnaires. These authors reported differences in the baseline QoL index favoring the non-SEMS group and went on to report one and six wk QoL data for the different treatment groups. Mean QoL index for the SEMS group at six wk was significantly lower than for the QoL index at baseline for the same group. The authors concluded that decreased QoL in the SEMS group at six wk, although not statistically significant, reflected the presence of pain following the intervention; the effect of pain on QoL may have significant implications for treatment with SEMS.

Sahlgrenska University Hospital (44) in their randomized controlled clinical trial published in 2005, compared endoluminal brachytherapy with endoscopic stent placement for newly diagnosed patients with advanced EC or gastroesophageal junction cancer, with a primary outcome being the detailed evaluation of HRQoL. Sixty-five patients eligible for the study were enrolled; 34 were randomized to stent treatment and 31 to brachytherapy. The authors assessed dysphagia improvement as a part of disease-specific HRQoL questionnaire EORTC OES-23 and found a statistically significant improvement in dysphagia grade, ability to swallow saliva, choking and coughing compared to baseline scores. There was no improvement in these outcomes for patients treated with brachytherapy. In an interim inter-group analysis at one mo a significant improvement in dysphagia scale favored the SEMS group. At three mo, some of the dysphagia-related parameters continued to show clinical improvement in the SEMS group but these did not achieve statistical significance. In the brachytherapy group, clinically significant improvements were noted in some of the parameters related to dysphagia at three mo and these were maintained at six mo. However, these data did not achieve statistical significance. General health QoL was measured using the EORTC QLQ-30 scale. In the stent group all functional scales and single symptom scales deteriorated compared to mean scores at inclusion. The largest deterioration was found for social function, followed by pain, role function and insomnia. In the brachytherapy group, a clinically relevant deterioration was found for most variables on the function and single symptom scales with physical function, global QoL and pain scales reaching statistical significance.

Madhusudhan *et al.* (45) in their prospective study

assessed the QoL using EORTC QLQ-C30 (version 3) and EORTC QLQ-OES 18 questionnaires before stenting, and at one, four and eight wk following placement of the stent. The results showed significant improvement following stenting. The general health scale and function scores increased significantly. Most symptom scores, except pain, showed improvement. The pain score deteriorated at one wk, as initial expansion of SEMS following its placement led to an increase in pain sensation. Over a period of two mo, the pain scores decreased to baseline values. The financial strain scores also showed a significant improvement. The studies did not specifically address the influence of stents on patient QoL; although anecdotally we have extrapolated that improved swallowing will result in improved QoL. Improvement of dysphagia is likely a result of stent placement along with decreased tumor burden from neoadjuvant therapy. A generous decrease in the dysphagia scores SDM -0.81 was observed in our investigation.

Other applications of stent implantation in perioperative and postoperative care of the carcinoma of the esophagus

Removable self-expanding silicone stents have previously demonstrated utility for relieving dysphagia from benign strictures and from both resectable and unresectable malignant disease (27,46-49). University Medical Centre Utrecht (50) performed a pooled analysis regarding placement of fully covered and partially covered SEMS (FSEMS and PSEMS) and SEPS for treating benign esophageal ruptures and anastomotic leaks. Twenty-five studies, including 267 patients with complete follow-up on outcome, were identified. Clinical success was achieved in 85% of patients and was not different between stent types (SEPS 84%, FSEMS 85% and PSEMS 86%, $P=0.97$). Time of stent placement was longest for SEPS (eight weeks) followed by FSEMS and PSEMS (both six weeks). In total, 65 (34%) patients had a stent-related complication. Stent migration occurred more often with SEPS [$n=47$ (31%)] and FSEMS [$n=7$ (26%)] than with PSEMS [$n=2$ (12%), $P\leq 0.001$], whereas there was no significant difference in tissue in- and overgrowth between PSEMS [12% *vs.* 7% (FSEMS) and 3% (SEPS), $P=0.68$].

Martin *et al.* (51) compared early esophageal stenting *vs.* repeated dilation in esophagectomy strictures. The median number of dilations were 2 (range, 1 to 3) for the 18 stent patients, with all stents placed for three months' duration, and 4 dilations (range, 2 to 12 dilations) in 24 patients treated solely with dilatation. An evaluation of median, high and low

total charges, net revenue, and direct margin demonstrated that the use of a removable stent after one failed dilation was more cost-efficient than repeated dilations.

In conclusion, self-expanding stents are a safe and effective method for endoscopic improvement of dysphagia in patients with malignant esophageal strictures receiving neoadjuvant therapy. The stents represent a new, alternative and cost-effective therapy for maintaining adequate oral nutrition. The QoL benefits gained by restoring the patient's ability to eat and enjoy food is admirable.

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Increased risk of death due to heart disease after radiotherapy for esophageal cancer

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Objective: To evaluate the risk of heart disease related death (HDRD) following radiation therapy (RT) for esophageal cancer (EC).

Methods: Using the Surveillance, Epidemiology, and End Results (SEER) database, two cohorts of patients with EC were created: (I) patients who received RT with their initial therapy; and (II) those who did not. Heart disease specific survival (HDSS) was analyzed using Kaplan-Meier methods. Cox proportional-hazards regression methods were used for univariate and multivariate analyses.

Results: We identified 40,778 patients with EC. A total of 26,377 patients received RT and 14,401 did not. HDSS analysis revealed increased risk of HDRD in those receiving RT ($P<0.05$), with an absolute risk of HDRD of 2.8%, 5.3% and 9.4% at 5-, 10- and 20-year, respectively. Log rank test of HDSS revealed the risk of HDRD became significant at 8 months ($P<0.05$). The following were associated with HDRD: RT, age, race, stage at presentation, time period of diagnosis, and known comorbid condition keeping one from esophagectomy. On multivariate analysis, RT remained predictive of HDRD [hazard ratio (HR) 1.46, $P<0.05$]. When considering only candidates for definitive therapy, RT remained predictive of HDRD on univariate (HR 1.53, $P<0.0001$) and multivariate (HR 1.62, $P<0.0001$) analyses.

Conclusions: The use of RT leads to increased risk of HDRD that is detectable as early as eight months from diagnosis. More research is needed to define optimal dose volume parameters to prevent cardiac death. Consideration should be given to this risk in relation to prognosis and the expected benefits of RT.

Keywords: Esophageal cancer (EC); radiation therapy (RT); heart disease

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Introduction

In the United States esophageal cancer (EC) represents 1.1% of all new cancer cases, with an estimated 18,170 new cases diagnosed in 2014 (1). Five year overall survival for this disease is poor but has improved over the last three decades. In 1975 only 4.0% of individuals diagnosed with EC survived 5 years. For individuals diagnosed in 2006, 5-year survival improved to 20.0%. This increase in survival partly reflects improvements and increased utilization of trimodality therapy [surgery, radiation therapy (RT) and chemotherapy (CT)] (2-6).

RT is an integral part of the current treatment paradigm. In a prospective, randomized trial for patients with locally advanced EC, van Hagen *et al.* demonstrated a doubling in median survival (24 *vs.* 49.4 months) with the addition of preoperative chemoradiotherapy (CRT) to esophagectomy (2). In counseling patients with EC, it is important to convey an accurate risk profile for both the short term and long term side effects of RT. Long term heart toxicity from RT has been described in both breast cancer and lymphoma, and includes pericardial disease, myocardial fibrosis, coronary artery disease (CAD), arrhythmias (including frequent persistent sinus tachycardia post-RT), and valvulopathies

(7-14). Cardiac complications from treatment of EC are not as well defined and given the heart's proximity to the esophagus, long term cardiac effects from RT are expected. With regards to short term cardiotoxic effects, imaging studies following CRT for EC have demonstrated increased myocardial perfusion abnormalities, decreased ejection fraction and pericardial effusions (15-17). These studies did not, however, correlate abnormal imaging findings with meaningful clinical outcomes, such as premature myocardial infarction or death from heart disease.

The purpose of this study was to define the long term risk of death from heart disease following RT for EC.

Materials and methods

The surveillance, epidemiology, and end results (SEER) database

The SEER Program is an authoritative source of information on cancer incidence and survival in the United States that collects data from 18 separate cancer registries representing approximately 28% of the US population. For each case submitted to the registry, important data are collected including: demographics, primary tumor site, tumor morphology and stage at diagnosis, first course of treatment, and follow-up for vital status. Data from the November 2013 SEER submission utilized for this project includes patients treated from 1973-2011 plus the Hurricane Katrina impacted Louisiana cases. Approval by an internal review board for our study was not required as all SEER database information is deidentified.

Case selection

Our study population included any patient diagnosed with EC in the database from 1973-2011. We used the SEER*Stat software (version 8.1.5) for data extraction. We identified our patient population by querying "Site recode ICD-0-3/WHO 2008" with the term "esophagus" as the primary site. For each case, we requested the following information: age, gender, year of birth, year of diagnosis, race, SEER historic stage, site specific surgery, reasons for not performing surgery, use of RT, presumed survival in months, vital status, and cause of death. Heart disease related death (HDRD) information was obtained from cause of death data extracted from the SEER database.

After extraction from the database, patients with unknown follow-up, survival less than 6 months or with

unknown utilization of RT were excluded. A 6-month survival cutoff was used to exclude patients who died in short succession to, or as a result of their initial treatments. Two cohorts were then created: (I) patients who received RT as part of their initial therapy; and (II) those who did not receive RT as part of their initial therapy.

Data analysis

Pearson chi-square analyses were used to compare treatment and tumor characteristics for categorical variables. Kaplan Meier methods were then employed to analyze the primary endpoint, death from heart disease. Only death from heart disease was counted as an event in Kaplan Meier analysis. Patients were censored if they died from any other cause. Univariate and multivariate survival analyses were performed using Cox proportional-hazards regression methods. To test when heart disease specific survival (HDSS) becomes significantly different among groups, log rank test of HDSS was performed using progressive follow-up cut off points starting at 6 months from diagnosis and increasing by one-month intervals. For the purpose of data analysis, extent of surgery was defined as esophagectomy versus other. Esophagectomy was defined as either partial or total esophagectomy. Other included: no surgery, unknown if surgery performed, photodynamic therapy, electrocautery, cryosurgery, and laser ablation.

Results

Initially, 71,595 patients were extracted from the SEER Registry with EC. After applying the exclusion criteria, 40,778 patients remained. The patient and tumor characteristics are listed in *Table 1*. A total of 26,377 patients received RT and 14,401 patients did not. Females, African Americans, patients diagnosed before 1990, patients with T3+ and/or node positive disease, and patients who did not undergo esophagectomy were more likely to receive RT.

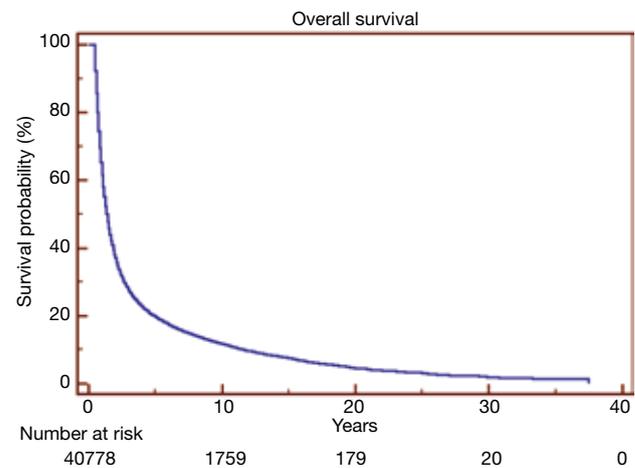
All patients

Overall survival for all patients at 5-, 10- and 20-year was 19.7%, 11.8% and 4.5%, respectively (*Figure 1*). HDSS analysis revealed increased risk for death from heart disease in those receiving RT as part of their initial therapy ($P<0.05$) (*Figure 2*). This survival analysis revealed an absolute risk of death from heart disease for those who received RT with their initial therapy of 2.8%, 5.3% and 9.4% at 5-,

Table 1 Patient and tumor characteristics

Characteristics	No RT, n=14,401 (%)	Yes RT, n=26,377 (%)	P value
Median follow-up (years)	1.4	1.25	
Age (years)			<0.0001
<50	1,179 (8.2)	2,079 (7.9)	
50-59	2,885 (20.0)	5,833 (22.1)	
60-69	4,409 (30.6)	8,545 (32.4)	
70-80	3,851 (26.7)	6,934 (26.3)	
80+	2,077 (14.4)	2,986 (11.3)	
Gender			0.0002
Female	3,370 (23.4)	6,603 (25.0)	
Male	11,031 (76.6)	19,774 (75.0)	
Race			<0.0001
White	12,235 (85.0)	21,039 (79.8)	
Black	1,404 (9.7)	3,927 (14.9)	
Other*	687 (4.8)	1,383 (5.2)	
Unknown	75 (0.5)	31 (0.1)	
Year of diagnosis			<0.0001
Prior to 1990	2,063 (14.3)	4,774 (18.1)	
1990-1999	2,713 (18.8)	5,365 (20.3)	
2000-2011	9,625 (66.8)	16,238 (61.6)	
SEER historic staging			<0.0001
Localized**	5,115 (35.5)	7,155 (27.1)	
Regional***	3,424 (23.8)	9,814 (37.2)	
Distant	3,273 (22.7)	5,865 (22.2)	
Unstaged	2,589 (18.0)	3,543 (13.4)	
Location			<0.0001
Cervical/upper thoracic	768 (5.3)	3,069 (11.6)	
Middle thoracic	2,273 (15.8)	5,931 (22.5)	
Lower thoracic	9,049 (62.8)	14,651 (55.5)	
Thoracic	357 (2.5)	989 (3.7)	
NOS	1,954 (13.6)	1,737 (6.6)	
Extent of surgery			<0.0001
Esophagectomy	9,568 (66.4)	10,288 (39.0)	
Other	4,833 (33.6)	16,086 (61.0)	

*, other race includes American Indian, Alaskan Native, Asian and Pacific Islander; **, localized defined as T1 or T2 with negative nodes; ***, regional defined as T3 or T4 with negative nodes or any T stage with positive nodes. RT, radiation therapy.

**Figure 1** Overall survival for patients alive at six months with esophageal cancer (EC).

10- and 20-year, respectively (*Figure 2*). Univariate analysis of both cohorts revealed that the following were found to be associated with risk of death from heart disease: RT, age, race, stage at presentation, time period of diagnosis, and known comorbid conditions keeping patients from esophagectomy (*Table 2*). Gender was not found to confer risk of death from heart disease. All variables found to be significant by univariate analysis were included in a multivariate analysis. RT remained predictive of death from heart disease on multivariate analysis [hazard ratio (HR) 1.46, 95% confidence interval (CI): 1.32-1.61, $P < 0.05$]. In addition, all other variables included remained predictive of death from heart disease (*Table 2*). Of note, by univariate analysis, risk of HDRD in patients with known comorbid conditions was increased (HR 1.63, 95% CI: 1.24-2.14, $P < 0.05$).

Time interval from diagnosis

Log rank test of HDSS performed at progressive monthly follow-up cut off points starting at 6 months from diagnosis revealed that the risk of HDRD became significant with a follow-up of 8 months with an absolute risk of HDRD of 0.4% ($P < 0.05$). On multivariable analysis (including significant variables from above), risk of HDRD remained significant at 8 months (HR 1.45, 95% CI: 1.14-1.83, $P < 0.05$).

Definitive therapy candidates

A subset analysis was performed on potential definitive

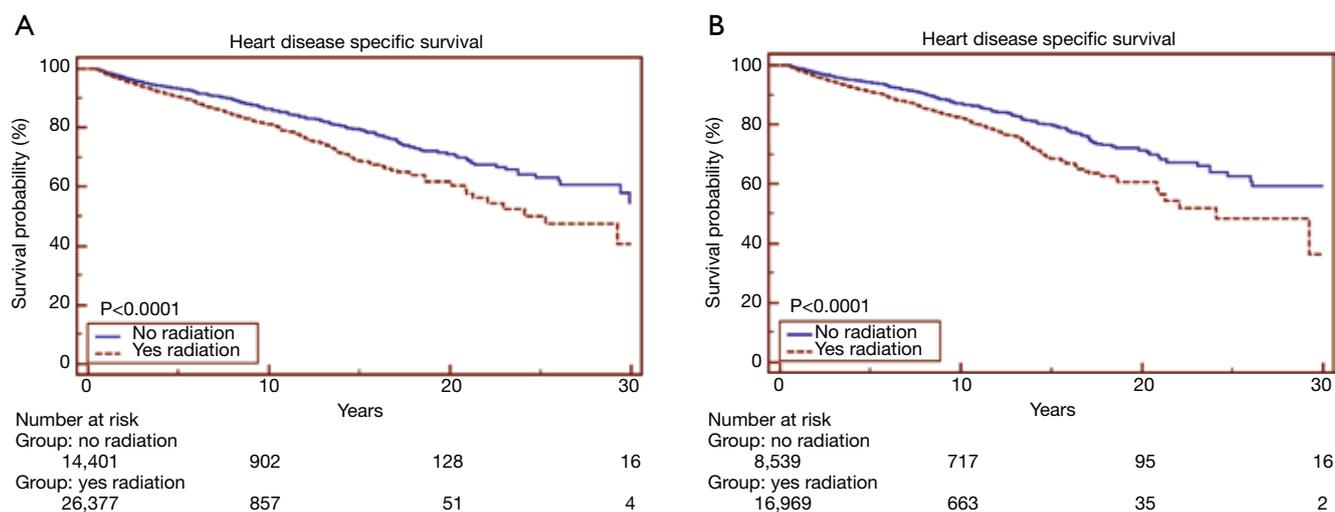


Figure 2 (A) Heart disease specific survival (HDSS) in EC with and without radiation (RT) in all patients surviving 6 months; (B) HDSS in EC with and without in patients with localized or regional disease. EC, esophageal cancer.

Table 2 Univariate and multivariate analysis for potential confounding factors for death from heart disease for all patients surviving 6 months

Variables	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
RT	1.42	1.29-1.57	<0.0001	1.46	1.32-1.61	<0.0001
Age	1.7	1.63-1.79	<0.0001	1.74	1.67-1.82	<0.0001
Gender	0.99	0.89-1.09	0.79			
Race	0.90	0.85-0.96	0.002	0.86	0.81-0.92	<0.0001
Extent of disease	1.06	1.05-1.08	<0.0001	1.04	1.02-1.05	<0.0001
Time period of diagnosis	0.72	0.68-0.76	<0.0001	0.72	0.67-0.76	<0.0001
Known comorbid conditions	1.63	1.24-2.14	0.0012	1.34	1.02-1.76	0.04

HR, hazard ratio; CI, confidence interval; RT, radiation therapy.

therapy candidates: patients presenting with localized or regional disease. After exclusion of those with distant or unknown stages, 16,969 and 8,539 patients remained in the RT and no RT cohorts, respectively. HDSS analysis revealed increased risk for death from heart disease in those receiving RT as part of their initial therapy (P<0.05) (Figure 2). This survival analysis revealed an absolute risk of death from heart disease for those who received RT with their initial therapy 3.0%, 4.8% and 10.9% at 5-, 10- and 20-year, respectively (Figure 2). By univariate analysis, the following were found to be associated with risk of death from heart disease: RT, age, race, stage at presentation, time period of diagnosis, and known comorbid conditions keeping patients from esophagectomy (Table 3). Gender was not found to

confer risk of death from heart disease. All variables found to be significant by univariate analysis were included in a multivariate analysis. RT remained predictive of death from heart disease (HR 1.62, 95% CI: 1.43-1.82, P value <0.05). In addition, all variables aside from extent of disease and known comorbid conditions remained predictive of death from heart disease (Table 3).

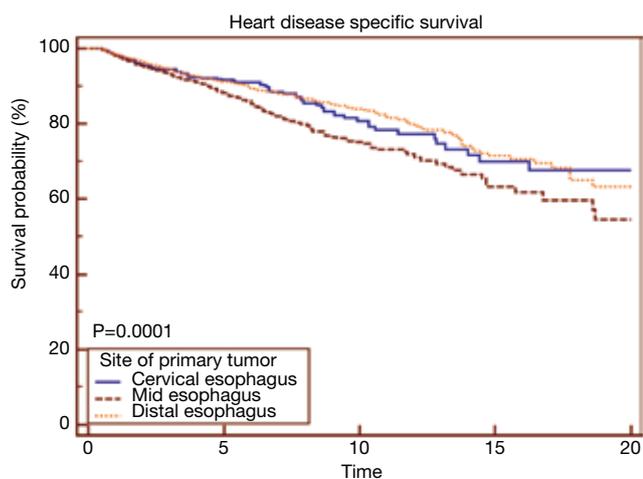
Heart disease by site of primary

When analyzing the cohort receiving RT by site of primary tumor, mid-esophageal location was associated with increased risk of death from heart disease (Figure 3) (P<0.05). When comparing cervical/upper thoracic esophageal versus

Table 3 Univariate and multivariate analysis for potential confounding factors for death from heart disease for patients with localized or regional disease

Variables	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
RT	1.53	1.36-1.73	<0.0001	1.60	1.42-1.81	<0.0001
Age	1.69	1.60-1.79	<0.0001	1.74	1.64-1.84	<0.0001
Gender	1.04	0.91-1.18	0.59			
Race	0.87	0.80-0.94	0.0003	0.84	0.78-0.91	0.0001
Extent of disease	0.84	0.75-0.95	0.004	0.92	0.82-1.03	0.12
Time period of diagnosis	0.75	0.70-0.81	<0.0001	0.73	0.67-0.78	<0.0001
Known comorbid conditions	1.84	1.33-2.55	0.0003	1.30	0.93-1.80	0.12

HR, hazard ratio; CI, confidence interval; RT, radiation therapy.

**Figure 3** HDSS by site of primary tumor in the esophagus. HDSS, heart disease specific survival.

mid-esophageal sites using univariate Cox proportional-hazards regression methods, mid-esophageal site was associated with increased risk of death from heart disease (HR 1.09, 95% CI: 1.02-1.16, $P < 0.05$). When comparing lower versus mid-esophageal sites, mid-esophageal site was again associated with increased risk of death from heart disease (HR 1.34, 95% CI: 1.17-1.53, $P < 0.05$). There was no difference in risk of death from heart disease when comparing cervical/upper thoracic versus distal esophagus (HR 0.97, 95% CI: 0.90-1.08, $P = 0.76$).

Discussion

The purpose of our study was to define the long term risk

of death from heart disease following RT for EC. We found that for all patients receiving RT and for definitive patients receiving RT, death from heart disease occurred at 1.46 and 1.62 times the rate of those not receiving RT, respectively. To our knowledge, this is the first study to quantify risk of death from heart disease after RT for EC.

Determining the risk of death from comorbid conditions and/or treatment toxicities has become increasingly important as combined modality therapy has resulted in long-term survival for more patients (2-6). Population-based databases such as SEER have the advantage of providing large numbers of patients to lend statistical power to answer questions such as these. In addition, SEER allows for identification of patients who were not deemed surgical candidates because of medical comorbidities, which helps differentiate the effects of these negative health factors compared to the side effects of treatment. It was found that patients not undergoing surgery as a result of comorbid conditions were at higher risk of dying from heart disease (HR 1.63, $P < 0.05$). However, when taking this into account via multivariate analysis, RT remained predictive of death from heart disease. These comorbidities may include heart disease or well-validated risk factors for heart disease including diabetes mellitus, smoking, hypertension, high cholesterol, family history and smoking (18,19). In addition, smoking (20) and other factors may potentiate the risk of RT induced cardiac toxicity.

Our analyses showed that age, race and time period of diagnosis were predictive of death from heart disease on both univariate and multivariate analyses. Time period of diagnosis was included as a variable as death from heart disease has decreased significantly over the last

three decades (21,22). RT remained predictive of death from heart disease despite inclusion of these covariates in multivariate analysis. Interestingly, later disease stages also were mildly predictive of risk of death from heart disease for all patients surviving six months (HR 1.06). A potential explanation for this may be that increased burden of disease results in increased cardiac strain, leading to death from cardiovascular causes. In addition, these patients potentially received more aggressive RT, CT or surgery leading to long-term heart sequelae.

A significant increase in HDRD was detected within the first year of diagnosis for patients receiving RT, a finding that remained significant by multivariate analysis. A similar timeline was demonstrated by Darby *et al.*, who showed a 16.3% increased relative risk for major coronary event from 0-4 years after RT for breast cancer (23). In Hodgkin's lymphoma, studies have also shown early increases in risk of heart disease (24-26). As clinicians, this information is important as screening and treatment of other potential cardiac risk factors should take place in close interval following RT to mitigate the risk of HDRD. Further research is needed to demonstrate the most effective measures to predict and manage heart disease before and after esophageal RT.

The results of this study point to the importance of minimizing cardiac dose in RT planning. Current knowledge about the dose/volume parameters that would best limit cardiac toxicity are based on series with limited numbers of patients, on models, and on experience with other cancer types. Current cooperative group esophageal chemoradiation protocols recommend limiting the volume receiving 40 Gy to less than 50%, and the mean heart dose to less than 27 Gy (27), which is expected to limit the rate of pericarditis to less than approximately 15% (28). A volume receiving 25 Gy of less than 10% is expected to limit the rate of cardiac mortality to less than one percent based on model estimates (29). A model using retrospective data on Hodgkin's disease and breast cancer has suggested that a uniform RT of 1/3 of the heart to 45 Gy would confer a 10% risk of long term cardiac mortality (29). In RT therapy for breast cancer, risk of HDRD has been shown to correlate with increasing dose, even in the setting of cardiac doses well below those seen in EC treatment. Darby *et al.* found that exposure of the heart to RT for breast cancer increased the relative rate of major coronary events by 7.4% per gray, with no apparent threshold (23). It is important to recognize that many of the patients in this study were treated before these currently understood cardiac risks and

dose parameters were known. Further work is essential to further define optimal dose/volume parameters in esophageal RT.

One method of limiting cardiac dose is through intensity modulated RT (IMRT). IMRT dosimetric studies show significant decreases in dose to the heart compared to 3D conformal techniques (3DCT) when treating EC (30-32). Dosimetric analysis of patients treated with IMRT showed significant reduction in average mean heart dose (22.9 *vs.* 28.2 Gy) compared to theoretical four field conformal plans in one study (33). A decrease in cardiac dose may have led to decreased deaths from heart disease in a study performed by Lin *et al.* comparing patients who received 3DCT versus IMRT for EC (34). Cancer specific mortality was similar, but death from other causes (including cardiac-related mortality) was increased in the 3DCT cohort, leading the authors to conclude that the dosimetric advantages of IMRT may translate to clinical benefit. However, a dosimetric comparison of dose delivered to normal tissues was not completed to validate their conclusion.

Any modification of radiotherapy field size or technique done in the interest of sparing cardiac dose should be done with consideration of the well-documented risk of locoregional failure (35), which points to the importance of locoregional RT. Local control remains an important component of patient outcomes.

Patients presenting with a primary esophageal tumor in the mid-esophagus were at higher risk of death from heart disease compared to the distal esophagus, which lies adjacent to the heart. The reasons for this observation are unclear. However, cardiac doses and field sizes are often elevated for mid-esophageal tumors because of the need to extend the field posteriorly to the celiac axis, which is covered because it is hard to fully dissect with an Ivor-Lewis Esophagectomy and it represents a major risk area for lymph node metastasis for all but cervical EC (36). It is also possible that cardiac structures, such as the atria, the semilunar valves (aortic and pulmonic), and the coronary artery origins, receive higher doses of RT in patients treated for mid-esophageal primary tumors, and that damage to these structures factors into subsequent cardiovascular events.

This study provides new insight regarding long term cardiac toxicity after RT for EC. There are, however, several important limitations. First, this study is limited by the inherent, biased nature of retrospectively collected data. Second, known risk factors for heart disease (age, race, and time period of treatment) were included in our multivariate

analysis to combat this bias; however, many potential risk factors for heart disease were not included in our analysis given the nature of the SEER database. Third, the SEER database does not include doses, and hence a dose response function could not be analyzed. Lastly, the SEER registry does not record information on CT, which is often used in conjunction with RT. Common chemotherapies used for EC are known to have cardiotoxic effects (37-40). It is possible that the increased risk for HDRD in patients receiving RT could reflect a combination of RT and chemo-related toxicities, and not RT-related toxicity alone.

In conclusion, while RT plays an essential role in the current treatment paradigm for EC, the use of RT in EC leads to increased risk of HDRD. Consideration of cardiac toxicity should always be done in relation to the probability of long term survival, other cardiac risk factors inherent to the patient, and the expected benefits of RT. Measures to avoid RT dose to the heart should be considered, and further work is necessary to elucidate the true risk of heart disease and the dose/volume parameters that may minimize this risk after RT for EC. The risk of HDRD becomes apparent within the first year from diagnosis. Further research is also needed to determine the most appropriate cardiac monitoring and management in the time before, during, and after definitive treatment of EC to best mitigate the risk of cardiac sequelae.

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Radiation therapy in the postoperative management of esophageal cancer

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Abstract: The optimal management of esophageal cancer is complicated since institutional preferences vary, patient characteristics often guide management, and there are data to support multiple approaches for locally advanced esophageal cancer. Although surgery is an important component of therapy, alone it results in unacceptably high rates of local relapse and poor long-term survival rates. Well-studied adjuvant approaches include upfront chemoradiation therapy with or without surgery, perioperative chemotherapy, adjuvant radiation or adjuvant chemoradiation. This review article seeks to examine thoroughly the role of postoperative therapeutic options for the management of esophageal cancer, and in so doing, also overviews prospective trials in the neoadjuvant, definitive and perioperative settings. Studies evaluating radiation field design are also discussed.

Keywords: esophageal cancer; radiation therapy; postoperative; chemoradiation therapy

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Introduction

Esophageal cancer is a rare disease with a poor prognosis, accounting for approximately 1% of all malignancies, with an estimated 16,640 cases in 2010 and 14,500 deaths (1). In the United States, the incidence of adenocarcinoma has risen, while squamous cell carcinoma has declined. It is now recognized in the AJCC staging system that these two histologies can carry different clinical outcomes (2). Institutional preferences and patient characteristics will often guide the management, as there are data to support multiple approaches for locally advanced esophageal cancer including upfront chemoradiation therapy (CRT) with or without surgery, perioperative chemotherapy, adjuvant radiation or chemoradiation. Surgery generally remains a mainstay in management of localized esophageal cancer, but as a single modality results in unacceptably high rates of local relapse and poor long-term survival rates, leading to the integration of radiation therapy and chemotherapy as neoadjuvant or adjuvant modalities. The results of many

studies have led to mixed results; therefore, there is no consensus about the optimal management of these patients.

There is a growing recognition that even in well clinically stage ultrasound T2 N0 esophageal cancer, between 20-25% may be upstaged to have pathologic T3 and/or node positive disease. Hence, these patients would often be referred for postoperative therapy. This review, while addressing the different sequencing of multimodality therapy, aims to focus mostly on how best to manage patients in the postoperative setting.

Definitive chemoradiotherapy

Along the lines of definitive management of esophageal cancer, it is important to discuss the RTOG 8501 trial which was instrumental in defining the superiority of chemoradiation over radiation therapy (3). The trial randomized patients to 64 Gy alone (n=60) to 50 Gy with concurrent cisplatin and 5-FU (n=61) for a total of 4 courses of chemotherapy. Overall survival at 2 years

	Pros	Cons
Preoperative therapy	<p>Smaller RT volumes and doses; sterilization of tumor bed in preparation for surgery</p> <p>Avoidance of surgery in those who may progress with systemic disease</p> <p>Tumor downstaging</p>	<p>Treatment based on clinical stage, may over treat patients</p> <p>Perception of increased surgical complications with preoperative CRT</p> <p>Preoperative dysphagia and issues of nutritional support due to tumor</p>
Postoperative therapy	<p>Treatment decision based on true pathologic stage, avoids CRT in patients who may not otherwise require it</p> <p>More accurate assessment of disease extent to allow for delineation of disease involvement</p> <p>Less concern about increase in perioperative morbidity and mortality after preoperative induction</p> <p>Dysphagia has been relieved and postoperative alimentation can be supported by surgically placed feeding tube, allowing for better tolerance of postoperative therapy</p>	<p>Larger RT volumes and difficulty of RT planning</p> <p>Usually higher radiation doses due to decreased oxygenation to the tumor bed</p> <p>Inability to assess radiation or chemotherapy tumor response</p> <p>Patient recovery after resection may be difficult precluding the use of postoperative CRT; reduced functional status after surgery</p>

increased from 10% with radiation alone to 38% in the combined therapy group ($p=0.001$). Distant and local recurrences were also reduced in the chemoradiation group. An update of this study showed that the 5-year survival rate with CRT was 27% compared to 0% with radiation alone (4). Approximately 85% of these patients had squamous histology. Of note, the 2010 NCCN guidelines recommend that T1 node positive or T2-T4 N_x esophageal cancer cases be treated with definitive chemoradiation or preoperative chemoradiation (50-50.4 Gy) followed by either esophagectomy (preferred) or observation for those achieving a complete clinical response, or for those with persistent local disease, either esophagectomy (preferred) or palliative treatment. It is recommended adenocarcinoma of the distal esophagus or GEJ be treated with preoperative chemotherapy followed by esophagectomy.

Preoperative versus postoperative therapy

From a radiotherapeutic standpoint, preoperative irradiation is advantageous compared to postoperative irradiation, because of an intact vascular supply allowing for improved oxygenation, generally smaller radiation portals and lesser radiation doses, sterilization of the operative bed, avoidance of surgery in patients with aggressive disease, and tumor downstaging. The advantage of postoperative therapy is the knowledge of the pathological stage to appropriately select

patients for therapy. The pros and cons of preoperative versus postoperative therapy are further discussed in *Table 1*.

With preoperative therapy, optimal tumor downstaging can result in complete pathological response of the tumor, portending improved survival outcomes for esophageal carcinoma. Pathological complete response (pCR) has often been used as a surrogate for efficacy of therapy and a measure by which various neoadjuvant therapies in esophageal cancer can be compared. Rohatgi *et al.* retrospectively analyzed 235 patients who underwent preoperative CRT for adenocarcinoma (82%) or squamous cell (18%) carcinoma of the esophagus and found that patients who experienced pCR had longer overall and disease free survival rates, fewer distant metastases, and less disease recurrences (6). At 37-month follow-up, patients with pCR had a 74% overall survival, compared to 65% for those with < 50% residual disease after CRT, and 40% for those with > 50% residual disease after CRT. In addition, pCR may be more predictive of survival for patients with adenocarcinoma than squamous cell carcinoma in those receiving preoperative CRT (7).

Preoperative chemotherapy

Investigators have evaluated multiple neoadjuvant regimens consisting of preoperative chemotherapy or perioperative chemotherapy. Despite the available studies, biases may still

remain about the benefit of perioperative chemotherapy versus CRT. RTOG 8911 compared surgery alone with chemotherapy followed by surgery, revealing no overall survival difference between the two arms. Patients who underwent less than an R0 resection had an ominous prognosis (5-year overall survival for R0 resection 32%, and R1 resection 5%) (8). Cunningham *et al.* evaluated surgery alone compared to a regimen consisting of 3 cycles of both preoperative and postoperative epirubicin, cisplatin, and 5-fluorouracil (ECF) for resectable gastroesophageal cancer and showed significant downstaging, but pathological complete response rates were zero. With the addition of chemotherapy, 5-year survival was improved from 23% to 36% with chemotherapy and progression free survival was also significantly improved (9). The Medical Research Council also demonstrated a significant 2-year overall survival benefit from 34% to 43% with the addition of 2 cycles of preoperative cisplatin and 5-FU ($p=0.004$) (10). A meta-analysis by Urschel *et al.* evaluated 11 randomized clinical trials including nearly 2,000 patients treated with neoadjuvant chemotherapy compared to surgery alone (11). Although higher rates of complete resection (R0) were seen with preoperative chemotherapy, no survival benefit was seen for combined chemotherapy and surgery. Preoperative chemotherapy is considered a standard option for resectable adenocarcinoma of the GEJ but remains controversial for the preoperative management of intrathoracic esophageal cancer.

Preoperative chemoradiotherapy versus surgery alone

Surgery is considered important in the management of esophageal cancers. The CALGB 9781 study randomized esophageal cancer patients (77% adenocarcinoma, 24% squamous cell carcinoma) to preoperative chemoradiation (cisplatin, 5-FU, and RT to 50.4 Gy) followed by surgery versus surgery alone (12). Despite poor accrual (56 out of a planned 475 patients), a significant survival advantage was seen in the trimodality group with 5-year survival of 39% versus 16% with surgery alone and median survival of 4.5 years compared to 1.8 years with surgery alone ($p=0.002$). The addition of chemoradiation in this setting afforded a convincing survival benefit and provided justification for the existing de-facto standard of care in patients with clinical stage II-III disease.

In an EORTC study reported by Bosset, 282 patients with squamous cell carcinoma were randomized to preoperative cisplatin with radiation therapy (split course

37 Gy using 3.7 Gy per fraction) followed by surgery versus surgery alone (13). Results showed significant improvements in favor of preoperative therapy for disease-free survival, local control, cancer-related deaths, and curative resection rates; however, there was no difference in overall survival (18.6 months for both groups). Significantly more postoperative deaths were seen in the group treated with preoperative CRT (12% versus 4% with surgery alone), mainly because of the higher number of patients with respiratory insufficiency, mediastinal infection or sepsis. The authors discussed that the increased number of postoperative deaths in the CRT could have been due to the “deleterious effects of high dose of radiation per fraction or of CRT on lung tissue.” They recommended future studies incorporate 2-Gy range fraction sizes, continuous radiation to overcome repopulation seen with split course therapy, and 5-FU chemotherapy. This trial therefore showed that preoperative CRT could prolong disease-free survival and local control but not overall survival although was likely limited by the radiation scheme.

An Australian study by Burmeister *et al.* evaluated 257 patients with both adenocarcinoma (63%) and squamous cell carcinoma (27%) of the esophagus (14). Patients were randomized to preoperative cisplatin and 5-FU with concurrent radiation therapy (35 Gy in 15 fractions) or immediate surgical resection. The CRT and surgery groups had significantly more complete resections with clear margins and fewer positive lymph nodes than the surgery alone group did. However, neither progression-free survival (16 months with CRT and surgery versus 12 months with surgery alone, HR=0.82, $p=0.32$) nor overall survival (22 months with CRT and surgery versus 19 months with surgery alone, HR= 0.89, $p=0.57$) differed between the groups. On subset analysis, patient with squamous cell tumors had a better progressionfree survival with CRT (HR 0.47, $p=0.014$) than those with non-squamous tumors (HR=1.02, $p=0.92$). Weaknesses of this trial included administration of only one cycle of chemotherapy and relatively low radiation doses.

Multiple trials have evaluated preoperative chemoradiation therapy with some improvement in survival outcomes and notable pathological complete response rates as detailed in *Table 2*.

Preoperative chemoradiotherapy versus definitive chemoradiotherapy

Some authorities believe that the role of surgery for

Table 2 Trials of preoperative chemoradiotherapy

Author	ACA/SCC (%) (n)	Regimens	pCR (%)	Survival	Other
Walsh (15)	100/0 (113)	Surgery vs. (5-FU + CDDP for 2 cycles) + RT (40 Gy/15 fx) → surgery	25%	3YS: 6% vs. 32% (sig)	Small patient numbers, nonstandard RT fractions, poor outcome of surgery alone
Bosset (13)	0/100 (282)	Surgery vs. CDDP for 2 cycles + RT (37 Gy/10 fx) → surgery	26%	3YS: 34% vs. 36% (NS)	Split course RT, nonstandard RT fractions, no 5-FU/single agent CDDP
Urba (16)	76/24 (43)	Surgery vs. (CDDP + 5-FU + vinblastine) + RT 45 Gy in 1.5 Gy BID	28%	3YS: 15% vs. 30% (NS)	Under powered
Burmeister (14)	62/37 (256)	Surgery vs. 5-FU + CDDP + RT (35 Gy/15 fx) → surgery	16%	3YS (ACA) 28% vs. 26% (NS); SCC: 35% vs. 50% (NS)	pCR more common in SCC, fewer R0 resections in surgery alone group, PFS was sig improved for CRT for SCC

Table 3 Trials postoperative radiotherapy versus surgery alone

Author	ACA/SCC (%) (n)	Radiation fields	Survival	Other
Xiao (24)	0/100 (495)	60 Gy to bilat SCV and mediast	5YS: 13% vs. 35% (sig)	No intention-to-treat analysis
Schreiber (27)	66/34 (1046)	Unknown (SEER analysis)	3YS: 18% vs. 29% (sig) for Stage III patients	No benefit for Stage II patients
Teniere (28)	0/100 (221)	45-55 Gy to bilat SCV and mediast + involved celiac LN	5YS: 19% in both arms (NS); node-positive: 38% vs. 7% (sig)	Improved local control in node-positive patients (85% vs. 70%, NS)
Fok (29)	(130)	49 Gy (curative resection)/52.5 Gy (palliat veresection) to 5 cm proximal and distal to tumor by barium swallow	Median survival: 15.2 mo (surgery) vs. 8.7 (postop RT)	Decreased LR for palliative resections with addition of RT 40% vs. 20% (sig); daily fraction size of 3.5 Gy possibly causing worse survival with RT

ACA, adenocarcinoma; SCC, squamous cell carcinoma; postop, postoperative; bilat: bilateral; SCV, supraclavicular regions; sig, significant; NS: non-significant; LR, local recurrence; YS, year survival; mediast, mediastinum; LN, Lymph nodes

Table 4 Prospective trials of postoperative chemoradiation

Author	ACA/SCC (%) (n)	Regimens	Survival	Other
MacDonald (34)	100 (556)	Surgery alone versus postoperative 5-FU + LV → RT (45 Gy) + 5FU + LV → 5-FU + LV	3YS: 41% (surg) vs. 50% (postop CRT)	LR reduced from 29% to 19% with radiation
Adelstein (5)	86/14 (50)	Surgery → 5-FU + CDDP + RT (50.4-59.4 Gy)	4YS: 51%	Phase II trial, local control: 86%

ACA, adenocarcinoma; SCC, squamous cell carcinoma; postop, postoperative; sig, significant; NS, non-significant; LR, local recurrence; YS, year survival; LV, leucovorin; CDDP, cisplatin

squamous cell carcinomas remains controversial based on two studies, one from France and another from Germany. The Federation Francophone de Cancerologie Digestive Study 9102 enrolled 444 patients with resectable squamous cell carcinoma (89%) or adenocarcinoma (11%), to receive one of two radiation schemes with 2 courses of concurrent cisplatin and 5-FU: 1) protracted radiotherapy (46 Gy over 4.5 weeks) (64% of participants) or 2) split course radiotherapy with two 1-week courses of 15 Gy with a 2 week break (36%) (17). 259 patients who responded to therapy were randomly assigned to surgery or additional chemoradiation. For the non-responders, they continued on a course of CRT with an additional 20 Gy for the protracted course and 15 Gy for the split course CRT. No significant differences were seen in median survival and (17.7 months in those who underwent surgery compared to 19.3 months in the definitive CRT arm) 2-year survival (34% in surgery cohort *vs.* 40% in the CRT arm, $p=0.44$). Nevertheless, the 2-year local control rate was higher with surgery (66%) compared to CRT (57%). The 3-month mortality rate was 9% in the surgery group and 1% in the CRT group. The results of this trial imply that for patients who respond to CRT, surgery may improve local control but not survival.

In a similar study design by Stahl *et al.*, 172 patients with locally advanced squamous cell carcinoma of the esophagus were randomized to either induction chemotherapy (5-FU, leucovorin, etoposide, and cisplatin for 3 cycles) followed by CRT (40 Gy with cisplatin and etoposide) followed by surgery or the same induction chemotherapy followed by CRT (total dose of 60-65 Gy with or without brachytherapy) without surgery (18). Overall survival at 2-years (40% with surgery *vs.* 35% with CRT) and median survivals (16 months *vs.* 15 months) were equivalent. Freedom from local progression was improved with surgery (64% *vs.* 41%, $p=0.003$). Surgery improved outcomes for non-responders to CRT who had 3-year survival rates of 18% with surgery compared to 9% with CRT alone. Treatment related mortality was also higher in the surgery arm (13% *vs.* 3.5%, $p=0.03$). The addition of surgery to CRT improved tumor control but not survival for squamous cell carcinomas.

Because many of the randomized clinical trials investigating surgery versus preoperative therapy have been underpowered, meta-analyses have been performed. GebSKI *et al.* showed a 13% absolute survival benefit at 2 years with the neoadjuvant CRT (hazard ratio 0.81, $p=0.02$) with similar results for squamous cell carcinoma (hazard ratio of 0.84, $p=0.04$) and adenocarcinoma (hazard ratio 0.75,

$p=0.02$). Neoadjuvant chemotherapy portended a 2-year absolute survival benefit of 7% with only a significant effect on all-cause mortality for adenocarcinoma of the esophagus and not squamous cell carcinoma (19). Urschel *et al.* also demonstrated improved 3-year survival, higher rates of R0 resection and tumor downstaging, and reduced local-regional recurrence with neoadjuvant CRT compared to surgery alone (20, 21). In sum, there does appear to be a survival benefit with the addition of CRT to surgery.

Adjuvant (postoperative) therapy

The goal of adjuvant radiation therapy for esophageal cancer is to decrease the risk of locoregional recurrence and in so doing, can contribute to a survival benefit. As noted earlier, it is not uncommon for patients with clinically staged ultrasound T2 N0 diseased to be upstaged to pathologic T3 or node positive status following resection (22). Rationale for postoperative radiotherapy includes advanced tumor stage (T3 or T4), nodal positivity, positive margins, or subtotal resection (23).

Postoperative radiation therapy versus surgery alone

Most of the series which will be discussed in the upcoming sections are based on populations of squamous cell carcinoma of the esophagus. There is a clear benefit in local control with the addition of radiation and possibly a survival advantage. However, many of these studies were conducted prior to the advent of PET staging by which we now can identify 10-15% of patients with occult metastatic disease which may change their management and survival outcomes.

The largest of these series is by Xiao and included 495 patients with squamous cell carcinoma of the esophagus who received postoperative radiation therapy ($n=220$) or surgery alone ($n=275$) (24). Radiation portals encompassed the bilateral supraclavicular areas and entire mediastinum to a total of 60 Gy (40 Gy prescribed to midplane and 20 Gy from horizontal portals, treated over 6 weeks). Survival was improved non-significantly with the addition of RT from 32% to 41% ($p=0.45$). Stage III patients had a distinct, significant overall survival improvement with the addition of RT from 13% to 35% at 5 years ($p=0.003$). This trial has been criticized for not employing an intention-to-treat analysis, since it excluded 54 patients who did not complete the planned course of treatment. The lack of informed patient consent called into question the ethical

standards of this trial (25).

In a separate retrospective analysis by Xiao *et al.* by extent of lymph node status, 549 patients were classified into three groups: Group 1: no lymph node involvement, Group 2: one to two positive lymph nodes, Group 3: three or more positive lymph nodes. The 5-year survival rate of patients with positive lymph nodes (Groups 2 and 3) was 18% with surgery alone compared to 34% with the addition of RT ($p=0.038$) (26). Also, for similar stage III patients, the number of lymph nodes predicted survival outcomes with 5-year survival at 58% for group 1, 31% for Group 2, and 14% for Group 3. Although there was no survival benefit for lymph node negative patients, those with one to two positive lymph nodes had an improvement in 5-year overall survival with the addition of RT from 24% to 45%. For patients with 3 or more positive lymph nodes, 5-year survival outcomes were 21% with RT versus no survivors with surgery alone. Not only is number of metastatic lymph nodes prognostic, but the addition of RT improved survival in patients with positive lymph nodes.

An analysis of the Surveillance Epidemiology and End Results (SEER) database evaluated the impact of adjuvant radiation in 1046 patients, who received surgery alone (65%) or postoperative radiation (35%) (27). For Stage III patients there was significant improvement in median (15 to 19 months), 3-year overall survival (18 to 29%) ($p < 0.001$), and disease specific survival (18 to 24 months) ($p < 0.001$) which was present for both adenocarcinoma and squamous cell carcinomas. No improvement in survival was seen with Stage II esophageal cancer (AJCC 6th edition) with the addition of postoperative RT. Multivariate analysis also confirmed that the addition of adjuvant RT was associated with an improved survival (HR 0.70, 95% CI 0.59-0.83, $p < 0.001$). This analysis is limited by the lack of information about chemotherapy, radiation fields and doses, and margin status.

Teniere *et al.* evaluated patients with squamous cell carcinoma of the middle to lower third of the esophagus and randomized them to observation ($n=102$) or postoperative RT ($n=119$) (45-55 Gy in 1.8 Gy per fraction to the bilateral supraclavicular regions, mediastinum, and involved celiac lymph nodes) (28). Patients were stratified by nodal involvement extent. Five-year survival in node negative patients was 38% versus 7% with involved nodes. Postoperative RT did not confer a survival benefit (5-year survival of 19% in both arms). Rates of local regional recurrence were lower in patients receiving postoperative radiation versus surgery alone (85% *vs.* 70%) but not statistically significant. Patients

without nodal involvement did have significant improvement in local regional recurrence with the addition of radiation therapy (90% *vs.* 65%).

Fok *et al.* included both squamous cell carcinoma and adenocarcinoma histologies in their study and stratified patients based on palliative ($n=70$) versus curative ($n=60$) resection prior to randomization to postoperative RT versus observation (29). Prescribed radiation doses of 49 Gy for curative resection and 52.5 Gy for palliative resection in 3.5 Gy per fraction were used, delivered to a 5 cm margin both proximal and distal to the initial tumor extent as delineated by barium swallow. Although they demonstrated a decline in local recurrence rates for those who underwent palliative resection followed by adjuvant RT (20% postoperative RT, 46% no RT, $p=0.04$), there was no statistical difference in local recurrence for those who had complete resection (15% with RT versus 31% with surgery alone, $p=0.06$). The overall median survival was significantly shorter for patients receiving postoperative RT (8.7 months) versus control (15.2 months). In patients with residual tumor in the mediastinum after resection, two died of tracheobronchial obstruction compared to nine in the control group. The authors concluded that the shorter survival of patients who underwent postoperative radiotherapy was the result of irradiation-related death and the early appearance of metastatic disease, although patients were less likely to have a recurrence obstructing the tracheobronchial tree. The major criticism of this trial has been the large fraction sizes and total dose delivered which may have contributed to the increased mortality rates and resulted in substantially higher gastric pull-up complications (37% with RT versus 6% with surgery alone) and six fatal bleeding events in the RT group. Similarly, Zieren *et al.* evaluated 68 squamous cell carcinoma patients who were randomized to either observation or postoperative RT, finding no difference in overall or disease-free survivals, but an increase in fibrotic esophageal strictures in the RT arm (30).

In a meta-analysis of postoperative radiotherapy trials, no significant difference in the risk of mortality with postoperative radiotherapy and surgery at one year compared with surgery alone was detected (RR, 1.23; 95% CI, 0.95 to 1.59; $p = 0.11$) (31). The rate of local recurrence with radiotherapy was lower in the trials of Xiao and Fok (24, 29), but the two trials of Teniere and Zieren (28, 30) noted this benefit was achieved at the expense of increased morbidity.

Given modern day techniques, improved treatment planning with strict dose volume histogram data, postoperative RT is expected to be safer with less toxicity

than previous studies. Based on the aforementioned studies, improvements in local control can be expected and is particularly important in the setting of nodal positivity or R1/R2 resection.

Postoperative radiation therapy versus postoperative chemo-therapy

The Japanese Esophageal Oncology Group evaluated postoperative radiotherapy (50 Gy to supraclavicular regions and upper mediastinum in 2 Gy/day) versus 2 cycles of cisplatin and vindesine (32). Of the 258 patients randomized, 73% had positive lymph nodes and 65-70% of patients had T3 or T4 disease, but histology was not delineated. Overall survival was no different (3-year survival rates were 51% (RT) and 52% (chemotherapy) and local recurrence rates were also equivalent. In contrast, in a retrospective study by Chen *et al.* of 366 patients with squamous cell carcinoma of the mid-thoracic esophagus, local recurrence rates were significantly lower with adjuvant radiation therapy compared to chemotherapy or observation (20%, 32%, 43%, respectively) (33).

Postoperative chemoradiation versus surgery alone

The INT-0116 trial published by MacDonald *et al.* prospectively randomized 556 patients with gastroesophageal junction (GEJ) (approximately 20%) or gastric adenocarcinoma patients, Stage IB-IV (AJCC 3rd Edition) who had undergone curative resection with negative margins to receive no further therapy or to postoperative chemoradiation (one cycle of 5-FU and leucovorin followed by concurrent radiation to 45 Gy with the same agents, followed by two additional cycles of 5-FU and leucovorin) (34). Patients were required to have sufficient caloric intake of 1500 Kcal per day. Because of the complicated nature of RT field design for gastric carcinomas, RT quality assurance was conducted prior to radiation delivery, and both minor and major deviations were detected in 35% of cases and corrected. Three-year overall survival improved with addition of chemoradiation from 41% to 50% as well as median survival from 27 months to 36 months with chemoradiation. (HR 1.35 for death with surgery alone group compared to adjuvant CRT, 95% CI 1.09-1.66, $p=0.005$). Local recurrence rates were also reduced from 29% with surgery alone to 19% with the addition of CRT. This trial provides the rationale for the

use of postoperative CRT for GEJ adenocarcinomas. In patients with GEJ adenocarcinomas, CRT is appropriate to improve survival and local control.

Of note, in the 6th Edition of the AJCC manual, GEJ carcinomas could be included in esophageal or gastric stage groupings and could produce different stage groupings depending on either the use of the esophageal or gastric stage groupings. GEJ carcinoma also previously included the locally advanced stages of T4 Nx or Tx N3 (Stage IV as stated above) when grouped with gastric cancer (35). In the AJCC 7th Edition, the GEJ carcinomas are now staged with esophageal, rather than gastric cancers, and include cancer within the first 5 cm of the stomach that extends into the GEJ or distal thoracic esophagus (2, 36). In addition, Stage IV disease currently only refers to M1 staging and does not include any locally advanced disease.

A phase II trial of postoperative CRT for poor prognosis esophagus and GEJ adenocarcinoma (86%) and squamous cell carcinomas (14%) investigated postoperative 5-FU, cisplatin and RT to 50.4-59.4 Gy in 50 patients with node positive or T3/T4 tumors (5). 4-year freedom from recurrence was 50%, distant metastatic control 56%, and locoregional control 86%, with a median survival of 53 months, comparing favorably with a historical median survival of 28 months in prior trials (37).

Bedard *et al.* retrospectively evaluated 28 node positive patients treated with surgery alone compared to 38 patients treated with surgery and postoperative CRT. There were more local recurrences with surgery alone (35% versus 13% with CRT, $p=0.09$) (38). Overall survival was significantly improved with postoperative CRT, and median survival was 47.5 months with CRT versus 14.1 months with surgery alone. Similarly, Rice *et al.*, on retrospective analysis, demonstrated a 28-month with CRT versus 14-month median survival with surgery alone (37, 39).

In modern day practice, it would be reasonable to add chemotherapy to postoperative radiation therapy as per NCCN guidelines, to maximize the benefit of radiosensitization with systemic therapy, especially if the patient could tolerate such a course. The available data do suggest that postoperative RT alone also would be appropriate. For adenocarcinomas of the GEJ, the MacDonald protocol is reasonable.

Postoperative chemoradiation versus postoperative radiation therapy alone

A non-randomized prospective study from Taiwan evaluated

postoperative patients with T3-4 and N0-1 esophageal carcinoma who were assigned to either CRT with weekly cisplatin followed by adjuvant chemotherapy consisting of cisplatin and 5-FU for four cycles (n=30) or postoperative RT alone (n=30) (39). RT was delivered to 55-60 Gy in both arms. A significantly better overall survival was seen with CRT (31 months *vs.* 21 months) and 3-year survival was improved to 70% with CRT versus 34% with RT alone (p=0.003).

Radiation therapy field design

Patients undergo a simulation with a contrast-enhanced computed tomographic (CT) scan, in the treatment position along with an immobilization device, usually in a supine position. Many investigators are utilizing four-dimensional CT scans (40). Appreciation of how the post-resection esophageal conduit moves with respiration, will aid the radiation oncologist in developing portals that cover sites at highest risk for loco-regional recurrence.

In pathological analysis of patients with esophageal and GEJ carcinoma, Gao *et al.* prospectively collected and evaluated 34 squamous cell carcinomas and 32 carcinomas of the GEJ to assess microscopic spread both proximally and distally in the specimens (41). For squamous cell carcinomas, mean microscopic tumor extension beyond the gross tumor was found to be 10.5+13.5 mm proximally (<30 mm in 94%) and 10.6+8.1 mm distally (<30 mm in 97%). In GEJ adenocarcinomas, the spread was 10.3+7.2 mm proximally (<30 mm in all cases) and 18.3+16.3 mm distally (<30 mm in 84%). Lymph node metastases were observed in 35% of patients with middle and lower esophageal squamous cell carcinomas and 47% of patients with GEJ carcinomas. The recommended Clinical Target Volume (CTV) margin was <30 mm in about 94% of esophageal cancers (pleural), except for distal microscopic spread in GEJ adenocarcinomas (pleural), in which 50 mm was needed to cover 94% of cases.

In a comparison of efficacy of regional and extensive clinical target volumes in postoperative radiotherapy for esophageal squamous cell carcinoma, 102 patients with T3/T4 or N1 disease treated with >50Gy were reviewed (42). In extensive portal irradiation (n=43) cohort, the CTV encompassed the bilateral supraclavicular regions, all mediastinal lymph nodes, the anastomotic sites, and the left gastric and pericardial lymphatics. In the regional irradiation group (n=59), the CTV was confined to the tumor bed and the lymph nodes in the immediate region of the primary lesion. The 1-, 3-, and 5-year survival rates between the

two groups were nearly identical. It is appropriate to use a regional portal which affords similar survival outcomes to an extended field and less acute and long-term toxicity.

At the University of Erlangen, Meier *et al.*, analyzed patterns of regional spread using pathology reports of 326 patients with adenocarcinoma of the GEJ who had undergone primary resection with >15 lymph nodes examined (43). Tumors were classified into Type I (distal esophagus), Type II (cardia), and Type III (subcardial) based on pathology and endoscopy reports. Marked esophageal invasion of GEJ Type II and III significantly correlated with paraesophageal nodal disease, and T3-T4 Type II/III had a significant rate of splenic hilum/artery nodes. Therefore, middle and lower paraesophageal nodes should be treated in T2-T4 Type I and II with > 15 mm of involvement above the Z line, and T3-T4 Type II. In addition, a study from Japan, in which 102 of cases were examined (85% squamous cell carcinoma), showed that the rates of lymph node metastases for the upper, middle, lower and abdominal esophagus were 37.5%, 32.5%, 46% and 70%, respectively (44).

It is helpful to know which lymph nodal stations are involved with metastatic disease in order to develop rationale field designs (41). Positive nodes may be seen in approximately one-third of resected middle and lower esophageal SCCA cases, with the subcardial, paraesophageal, and left gastric nodal stations being the most common sites (41). Distal adenocarcinoma lesions may harbor node positive disease almost half of the time with the left gastric and para-cardiac nodal stations being the most common (*Figure 1 and 2*).

In the postoperative setting, it seems reasonable to treat a regional field encompassing the preoperative intrathoracic esophageal tumor volume with a 3 cm cephalad and caudal margin for the clinical target volume (CTV), and 3-5 cm cephalad and caudal margins for GEJ carcinomas. Regional lymph nodes will also be treated as well as anastomotic sites. If daily image guidance techniques, such cone-beam CT scans are utilized, it may be possible to reduce the planning target volume (PTV). Postoperative doses of 45-50.4 Gy for R0 complete surgical resection with negative margins are appropriate to reduce long-term complications such as stricture. Higher doses of 54-60 Gy would be recommended for patients with R1 resections.

Conclusions

Adjuvant chemoradiation is a suitable option for the management of the resected, locally advanced esophageal

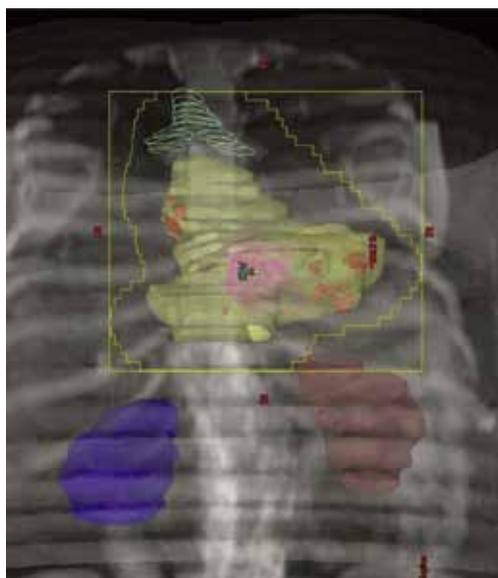


Figure 1 Lower esophageal ACA status post esophagectomy and partial gastrectomy with gastric pull up. Blue: right kidney; Brown: left kidney; Red: clips; Pink: preoperative tumor volume; Yellow: gastric remnant; Green: Carina. An anterior inferior oblique field is used to spare the kidneys.

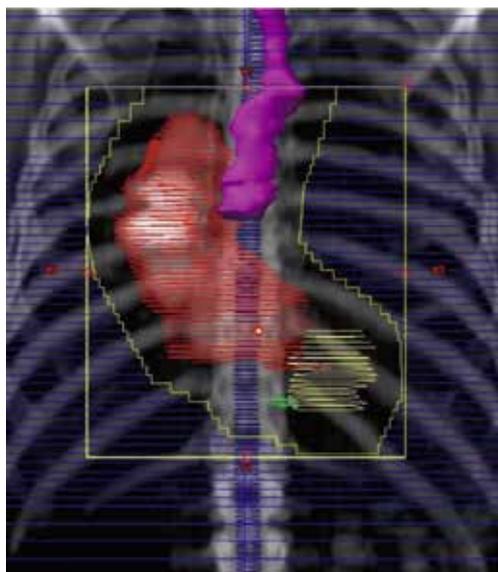


Figure 2 Mid-esophageal adenocarcinoma status post Ivor-Lewis esophagectomy. Red: stomach; Magenta: residual esophagus; Yellow: preoperative tumor volume; Blue: spinal cord. Anterior-posterior field demonstrated.

cancer patient, especially for T3/T4 disease, nodal positivity, and R1 or R2 resection. Doses of 45 to 50.4 Gy can be used for R0 to R1 resections, but for gross residual disease, a boost of 5-9 Gy may be considered. For tumors of the intrathoracic esophagus, concurrent cisplatin and 5-FU can be used, and for GEJ carcinomas, the INT-0116 protocol can be recommended. The available data suggests an improvement in local control and a possible survival improvement with the use of postoperative radiation therapy.

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None.

Footnote

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

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Concurrent chemoradiotherapy with protracted infusion of 5-fluorouracil (5-FU) and cisplatin for locally advanced resectable esophageal cancer

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Background: Neoadjuvant concurrent chemoradiotherapy (CCRT) has become the standard treatment for esophageal cancer (EC) in North America. The cisplatin/5-fluorouracil (5-FU) combination has been the most commonly used regimen. For the last 15 years we incorporated a daily continuous infusion of 5-FU and 2 doses of cisplatin into our neoadjuvant CCRT for potentially resectable EC.

Patients and methods: Between July 1997 and June 2012, 129 patients with locally advanced EC (T3 or N1 and higher), received neoadjuvant CCRT with cisplatin 75 mg/m² on day 1 and day 29 and continuous infusion of 5-FU (225 mg/m²/day) on the days of radiation.

Results: The median age of patients was 63 years, 85% had adenocarcinoma, 29, 74 and 26 patients had stage II, III and IVa disease respectively, 110 patients had N1 disease based on the American Joint Committee on Cancer (AJCC) 6th edition, 118 patients experienced weight loss during treatment. All patients completed treatment. Treatment was well tolerated with 14% of patients having ≥ grade 3 toxicity and 18 patients requiring hospital admission. Sixty-four percent of patients had surgical resection following CCRT, with disease progression and patient refusal being the most common reasons for not proceeding with surgery. An R0 resection was achieved in 96% of patients. A pathological complete response (pCR) was achieved in 45% of patients. With a median follow up of 26 months (1.2-144 months), 48/129 patients recurred and 60/129 died of their disease.

Conclusions: Our study has its limitation, however, and compared to the conventional chemotherapy regimens containing the cisplatin/5-FU doublet, our treatment strategy for locally advanced EC CCRT seems to be feasible and well tolerated.

Keywords: 5-fluorouracil (5-FU); cisplatin; esophageal cancer (EC)

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Introduction

Esophageal cancer (EC) is an aggressive and lethal malignancy. In the United States (US), 15,070 patients died from EC last year and the incidence is increasing worldwide (1). Advances in the treatment of patients with EC, which accounts for more than 400,000 deaths a year worldwide (1),

have been slow compared to other malignancies.

Surgical resection and definitive chemotherapy and radiation as a single modality treatment for EC produce poor long-term survival which prompts the evaluation of neoadjuvant therapy in the form of chemotherapy and/or radiation. Several clinical trials have explored the optimal

neoadjuvant therapy paradigm; however, stage migration and the temporal variation in incidence between the two major histological types of EC make interpreting and applying these trials to clinical practice a daunting task.

The poor long-term outcome associated with surgery alone and the high locoregional recurrence with definitive chemoradiation provided the rationale for evaluating neoadjuvant chemoradiation followed by surgery in patients with potentially resectable EC.

To evaluate the role of neoadjuvant chemoradiation followed by surgery in patients with potentially resectable EC, several randomized trials have compared neoadjuvant chemoradiation followed by surgery to other treatment modalities. The majority of these studies were criticized for being underpowered; the Irish trial reported by Walsh *et al.* randomized 113 patients to 40 Gy radiation in 3 weeks concurrently with cisplatin and 5-fluorouracil (5-FU) followed by surgery versus surgery alone (2). The trial resulted in significant survival improvement in survival; however, it was highly criticized for the low survival in the surgery only arm. A US study by the Cancer and Leukemia Group B (CALGB) intended to randomize 475 EC patients to neoadjuvant chemoradiotherapy with 50.4 Gy over 5.5 weeks concurrent with cisplatin and 5-FU and surgery versus surgery alone. The trial was closed prematurely. In the 56 randomized patients (3), median survival was 4.5 years for chemoradiation patients compared to 1.8 years for surgery only patients. More recently, the CROSS trial (4) randomized patients with resectable EC to receive surgery alone or to receive weekly carboplatin and paclitaxel for 5 weeks concurrently with radiation followed by surgery. Median overall survival (OS) was 49.4 months in the chemoradiotherapy-surgery group versus 24.0 months in the surgery group ($P=0.003$).

To date, several chemotherapy combinations have been used concurrently with radiation therapy for the neoadjuvant treatment of EC with the combination of cisplatin and 5-FU being the most common. Most clinicians use two courses of chemotherapy in weeks 1 and 5 (5-FU continuous infusion for 5 days, and cisplatin 75 mg/m² for 2 doses at the beginning and the end of treatment). Tepper *et al.* (3) used cisplatin 100 mg/m² and 5-FU 1,000 mg/m²/day for 4 days on weeks 1 and 5 concurrent with radiation therapy, while in the University of Michigan study (5), patients received cisplatin 20 mg/m²/day on days 1 through 5 and 17 through 21, 5-FU 300 mg/m²/day on days 1 through 21, and vinblastine 1 mg/m²/day on days 1 through

4 and 17 through 20. In older trials (6), patients received four courses of combined 5-FU (1,000 mg per square meter of body-surface area daily for 4 days) and cisplatin (75 mg per square meter on the first day).

The combined chemotherapy and radiation in the above mentioned trials is, as expected, more toxic than surgery or radiation treatment. Herskovic *et al.* (6) reported one death related to treatment and severe side effects reported in 44% of patients with 20% life threatening events. In the Irish trial (2), 10% of patients treated with combined therapy had grade 3 toxicity; two patients had grade 4 toxicity and one patient died during treatment. In the Michigan study (5), 78%, 39%, and 31% of patients experienced grade 3/4 neutropenia, neutropenic fever and thrombocytopenia respectively and 63% of patients required feeding tubes. In the CALGB 9781 trial (3), 57% of patients receiving preoperative therapy experienced grade 3 or greater hematological toxicity and 42, 34, 24 and 4 percent experienced esophagitis, infection, pain and treatment-related death respectively. Complete pathological response in these studies ranged from 25-40% and OS rate was between 10-39%.

At our institution, for the last 15 years, and in order to increase compliance and decrease toxicity, we adopted a regimen consisting of continuous infusion low-dose 5-FU combined with 2 doses of cisplatin concurrently with radiation as neoadjuvant treatment for patients with potentially resectable EC. Patients presenting at our institute with locally advanced (T3-T4) and/or lymph node (LN)-positive EC who were potentially eligible for surgery have been considered for cisplatin-based combination chemotherapy plus radiation. We analyzed the outcome of all patients that were treated with this regimen since 1997.

Patients and methods

Patients

Patients with potentially resectable EC (>T2) and/or LN-positive disease ($\geq N1$), who were treated with cisplatin/5-FU combination concurrently with radiation, and were scheduled for surgery between 1997 and 2012, were identified from an institutional review board (IRB) approved institutional EC database. These patients were discussed in multidisciplinary fashion with representatives from the departments of surgery, medical oncology, pathology, radiation oncology and radiology. All patients were analyzed for survival and toxicity including patients who did not have their planned resection due to poor

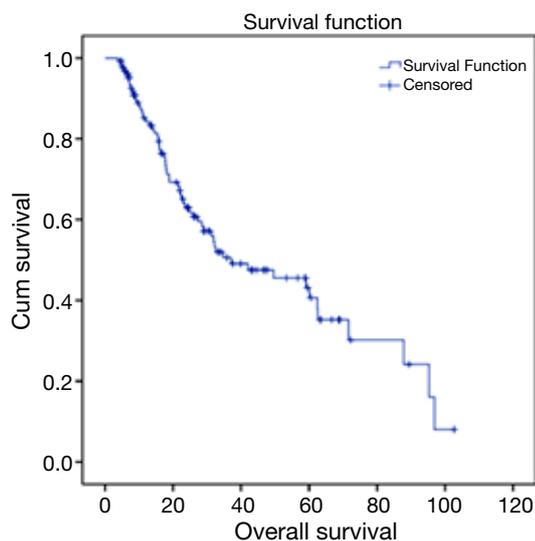


Figure 1 Kaplan-Meier plot of survival in patients with esophageal cancer treated with concurrent cisplatin and protracted infusion 5-fluorouracil (5-FU).

condition, metastatic or unresectable disease or refusal. Patients who refused surgery following neoadjuvant therapy went on to receive either more chemotherapy or other modality or they were simply placed on surveillance.

Staging

Staging was done according to the American Joint Committee on Cancer (AJCC) 6th edition, with clinical staging pre- and post-chemotherapy based on thoracic/abdominal and pelvis computer tomography (CT) scans, positron emission tomography (PET) scans, endoscopic ultrasound (EUS) and pathological staging after surgery. Prior to treatment, LN status was confirmed either by imaging/EUS only or in combination with fine-needle aspiration (FNA). All pathology specimens from the initial endoscopic biopsies were read and confirmed by pathologists with specialization in gastrointestinal malignancies. All operations were performed with curative intent and included removal of the primary tumor en bloc with its draining LN. Surgical approaches to esophagectomy included transthoracic, thoracoabdominal, and transabdominal techniques. Generally, the surgery was performed within 12 weeks after the final course of radiation.

Patients were seen and examined every 3 months for the first 2 years, then at every 6 months for years 2-5, and then annually. Routine follow-up exams included, physical exam, history, CT scans of chest/abdomen and pelvis. Endoscopy

was performed if clinically indicated.

Chemotherapy and radiation

Chemotherapy

Chemotherapy consisted of a cisplatin-based regimen. Patients who were considered unfit secondary to impaired renal function, co morbidity or low performance status received other regimens (Data not shown). A small number of patients received carboplatin/paclitaxel concurrently with radiation after the publication of the CROSS trial (4).

All patients received cisplatin 75 mg/m² on days 1 and 29. They received 5-FU continuous infusion 225 mg/m²/day Monday through Friday (*Figure 1*).

Evaluation of clinical response to therapy was performed by imaging 6-8 weeks following treatment and included CT scans and/or PET scans. Patients with no evidence of metastatic disease and good performance status were referred for surgical resection.

Radiation

Radiation therapy treatment technique was delivered at the discretion of the radiation oncologist; CT-based planning was performed with the patients lying supine with arms up on a Vac-Lock (Civco Medical Solutions, Kalona, IA) immobilization device. Four dimensional (4D) CT simulation scans were obtained to assess tumor motion by respiration.

A clinical target volume (CTV) encompassing a 3-4 cm superior margin, 3-4 cm distal margin, and 3-5 mm radial margin was contoured. For upper thoracic tumors, bilateral supraclavicular lymphatics were included. For distal esophageal and gastroesophageal cancers, celiac nodes and nodes along the left gastric artery were always included in the CTV. For gastroesophageal junction adenocarcinomas, other regional abdominal nodal groups were included based on the Siewert classification.

Surgery

All patients underwent restaging with PET-CT scans 6-8 weeks following chemotherapy and radiation. Patients who were without evidence of metastatic disease and who were deemed medically operable underwent either transhiatal or transthoracic esophagectomy using either open versus laparoscopic versus robotic esophagectomy at the discretion of the surgeon. Patients who underwent surgery were included in the pathological complete response (pCR) analysis. Patient was considered to have pCR if he

Table 1 Characteristics of patients with esophageal cancer treated with combined chemotherapy and radiation

Patient characteristics	Number of patients
Median age [years]	63 [28-76]
Sex	
Male	111
Female	18
Tumor type	
Squamous cell carcinoma	19
Adenocarcinoma	110
Tumor stage	
II	29
III	74
IVa	26
N1 disease	110

Table 2 Treatment toxicity of patients with esophageal cancer treated with combined chemotherapy and radiation

Toxicity	Number of patients (%)
Neutropenic fever	1 (0.6)
Nausea grade ≥ 2	0 (0)
Vomiting grade ≥ 3	0 (0)
Renal failure grade ≥ 2	5 (4.0)
Hospital admission	18 (14.0)

had no vital residual tumor cells in the surgical specimen.

Follow-up

Patients were seen at a minimum once a week during treatment and followed after treatment according to the National Comprehensive Cancer Network (NCCN) guidelines. Toxicity was graded based on Common Terminology Criteria for Adverse Events (CTCAE), version 4. Acute toxicities were considered if they occurred during or shortly after chemotherapy and radiation.

Data collection and statistical analysis

For this study, our IRB approved comprehensive EC database was queried according to our inclusion criteria for all patients who received cisplatin and 5-FU concurrently with radiation. A total of 129 patients out of 709 patients

were determined to be eligible for the analysis.

Recurrence rates, recurrence free survival (RFS) and OS were analyzed using the Kaplan-Meier method. OS was defined as the time from diagnosis to any cause of death: patients who were alive at the end of follow-up were censored at that date. Recurrence was defined as first relapse of disease, either loco-regional or distant. RFS was defined as the time from diagnosis until first recurrence or death.

Results

Demographic data

Between July 1997 and June 2012, a total of 129 patients were retrieved from an institutional EC database of 709 patients. Median age of patients was 63 years (range, 28-76 years). Fourteen percent of patients were female and 85% had adenocarcinoma. Twenty-nine, seventy-four and twenty-six patients had stage II, III and IVa disease respectively. One hundred and ten patients had N1 disease based on the AJCC 6th edition. Patient characteristics are shown in *Table 1*. All patients completed treatment.

Toxicities

In general, patients tolerated the concurrent chemotherapy and radiation well. All patients completed treatment. Even during hospitalization, patients continued to, at least, receive radiation therapy if clinically appropriate. Less than 10% of patients required dose reduction (25% of the total dose). Fourteen percent of patients had \geq grade 3 toxicity including constipation, chest pain, confusion, neutropenia in one patient each and anorexia in 18 patients requiring esophageal dilation and/or feeding tube placement +/- esophageal stent. Overall, 18 patients required hospital admission mostly for failure to thrive. Oral mucositis, diarrhea and neuropathy were rarely seen and were mostly grade 1. Treatment related toxicity is summarized in *Table 2*.

Outcome

Out of 129 patients, 83 (64%) patients underwent surgical resection between 37 and 149 days following concurrent chemoradiotherapy (CCRT) (median 62 days). R0 resection was achieved in 96% of patients. A pCR was achieved in 38 of 83 patients (46%) who underwent surgical resection. For the entire population, and with a median follow up of 26 months (range, 1.2-144 months); 37% of patients recurred,

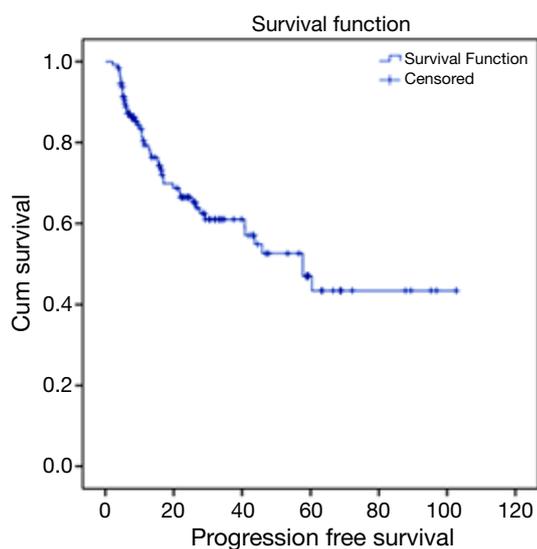


Figure 2 Kaplan-Meier plot of progression free survival in patients with esophageal cancer treated with concurrent cisplatin and protracted infusion 5-fluorouracil (5-FU).

38 patients recurred distally and 10 recurred locally. A total of 46% of patients died (*Figures 1,2*).

Discussion

Concurrent neoadjuvant chemotherapy and radiation in the management of potentially resectable T3-4 and/or LN-positive EC is the most accepted standard of care. Neoadjuvant therapy leads to better delivery of the drugs in untreated, well-vascularized tumors and helps in eradication of the micrometastases. The optimal chemotherapy to be used in this patient population is not known. Our data supports that neoadjuvant protracted infusion of 5-FU plus cisplatin concurrently with radiation therapy is feasible and efficacious in patients with potentially resectable EC. Our patients were able to receive all planned chemotherapy and radiation, allowing for optimal potential benefits of both treatments. Tolerability was reflected in the completion rates of the prescribed treatment. We report the highest pCR in patients who underwent surgical resection and comparable or even superior R0 resection rate and OS.

Several phase II and phase III trials have explored the role of two- or three-drug combination in the neoadjuvant therapy of EC. In these studies, different response rates and complete responses rates have been reported. No randomized trials have been conducted to directly compare chemotherapy regimens, and the optimal combination in

this setting remains undefined. The recently published phase III CROSS trial showed significant improvement in outcomes with neoadjuvant therapy compared to surgery alone; however, the dose of radiation used in that trial is lower than the dose recommended by NCCN consensus guidelines. Whether cisplatin/5-FU combination is superior to carboplatin/paclitaxel combination and the optimal doses of chemotherapy and radiation is yet to be established.

In our series, out of the 129 treated patients, all were eligible for survival and toxicity evaluation. Forty-five percent of patients who underwent surgical resection had a pCR which is comparable to the published literature. Grade 3 and 4 toxicities were uncommon. The low number of patients undergoing surgical resection in this series can be explained, at least in part, by the fact that it has been only recently that data has shown improved outcomes with incorporation of surgery. This single institutional data shows the feasibility of the use of neoadjuvant cisplatin and protracted 5-FU in the treatment of EC. Our study has several limitations given its retrospective nature; however, it is encouraging that our results are comparable with previously published data.

Goals of future studies should be to define the most active and safe chemotherapy regimens and radiation modalities. Selecting patients who will most likely benefit from platinum, taxanes or other agents is important and incorporating targeted therapy in adequately powered, randomized trials is necessary. Biomarker driven trials and correlation with treatment outcomes is crucial to identify patients most likely to benefit from personalized treatment approach.

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Immunotherapy for advanced gastric and esophageal cancer: preclinical rationale and ongoing clinical investigations

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Abstract: Gastric and esophageal cancers represent a major global cancer burden and novel approaches are needed. Despite recent improvements in outcomes with trastuzumab and ramucirumab the prognosis for advanced disease remains poor, with a median overall survival of 1 year. Comprehensive genomic characterization has defined molecular subgroups and potentially actionable genomic alterations, but the majority of patients do not yet benefit from molecularly directed therapies. Breakthroughs in immune checkpoint blockade have provided new therapeutic avenues in melanoma, and continue to expand into other tumor types, with ongoing investigations in gastrointestinal (GI) malignancies. The frequency of programmed death ligand 1 (PD-L1) overexpression, a putative response biomarker, approaches forty percent in gastric cancers. Translational studies and molecular classification suggest gastric and esophageal cancers are candidate malignancies for immune checkpoint inhibition trials and early clinical data is promising. Here we review the mechanisms, preclinical, and early clinical data supporting the role for immune checkpoint blockade in gastric and esophageal cancer.

Keywords: Immunotherapy; gastric; esophageal; cancer; programmed death ligand 1 (PD-L1); checkpoint; programmed cell death protein 1 (PD-1)

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Introduction

Despite therapeutic advances in oncology, the prognosis of late stage gastric and esophageal carcinoma remains exceedingly poor. Gastric cancer is the second leading cause of global cancer-related death, with an estimated 723,000 deaths in 2012 (1). Nearly 1 million new gastric cancers are diagnosed annually making this the fifth most common malignancy overall (1). Esophageal cancer affected an additional 456,000 people in 2012 and caused approximately 400,000 deaths, making it the sixth most common cause of cancer-related death and eighth most common cancer globally (1). While the overall incidence gastric cancer is on the decline, the prevalence of esophageal cancer is rising (2-4).

The majority of gastric and esophageal cancer patients present with advanced disease and evidence-based therapeutic options are limited. First line systemic therapy

for metastatic disease is largely based on a platinum/5-fluoropyrimidine backbone, which produces moderate survival benefits in patients with good performance status (5). The addition of an anthracycline or taxane to platinum/5-fluoropyrimidine regimens may provide additional survival benefit in select patients (5-7). In Her2 amplified adenocarcinoma incorporation of the anti-Her2 monoclonal antibody, trastuzumab, significantly improves survival, and is the first molecularly targeted agent to improve outcomes in advanced gastric and esophageal cancers (8). The recently approved vascular endothelial growth factor receptor 2 (VEGFR-2) antibody ramucirumab has also been shown to improve survival in patients with gastric and gastroesophageal junction (GEJ) adenocarcinoma who progressed on first line therapy (9). While ramucirumab and trastuzumab are meaningful additions to the gastroesophageal armamentarium, overall

survival outcomes remain poor and novel approaches are needed.

Immunotherapy has caused a paradigm shift in the treatment of melanoma and its use continues to expand to include other tumor types (10-12). With increasing clinical experience, biomarker analyses, and improvements in preclinical models, the potential role for immunotherapy in gastric and esophageal cancers is emerging. The major approaches to harnessing immunotherapeutic anticancer effects have come from the development of inhibitory antibodies which modulate immune check points, such as cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed death ligand 1 (PD-L1). Here we review the basic immunotherapeutic mechanisms of CTLA-4 and PD-L1, existing preclinical data, and available clinical results incorporating immunotherapy into the treatment of advanced gastric and esophageal cancers.

Immunotherapeutic mechanisms

Numerous co-stimulatory and inhibitory molecules interact to form a network of activating and inhibitory pathway “checkpoints” which serve to regulate the human immune system. This molecular interplay allows for uninterrupted pathogen-fighting capabilities while simultaneously preventing autoimmunity and persistent immune response (13). Many of these pathways converge on T lymphocytes, which play a central role in triggering adaptive immune responses to both foreign pathogens as well as neoplastic cells. However, in cases of malignancy, tumor cells frequently escape immune detection by hijacking elements of these checkpoint pathways thereby inhibiting T cell effector function. Ultimately this results in reduced tumor surveillance and tumor recognition (14). The development of antibodies to immune checkpoints, known collectively as immune checkpoint inhibitors, has now translated to improved patient outcomes in several malignancies (11,15).

CTLA-4 is a ubiquitous T-cell receptor belonging to the immunoglobulin superfamily. CTLA-4 shares many similarities with the T-cell co-stimulatory protein CD28, and like CD28, is activated upon binding with CD80 (B7-1) or CD86 (B7-2) (16). In fact, CTLA-4 has been shown to compete with CD28 for CD80 and CD86 binding (17). However, unlike CD28, which stimulates T cells, the effects of CTLA-4 activation differ between T-cell subsets. In CD4⁺ helper T cells activated CTLA-4 down modulates activity, whereas in CD4⁺T regulatory cells (T_{Reg}) CTLA-4

up-regulates function (18). The net effect of endogenous CTLA4 activation is immune tolerance (19) (*Figure 1*).

Similarly, the T-cell surface receptor PD-1, also a member of the immunoglobulin superfamily, inhibits T cell function upon binding to its ligands PD-L1 (B7-H1) and PD-L2 (B7-DC) (20) (*Figure 1*). The PD-1 ligands are also members of the B7 family, although the inhibitory pathway that PD-1 participates in is thought to be mutually exclusive to that of CTLA-4 (21). PD-L1 is expressed on T cells, B cells, NK cells, dendritic cells, monocytes/macrophages, mast cells, and various tumor types where it is thought to play a role in tumor immune escape (22) (*Figure 1*). It has been suggested that while CTLA-4 may play a significant role in early immune response, primarily occurring in lymphoid tissues, PD-1 whose expression is up regulated after T cell activation in peripheral tissues may be more involved in late immune response (23). Although CTLA-4 inhibition highlighted the power of immune checkpoint modulation, therapeutic focus is shifting towards the use of PD-1 and PD-L1 blockade, which offer benefits of potentially fewer side effects and perhaps improved outcome data.

Preclinical observations in gastric and esophageal cancers

Distribution of PD-L1/PD-L2

PD-L1 is broadly expressed in many human tissues and organs. In addition to immune cells PD-L1 has been identified on endothelial cells, mesenchymal stem cells, cells of the eye and placenta (22). In contrast, PD-L2 expression is restricted to lymphoid tissues and has only been observed on macrophages and dendritic cells, suggesting non-redundant roles for these two ligands (24). Varying levels of PD-L1 and PD-L2 are expressed on a majority of human cancer cells including: melanoma, renal cell carcinoma (RCC), multiple myeloma, breast, bladder, colon, and lung cancer (22,25,26). Melanoma, RCC, and non-small cell lung cancer (NSCLC) tumor series have shown high levels of PD-L1 expression by both immunohistochemical and RNA analysis, ranging from 66-100% (27-29).

Until recently, few studies had attempted to quantify PD-L1 and PD-L2 expression in gastric and esophageal cancers. Work by Ohigashi *et al.* using immunohistochemical and RT-PCR approaches to examine expression from 41 esophageal squamous cell cancer (ESCC) patients found that 43.9% of samples had either PD-L1 or PD-L2

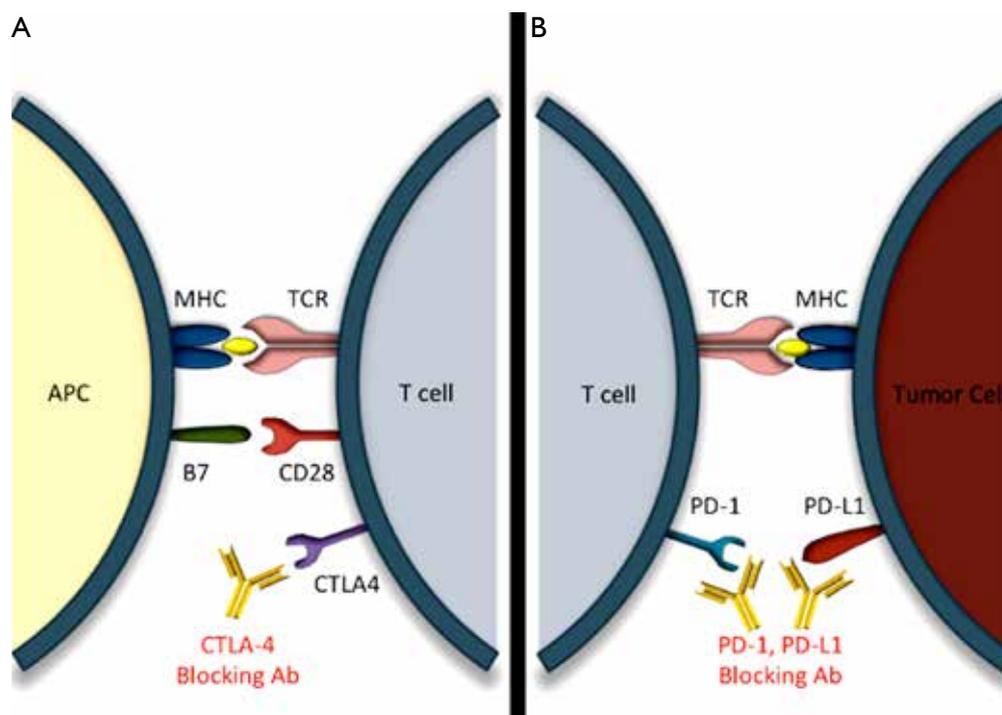


Figure 1 Immune checkpoint blockade in central and peripheral immune compartments. (A) Expression of CTLA-4 is up regulated on T cells in lymphoid tissues following activation via MHC/TCR and M7/CD28 mediated signaling. Once activated, CTLA-4 inhibits T cell function leading to immune tolerance. In the presence of blocking antibodies this tolerance can be broken, allowing for enhanced antitumor response; (B) PD-1, also expressed on T lymphocytes, inhibits the action of T lymphocytes upon binding to its ligands PD-L1/2; this process likely occurs in the tumor microenvironment, between PD-L1/2 expressing tumor cells and PD-1 expressing T lymphocytes; (A,B) blocking antibodies to either PD-1 or its ligands allows for T cell activation, enhancing anti-tumor effects peripherally. CTLA-4, cytotoxic T-lymphocyte antigen 4; PD-1, programmed death 1; PD-L1, programmed death ligand 1; APC, antigen presenting cell; MHC, major histocompatibility complex; TCR, T cell receptor.

overexpressing tumor cells (30) (*Table 1*). Similarly, PD-L1 expression was detected in 42.2% of gastric adenocarcinoma samples (n=102) and was undetectable in normal gastric tissue controls and only weakly detectable in gastric adenomas using an IHC approach (31). A recent Chinese series (n=111) suggested PD-L1 positivity in 63% (70/111) of gastric adenocarcinoma resection specimens (32) (*Table 1*). Data from the phase Ib KEYNOTE-012 trial corroborated the above results and found a 40% rate of PD-L1 overexpression in advanced gastric adenocarcinomas (33). Few studies have yet to specifically address rates of PD-1 and PD-L1 positivity in GEJ adenocarcinomas, the predominant location and histology in US patients. Although more studies will be necessary to substantiate these findings in gastric and esophageal cancers, PD-L1 expression levels are comparable to cancers in which anti-PD-L1 directed therapies have demonstrated early success.

PD-1 expression and tumor infiltrating lymphocytes (TILs)

The presence of lymphocytes in close tumor proximity has been used as a crude surrogate for immune responsiveness to tumor presence. Multiple large studies in melanoma, colorectal, ovarian, and breast have shown a correlation between increased immune infiltrates and favorable outcomes (34-37). Previous work has also correlated a higher density of TILs with improved outcomes in GI malignancies (38). Recently, work by Turcotte *et al.* defined the presence of endogenous CD8⁺ tumor infiltrating T-cells in a small series of patients with advanced gastrointestinal (GI) malignancies, including gastric cancer. They were able to demonstrate that naturally occurring CD8⁺ TILs can recognize specific autologous tumor-derived cell lines (39). However, despite the presence of TILs in the tumor microenvironment, tumor regression of late stage gastric

Table 1 Frequency of PD-L1 expression and correlation with clinical outcomes in gastric and esophageal cancer

Investigational compound	Target	Phase	ClinTrials identifier	Primary endpoint	Secondary endpoints
Ipilimumab	CTLA-4	II	NCT01585987	irPFS	PFS, OS, irBORR
Nivolumab	PD-1	I-II	NCT01928394	ORR	AE
	PD-1	I	NCT00836888	Safety, PK	PD, RR
Lirilumab + nivolumab	KIR, PD-L1	I	NCT01714739	Safety	BOR, irRECIST, PK, PD
MSB0010718C	PD-L1	I	NCT01943461	DLT	irBORR, PD-L1 expression, irPFS, OS
	PD-L1	I	NCT01772004	DLT	irBORR, PD-L1 expression, irPFS, OS
MPDL3280A	PD-L1	I	NCT01375842	DLT	AE
Pembrolizumab	PD-L1	I (KEYNOTE-012)	NCT01848834	ORR, AE	Cohort RR
	PD-L1	II (KEYNOTE-059)	NCT02335411	ORR, AE	PFS, discontinuation
MEDI4736	PD-L1	I-II	NCT01693562	ORR, AE	OS, PFS, DCR, PK

PD-L1, programmed death ligand 1; irPFS, immune related progression free survival; PFS, progression free survival; OS, overall survival; irBORR, immune related best overall response rate; PD-1, programmed cell death protein 1; ORR, overall response rate; AE, adverse events; PK, pharmacokinetics; PD, pharmacodynamics; RR, response rate; irRECIST, immune related response evaluation criteria in solid tumors; DCR, disease control rate.

and esophageal cancers is rarely seen suggesting endogenous mechanisms are likely inadequate. Preclinical models have suggested that there are greater TIL numbers in earlier stage disease, and that advanced GI malignancies are less immunogenic due to selection of the least immunogenic cancer cell clones during disease progression (40,41). Several studies have identified up regulation of PD-1 on TILs in both RCC and hepatocellular carcinoma and correlated increased PD-1 expression with worse prognosis (42,43). In gastric cancer, PD-1 expression on CD8⁺ lymphocytes is significantly higher than that of normal gastric mucosa and peripheral blood (44). Further studying the relationship of TIL density to stage and immunotherapy response may help refine the optimal disease setting in which to pursue immune checkpoint inhibition in gastric and esophageal cancer.

PD-L1/PD-L2 expression and patient outcomes

In many cancers increased PD-L1 and PD-L2 expression correlate with worse prognosis, and ongoing investigation is needed to determine the prognostic power of PD-L1 expression in gastric and esophageal cancers (45-50). Increased PD-L1 expression in both gastric and esophageal cancer is associated with nodal metastases, advanced stage, and worse outcomes (31,32). Jiang *et al.* demonstrated a positive correlation between expression of B7-H4, another B7

family member, and gastric cancer invasiveness and metastasis. The median overall survival is significantly reduced in gastric cancer patients with higher B7-H4 expression (51). Similarly, higher levels of PD-L1 and PD-L2 expression have been shown to be negative prognostic markers in esophageal cancer, especially in cases in which both ligands are expressed (30). Higher tumor B7-H4 levels, detected by IHC, were associated with worse prognosis and inversely correlated with CD3⁺ and CD8⁺ T-cells in 112 ESCC samples (52). PD-L1 overexpression, particularly at higher levels, may also serve as a predictive response biomarker in gastric cancer. Updated analysis from the KEYNOTE-012 phase I study suggests a trend toward improved overall response rate (ORR), progression free survival (PFS) with higher levels of PD-L1 overexpression (33). Further support for the predictive power has come from pembrolizumab melanoma and NSCLC cohorts suggesting increased tumor PD-L1 expression correlates with response rate (53,54).

Previous gastroesophageal immunotherapies

The role for immune modulating therapies in gastric cancer has been a subject of multiple prior investigations, largely in Asian patients. Non-specific immune potentiators such as polysaccharide-K, OK-432, and BCG have been previously investigated dating back to 1975 (55-60). The pleiotropic

immune modulator protein-bound polysaccharide (PSK), derived from the CM-101 strain of the fungus *Coriolus versicolor*, has been shown to increase leukocyte activation, shift the Th1:Th2 balance and inhibit tumor growth in several cancer models (61-63). In Japanese gastric cancer patients undergoing gastrectomy the addition of PSK to mitomycin/5-FU adjuvant therapy improved the five year disease free survival (DFS) (70.7% *vs.* 59.4%) and 5-year OS (73% *vs.* 60%) (57). The sclerosant OK-432 (penicillin-killed lyophilized *Streptococcus pyogenes*) induces IL-12, stimulates NK and T-cells favoring a Th1 response, and may improve the function of antigen presenting dendritic cells (64-68). In a small Japanese trial the combination of OK-432 with 5-FU/leucovorin and cisplatin was safe and produced a response rate of 40%, however, a larger adjuvant trial comparing S-1 *vs.* S-1 and OK-432 failed to demonstrate a survival difference (58,69). Similarly, the non-specific immune upregulation following BCG has translated to some anti-tumor responses without a reliable improvement in overall survival in combination studies (55,70). More recently, a small Chinese trial investigating cytokine-induced natural killer cells given after adjuvant 5-FU based chemotherapy for resected gastric cancer demonstrated a trend toward improved OS and a 6-month improvement in median DFS (34.1 *vs.* 40.4 months) (71). Retrospective analysis of this data suggested that benefits might be restricted to intestinal type histology (71). The combination of cytotoxic chemotherapy with non-specific immune modulators (chemoimmunotherapy) has largely been restricted to Asian patients and the lack of reproducible survival improvements has limited clinical adoption.

Early checkpoint inhibitor clinical experience

The first clinical success with immune checkpoint blockade was observed in patients with metastatic melanoma treated with the anti-CTLA-4 monoclonal antibody (mAb) ipilimumab (15). Subsequently, ipilimumab, and another anti-CTLA-4 mAb, tremelimumab, have shown promising results in phase I-III clinical trials in several cancer types including, gastric/GEJ carcinomas (72). Several anti-PD-1 mAbs including nivolumab, pembrolizumab (MK-3475), and pidilizumab have been developed and early data with these agents has shown significant response rates in melanoma, NSCLC, RCC, and diffuse large B-cell lymphoma (73-75). PD-L1 blocking antibodies have also demonstrated favorable outcomes in early trials (12).

Gastric and esophageal cancers have represented a small

minority of patients in early phase immune checkpoint inhibitor trials. In the multicenter phase I trial of the anti-PD-L1 mAb BMS-936559 only 7 of 207 enrolled patients had gastric cancer. The gastric cancer cohort were assigned to the safety arm as opposed to the efficacy arm, and limited efficacy data in gastric cancer is available (12). In a second line gastroesophageal-specific phase II trial (n=18) with tremelimumab (anti-CTLA4 mAb) the observed response rate (RR) was 5%, below the observed response rate to second-line cytotoxic chemotherapy (76). Although this trial failed to meet its pre-specified RR endpoint several patients achieved stable disease (SD) and one patient achieved a partial response (PR), which is quite impressive given the aggressive natural history of advanced gastric and esophageal cancer. Further support comes from the interim analysis of the anti-PD-L1 mAbs MPDL3280A and MEDI4736 (77,78). In the MEDI4736 gastroesophageal cohort (n=16) two heavily pretreated patients remained on study over 24 weeks in the early reporting, beyond the median PFS for second line gastric and esophageal cancer therapies (78). In the most recent ESMO conference preliminary data from the phase IB anti-PD-1 antibody pembrolizumab trial (KEYNOTE-012) in advanced gastric cancer was presented. Patients with PD-L1 positive advanced gastric adenocarcinoma (IHC positive in >1% cells) received pembrolizumab 10 mg/kg every 2 weeks until progression or toxicity. A total of 39 patients were enrolled after screening 162 samples for PD-L1 (65 positive samples, 40% IHC+) (33). An updated analysis of this trial has suggested an ORR of 22% and a median response duration of 24 weeks in this heavily pre-treated population (33). There was a positive correlation with PD-L1 positivity and PFS (P=0.032). Results of this trial have prompted the planned KEYNOTE-059 phase II trial of cisplatin/5-FU in combination with pembrolizumab (33). The toxicity profile and early efficacy signals have prompted expansion of immune checkpoint inhibitors in advanced gastric and esophageal cancers (Table 2).

Conclusions and future directions

Advanced gastric and esophageal cancers carry a poor prognosis with limited therapeutic options, and few major therapeutic advances. While improving molecular characterization will continue to identify subsets of patients who may benefit from genotype-directed targeted therapies, a majority of patients do not yet benefit and therefore further therapies are needed.

Table 2 Ongoing clinical investigations targeting immune checkpoint blockade in gastric and esophageal cancer

Study population	Histology	Number of samples	PD-L1 positive (%)	Outcome	Reference
Esophageal	Squamous	41	44.0	Worse outcomes	(30)
Gastric	Adenocarcinoma	102	42.2	Nodal mets, advanced stage	(31)
	Adenocarcinoma	111	63.0	Advanced stage, worse outcome	(32)
	Adenocarcinoma	243	43.6	Improved DFS, lower stage	(49)

PD-L1, programmed death ligand 1; DFS, disease free survival.

The recently published Cancer Genome Atlas (TCGA) gastric cancer analysis has provided molecular rationale for division of gastric adenocarcinoma into four distinct molecular subtypes (79). Interestingly, the EBV-positive gastric cancer subgroup demonstrated high levels of PD-L1/L2 overexpression highlighting a molecularly defined patient population possibly most likely to derive benefit from immune checkpoint blockade (79). Early translational efforts have suggested comparable rates of PD-1 and PD-L1 expression in gastric and esophageal cancers, strengthening the argument that immune checkpoint inhibitors warrant further clinical investigation. Development and validation of predictive biomarkers for response to immune checkpoint blockade will help to refine the optimal location for immunotherapy in gastric and esophageal cancers. Some recent biomarker analyses suggest that PD-L1 directed therapy is most effective in patients with higher pre-treatment CTLA4 expression, absence of fractalkine (CX3CL1) in pre-treatment biopsies, and T-helper type 1 gene expression patterns (80). Interesting preclinical work continues to expand immunotherapy combination approaches including low dose chemosensitization with alkylating agents (81). Irradiation is known to induce antigen presentation and upregulate PD-L1 expression (82-84). The frequent use of adjuvant chemoradiation and high recurrence rates despite adjuvant therapy may make the use of anti-PD-L1 therapies an interesting adjunct to adjuvant therapy, a concept currently under investigation in NSCLC. Here we have presented a review of the current landscape of immunotherapy in gastric and esophageal cancer with attention to translational studies and early clinical investigations.

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A nomogram that predicts pathologic complete response to neoadjuvant chemoradiation also predicts survival outcomes after definitive chemoradiation for esophageal cancer

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Background: Pathologic complete response (pCR) to neoadjuvant chemoradiation for esophageal cancer is associated with improved outcomes. We evaluated whether a nomogram designed to predict who would have a pCR after trimodality therapy could also predict outcome after definitive chemoradiation.

Methods: Patients in this retrospective, single-institution analysis had received chemoradiation without surgery for esophageal cancer from 1998 through 2010; 333 such patients had complete information on all variables required for the pCR nomogram: sex; T status (by endoscopic sonography); tumor grade; tumor avidity on positron emission tomography (PET); and esophagogastroduodenoscopy (EGD)-directed biopsy results after chemoradiation. We used multivariate Cox regression to test potential associations between clinical outcomes [overall survival (OS), locoregional recurrence, and distant metastasis] and patient or treatment factors and the pCR nomogram score; the component variables of the nomogram were not reintroduced into the multivariate analysis.

Results: The median follow-up time for all patients (median age 66 years) was 18.2 months (30.7 months for those alive at the time of analysis). Patients with nomogram scores ≤ 125 (median for all patients) had significantly worse outcomes than patients with scores >125 : median OS time 19.7 *vs.* 48.2 months; disease-free survival (DFS) time 6.1 *vs.* 31.1 months; locoregional failure-free survival time 17.7 months *vs.* not reached; and distant metastasis-free survival time 11.7 months *vs.* not reached (all $P < 0.001$). Multivariate Cox regression analysis indicated that nomogram score independently predicted each survival outcome, along with other patient and disease factors.

Conclusions: The pCR nomogram score predicted survival outcomes in patients receiving definitive chemoradiation for esophageal cancer. Although this nomogram requires further validation, it may prove useful for stratifying patients for clinical trials designed to intensify treatments for patients at the highest risk of relapse.

Keywords: Pathologic complete response (pCR); nomogram score; esophageal cancer; chemoradiation

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Introduction

Esophageal cancer is relatively rare but deadly. Despite advances in diagnosis and treatment, the overall 5-year survival rate has improved from 3% to only 15-20% since

the mid-1970s (1). Neoadjuvant chemoradiation, followed by surgery if possible, is currently the standard of care for nonmetastatic esophageal cancer, as randomized trials have shown that this therapy produces a survival benefit over

surgery alone (2-5). However, even though this combined therapy has led to prolonged survival outcomes, this benefit is balanced by the risk of surgical complications, which include a postoperative death rate of 4-10% (4,6), and the risk of long-term detrimental effects from postoperative pulmonary and gastrointestinal complications (7) that can lead to lifelong deterioration in terms of gastroesophageal reflux, eating restrictions, dyspnea, and fatigue (8).

About 25-30% of patients experience pathologic complete response (pCR), the absence of residual viable tumor cells in the resected specimen, after neoadjuvant chemoradiation (3,5). A pCR after trimodality therapy is known to predict lower rates of local recurrence (9,10) and better overall survival (OS) (10,11); a pCR can also indicate long-term cure in about 20% of patients with unresected disease who receive definitive chemoradiation (12). Thus the question remains: if chemoradiation eradicates the esophageal tumor, can some patients forego surgery (and be spared the perioperative and long-term morbidity of esophageal resection), and if so, how would such patients be identified?

One way of addressing this question would be to develop a surrogate measure with which to identify pCR in patients who do not undergo surgery; such a surrogate could allow surgery to be reserved for use as salvage therapy if needed rather than being used in all cases. Until recently, no combinations of clinical variables, imaging findings (13-15), or biomarkers (16,17) had been identified that can accurately and reliably predict which patients will achieve a pCR. To address this need, a nomogram comprising five clinical variables was recently developed that can collectively predict pCR after trimodality therapy with $\geq 60\%$ probability: (I) sex; (II) baseline T status (by endoscopic sonography); (III) tumor grade; (IV) standardized uptake values (SUVs) on positron emission tomography (PET) after chemoradiation; and (V) esophagogastroduodenoscopy (EGD)-guided biopsy findings after chemoradiation (18). For the current study, we hypothesized that this same nomogram pCR score can also predict clinical outcomes in patients treated with definitive chemoradiation alone, and our aim was to further validate this nomogram for future use in clinical decision-making.

Patients and methods

Patients

In this retrospective analysis, we identified 333 patients

who received definitive chemoradiation for stage IB-IVA esophageal carcinoma at a single institution from 1998 through 2010. All patients had no evidence of distant metastases at presentation, all had received definitive concurrent chemoradiation, with or without induction chemotherapy, and all had complete information on all of the variables required for the pCR nomogram (*Figure S1*). The 333 patients were separated into two groups according to the median pCR nomogram score: those with score ≤ 125 (n=183) and those with score >125 (n=150). Disease was staged according to the 6th [2002] edition of the American Joint Committee on Cancer staging system. All analyses were approved by the appropriate institutional review board.

Chemoradiation treatment

Chemotherapy consisting of a fluoropyrimidine (IV or oral) and either a platinum compound or a taxane was given concurrently with radiation therapy to a median dose of 50.4 Gy (range, 25-66 Gy), delivered in daily 1.8-Gy fractions on Monday-Friday. Radiation was delivered by 3-dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT), or proton beam therapy (PBT) techniques. A total of 122 (36.6%) patients also received induction chemotherapy.

Nomogram score and outcome measures

As noted, the nomogram scores were based on five clinical variables: (I) sex; (II) baseline T status (by endoscopic sonography); (III) tumor grade; (IV) SUV of the primary tumor by PET after chemoradiation; and (V) EGD biopsy results after chemoradiation (18). The total number of points on the nomogram ranges from 0 to 180; in the original study, a nomogram score of >160 was found to predict pCR with $\geq 60\%$ probability. However, because very few patients in our dataset had a nomogram score >160 , we used the median score of the entire group of 125 as the cutoff point for our current analysis.

Dates of death were determined from the medical records and the Social Security Death Index. OS was calculated from the date of diagnosis to the date of death or last follow-up. Disease-free survival (DFS) was calculated from the date of diagnosis to the date of documented disease recurrence. Patients who had not experienced progression or recurrence or had died by the last follow-up were censored.

Table 1 Patient, tumor and treatment characteristics

Characteristic	Score ≤125	Score >125	All patients	P value
No. of patients	183	150	333	–
Sex				<0.001
Female	14	53	67	
Male	169	97	266	
Ethnicity				0.591
Caucasian	153	132	285	
Other	30	18	48	
Age at Dx, y				0.563
Median	66	67	66	
Mean	65.09	66.56	65.75	
Smoking at Dx				0.815
No	149	119	268	
Yes	34	29	63	
Tumor histology				0.001
Adeno	143	94	237	
Squamous	36	56	92	
Other	3	0	3	
Tumor differentiation				<0.001
Well	2	2	4	
Moderate	40	100	140	
Poor	141	48	189	
Overall clinical stage				<0.001
IB	0	8	8	
II	50	54	104	
III	105	79	184	
IVA	24	7	31	
Clinical T status				<0.001
T1	2	10	12	
T2	6	25	31	
T3	173	99	271	
T4	1	15	17	
Clinical N status				0.058
N0	49	56	105	
N1	129	93	222	
Clinical M status				0.005
M0	157	143	300	
M1a	24	7	31	
Induction chemo				0.104
N0	35	39	74	
Yes	73	49	122	
Radiation modality				0.753
3D conformal	35	25	60	
IMRT	113	93	206	
Proton	34	32	66	
Total dose, Gy				0.129
Median	50.4	50.4	50.4	

IMRT, intensity-modulated radiation therapy; Dx, diagnosis.

Statistical analysis

Data were collected retrospectively. The nomogram score was examined as a binary variable (≤ 125 points and > 125 points) as described above. Chi-square or Fisher's exact tests were used to compare differences between nomogram groups with respect to categorical variables. Wilcoxon rank-sum tests or Kruskal-Wallis tests were used to assess associations between nomogram group and continuous variables. Multivariable Cox regression tested the association between clinical outcomes (OS, locoregional recurrence, and distant metastasis) and patient or treatment factors and the pCR nomogram score. The individual variables for the nomogram score were not re-introduced in the multivariable analysis. Survival curves were constructed with the Kaplan-Meier method and compared between nomogram groups with the log-rank test. The clinical variables for the multivariable cox regression model were selected by backward selection with an adjusted P value ≤ 0.05 .

Results

Patient, tumor, and treatment characteristics

Table 1 summarizes patient, tumor, and treatment characteristics. The median age at diagnosis was 66 years; most patients were white men; most tumors were adenocarcinomas of moderate to poor differentiation; and most patients had stage II or III disease. Compared with patients with ≤ 125 nomogram points, patients with > 125 points were more likely to be female, to have squamous cell carcinomas of well- or moderately differentiated histology, and to have lower stage disease (P for all < 0.05). In terms of characteristics after chemoradiation, patients with > 125 points (*vs.* those with ≤ 125) were more likely to have shown a complete response (CR) on PET/computed tomography (CT), to have had lower SUV_{max} values, and to have had no evidence of residual cancer cells in EGD biopsy samples obtained after chemoradiation (data not shown).

Survival outcomes

The median follow-up time for all patients was 18.2 months (30.7 months for those alive at the time of this analysis). The median OS, DFS, locoregional failure-free survival, and distant metastasis-free survival times for the entire group were 31.4, 10.7, 31.8, and 35.3 months. When patients were stratified by ≤ 125 *vs.* > 125 nomogram

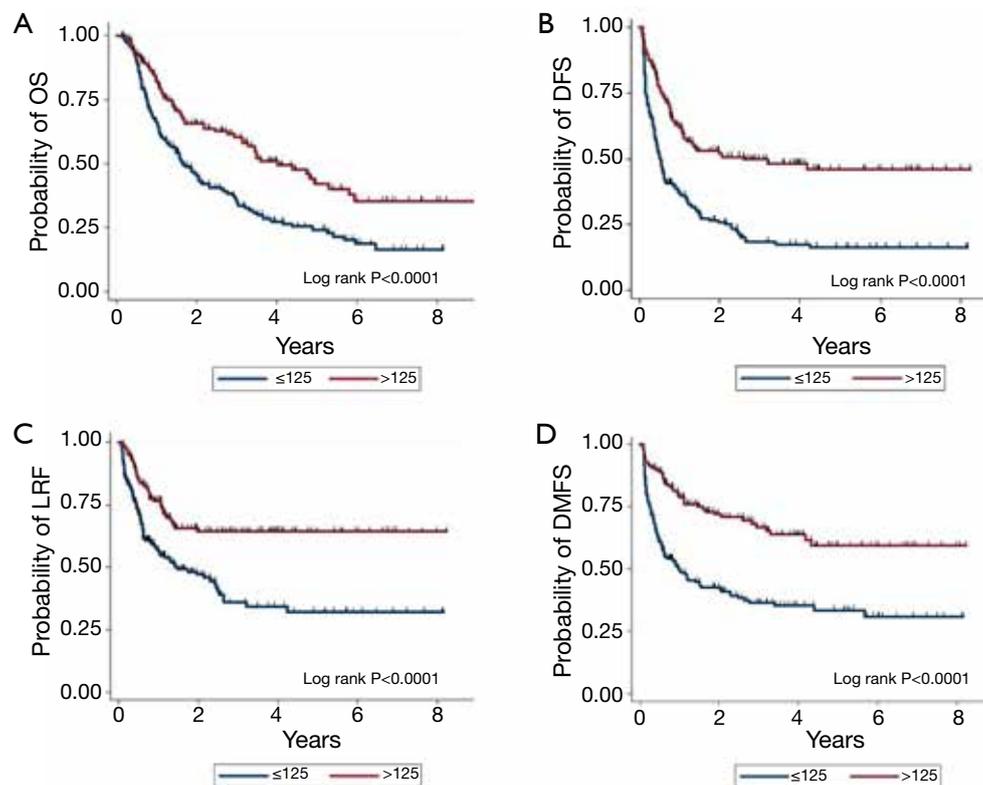


Figure 1 Pathologic complete response (pCR) nomogram score predicts disease outcomes for patients with esophageal cancer after definitive chemoradiation. Nomogram scores predicted (A) overall survival (OS); (B) disease-free survival (DFS); (C) locoregional failure (LRF)-free survival; (D) distant metastasis-free survival (DMFS) after definitive chemoradiation therapy. The cut-off point, 125, was the median value for the entire patient cohort.

points, the corresponding median OS times were 19.7 *vs.* 48.2 months, DFS times 6.1 *vs.* 31.1 months, locoregional failure-free survival times 17.7 months *vs.* not reached, and distant metastasis-free survival times 11.7 months *vs.* not reached (P for all < 0.001) (Figure 1).

Univariate analysis

On univariate analysis, older age at diagnosis, shorter tumor length, lower overall disease stage (I/II *vs.* III/IV), lower baseline T status (T1/2 *vs.* T3/4), node-negative disease, lower baseline PET SUV, CR in the primary tumor on restaging PET/CT at 3 months after chemoradiation therapy, and absence of cancer cells on the EGD biopsy specimens obtained after chemoradiation were also associated with improved OS, locoregional failure-free survival, and distant metastasis-free survival outcomes (P < 0.05). These and additional factors associated with improved locoregional-failure free survival and prolonged distant metastasis-free survival are shown in Table 2.

Multivariate analysis

Variables were selected for inclusion in multivariate analysis on the basis of their significance in the univariable analysis; other factors known to predict prognosis were included as well. As noted previously, the individual clinical variables constituting the five components of the nomogram score (sex, baseline T status, tumor grade, PET SUV and EGD biopsy results after chemoradiation) were not re-introduced in the multivariable analysis. In multivariable Cox regression analysis, the nomogram cutoff score remained an independent predictor of all survival outcomes even after adjusting for other prognostic factors (Table 3).

Discussion

In this study, we found that the pCR nomogram score, developed from patients treated with trimodality therapy (18), also predicted clinical outcomes in patients who did not undergo surgery. The nomogram score along with other

Table 2 Univariate analysis of potential predictors of survival outcomes

Factor	Overall survival		Locoregional failure-free survival		Distant metastasis-free survival	
	HR	P value	HR	P value	HR	P value
Nomogram score: >125 vs. ≤125	0.54	<0.001	0.45	<0.001	0.38	<0.001
Age at diagnosis (continuous)	0.99	0.056	0.97	0.001	0.96	<0.001
Sex: male vs. female	1.11	0.585	1.33	0.218	2.05	0.004
Non-white vs. white	1.53	0.032	1.14	0.597	1.26	0.314
Karnofsky performance status ≤60 vs. 100	4.54	0.033	1.78	0.49	0.90	0.893
Tumor length (continuous)	1.05	0.005	1.05	0.003	1.05	0.001
Tumor differentiation/grade: poor vs. well	0.76	0.695	1.62	0.631	1.44	0.034
Disease stage: III/IV vs. I/II	2.43	<0.001	1.46	0.042	2.75	0.000
Tumor status: T3/4 vs. T1/2	2.76	<0.001	2.07	0.017	2.99	0.001
Nodal status: node+ vs. node-	2.49	0.000	1.43	0.059	2.70	0.000
Metastasis status: M1a vs. M0	1.46	0.097	1.74	0.030	1.97	0.004
Induction chemotherapy: yes vs. no	1.35	0.043	1.25	0.201	1.48	0.019
Baseline PET scan: yes vs. no	0.42	0.019	1.33	0.625	0.67	0.384
Baseline PET SUV (continuous)	1.02	0.006	1.02	0.039	1.03	0.000
Primary tumor response on PET at 3 mo: < PR vs. CR	1.83	0.006	2.46	0.001	2.62	0.000
PET SUV after chemoradiation (continuous)	1.08	0.003	1.16	<0.001	1.05	0.092
CR on PET: yes vs. no	0.80	0.185	0.6	0.012	0.84	0.339
Residual disease on EGD after chemoradiation: yes vs. no	3.18	<0.001	5.67	<0.001	4.29	0.000

HR, hazard ratio; PET, positron emission tomography; SUV, standardized uptake value; PR, partial response; CR, complete response; EGD, esophagogastroduodenoscopy.

Table 3 Multivariable analysis of potential predictors of survival outcomes

Factor	Overall survival		Locoregional failure-free survival		Distant metastasis-free survival	
	OR	P value	OR	P value	OR	P value
Nomogram score: >125 vs. ≤125	0.57	<0.001	0.48	<0.001	0.57	<0.001
Age at diagnosis	NS	NS	0.98	0.025	0.96	<0.001
Tumor histology: squamous vs. adeno	NS	NS	1.59	0.025	0.51	0.005
Disease stage: III/IV vs. I/II	2.28	<0.001	NS	NS	NS	NS
Tumor length	NS	NS	1.05	0.015	NS	NS
Nodal status: node+ vs. node-	NS	NS	NS	NS	2.63	<0.000
Total radiation dose, Gy	NS	NS	NS	NS	0.95	0.048
Baseline PET scan: yes vs. no	0.40	0.02	NS	NS	NS	NS
Baseline PET SUV (continuous)	NS	NS	NS	NS	1.03	0.001
Primary tumor response on PET at 3 mo: < PR vs. CR	NS	NS	1.63	0.029	1.98	0.011

OR, odds ratio; NS, not significant; PET, positron emission tomography; SUV, standardized uptake value; PR, partial response; CR, complete response.

known prognostic factors such as clinical disease stage, independently predicted OS, locoregional control, and distant metastasis-free survival. The five factors used in the pCR nomogram score seem to represent a set of clinical and tumor-specific variables that distinguish favorable from less-favorable disease, pointing to the possibility that this set of factors could help in the choice of treatment after chemoradiation.

Preoperative chemoradiation followed by surgery is currently considered the standard of care over surgery alone in the United States and elsewhere based on results of the CROSS trial (4). However, the role of surgery after chemoradiation has been controversial because of two trials that failed to show an OS benefit from the addition of surgery to chemoradiation (19,20). However, the high perioperative mortality rate in these trials (8-12%) may have obscured a survival benefit in the surgical group. Certainly esophagectomy improves local control by resecting disease that did not respond to chemoradiation; however, esophagectomy comes at the price of significant perioperative morbidity, including pulmonary, gastrointestinal, and wound-healing complications (8). It is therefore desirable to avoid surgery for patients who achieve pCR after chemoradiation, if a reliable surrogate method of identifying pCR other than surgery can be identified.

Significant effort has been expended to identify molecular biomarkers of clinical response. Molecular analyses of pretreatment biopsy specimens may help to identify tumors that will not respond well to chemoradiation; for example, two groups have shown that specimens expressing high levels of NF- κ B predicted poorer pCR rates and more aggressive tumor biology (lymph node metastasis, perineural and vascular invasion) (16,21). Further, tumors that express low levels of NF- κ B before therapy but higher levels after chemoradiation were also associated with poorer prognosis (22). Other investigators have found a 3-gene "signature" to predict pathologic response (17,23). However, marker studies are limited in that assessments of gene expression depend on the condition of the tissues and how they are collected and processed, and the findings thus may not be generalizable to those of other studies. Another approach using imaging-based biomarkers may circumvent potential problems with tissue collection and handling bias. For example, several groups have shown that PET SUV_{max} after treatment is a good predictor of pCR (13,15,24). However, a meta-analysis of several esophageal-cancer trials showed that fluorodeoxyglucose (FDG)-based PET has a predictive

value of only about 70% (25). Diffusion-weighted magnetic resonance imaging (MRI), at baseline and at 2 weeks after the start of chemoradiation, has been shown to be highly accurate for predicting pathologic response (26,27). However, any biologic imaging technique will require prospective validation before it can be used to stratify patients for treatment intensification or for predicting pCR. We believe that the best predictors of response will come not from one set of marker or imaging correlates but rather from a combination of clinical and tumor response factors (as we included in the pCR nomogram), a variety of tumor-specific imaging findings, and molecular biomarkers.

The limitations of this study are the retrospective nature of the analysis and our need to restrict the analysis to patients who had information available on all five factors used to create the nomogram score. This restriction could have introduced bias in terms of excluding patients who did not have these tests because of poor condition or early death, which would have artificially improved the outcomes of the study cohort relative to all patients who received chemoradiation during the same period. Nevertheless, the nomogram score was still able to separate patients into risk groups, which underscores the robustness of this tool. Another limitation is that the factors used to build the nomogram may not be fully exportable to other centers. Some factors represent procedures that are standard at our institution, such as repeat endoscopy and biopsy after chemoradiation and repeat FDG-PET staging after treatment, but these procedures may not be considered standard practice elsewhere. Further research is needed to determine if other more generalizable factors could be used to generate a predictive nomogram.

In conclusion, the pCR nomogram score independently predicted survival outcomes after definitive chemoradiation therapy for esophageal cancer. It successfully stratified patients into low-risk and high-risk groups, with the latter developing rapid systemic and local relapses. The pCR nomogram score may be helpful for identifying patients at higher risk of relapse who may benefit from clinical trials of intensified therapy.

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Breast cancer resistance protein (BCRP) and excision repair cross complement-1 (ERCC1) expression in esophageal cancers and response to cisplatin and irinotecan based chemotherapy

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Background: Esophageal cancer patients face a dismal outcome despite tri-modality management and median survival remains 15-18 months. Breast cancer resistance protein (BCRP) is an ATP-dependent efflux protein associated with chemotherapy resistance. The role of BCRP expression in esophageal cancer and normal esophageal cells is not known. Excision repair cross complement-1 (ERCC1) overexpression has been correlated with poorer response to cisplatin based chemotherapy. We examined the expression of BCRP and ERCC1 in patients with esophageal cancer and correlated it with survival in patients receiving irinotecan and cisplatin based chemotherapy.

Methods: With IRB approval, 40 cases of esophageal cancer diagnosed from 2004-2008, were stained for BCRP and ERCC1 expression by immunohistochemistry and scored by a pathologist blinded to clinical data. Baseline demographics, therapy given and survival data were collected and correlated with BCRP and ERCC1 expression. Fisher's exact test was used to determine association between BCRP and ERCC1 expression and demographics. Cox proportional hazards model was used for association of BCRP and ERCC1 with survival.

Results: On immunohistochemistry, 30/40 cancers (75%) expressed BCRP. Interestingly, down-regulation of BCRP expression in tumor compared with normal cells was seen in 40% of patients. ERCC1 positivity was seen in 15/30 cases (50%). Median overall survival (OS) was 19 months with no difference in survival between BCRP positive and negative patients (P=0.13) or ERCC1 positive and negative patients (P=0.85). Estimated hazard ratio (HR) of death for BCRP positive patients was 2.29 (95% CI: 0.79-6.64) and for ERCC1 positive patients was 1.09 (95% CI: 0.46-2.56). There was no association of BCRP and ERCC1 expression with disease stage, age, gender or histology. For patients who received cisplatin and irinotecan as first line chemotherapy, there was no difference in survival based on BCRP or ERCC1 status.

Conclusions: BCRP expression is seen in a majority of esophageal cancers and normal esophageal mucosa. ERCC1 expression is seen in about half of the patients with esophageal cancer. Irinotecan based studies with esophageal and gastric cancer suggest response rates of 14-65%. Whether the 40% of tumors in our study found with down regulation of BCRP expression, constitute a majority of these responders needs to be prospectively validated in a larger data set. It should include markers such as ERCC1 predicting response to 5-fluorouracil and platinum based chemotherapy, to enable individualizing therapy for this cancer.

Keywords: Breast cancer resistance protein (BCRP); excision repair cross complement-1 (ERCC1); expression; esophageal cancer; chemotherapy response

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Introduction

Breast cancer resistance protein (BCRP)/ABCG2/MXR/ABCP is a member of the ATP-binding cassette superfamily of transporters present on cell membranes, which was first identified in Adriamycin resistant breast cancer cell lines (MCF-7/AdrVp) (1). It was found to confer resistance to mitoxantrone, doxorubicin, and daunorubicin as it reduced intra-cellular accumulation and retention of these drugs. Apart from tumor cells, it is widely expressed in the body, in stem cells and apical membranes of epithelial cells involved in drug metabolism and distribution in the liver, intestines, kidneys, placenta and the blood-brain barrier (2).

In addition to endogenous substrates such as estrogens, folic acid and protoporphyrin, a number of antitumor drugs (e.g., mitoxantrone, topotecan, methotrexate, irinotecan and flavopiridols) and toxins are substrates of BCRP. Doxorubicin and mitoxantrone interfere with topoisomerase II activity while topotecan inhibits topoisomerase I. All three drugs are substrates of BCRP which would explain cross-resistance to these drugs by reduced cellular drug accumulation due to BCRP expression (3). Irinotecan and its active metabolite SN-38 are camptothecin analogues similar to topotecan. BCRP mediated resistance to camptothecins in human ovarian cancer cells lines (T8 and MX3) was overcome by using an inhibitor of BCRP (GF120918) (4). In another study, co-administration of topotecan with GF120918 in a group of patients was found to increase the bioavailability of topotecan by approximately two fold (5). Other inhibitors of BCRP include imatinib, gefitinib, taxanes, HIV protease inhibitors, glucocorticoids, diethylstilbesterol, tamoxifen, fumitremorgin C and novobiocin (2). Understanding the interaction BCRP substrates and BCRP inhibitors may help us to make rational decisions regarding chemotherapy drug combinations for those cancers which show BCRP expression.

In addition, BCRP expression has been correlated to clinical outcome with chemotherapeutic agents that are known substrates for BCRP. Higher BCRP expression on acute myeloid leukemic blast cells has been associated with a lower likelihood of achieving complete remission as well as shorter duration of remission (6). BCRP negative patients with locally advanced or metastatic non-small cell lung adenocarcinoma treated with platinum based therapy had higher response rates and overall survival (OS) as compared with BCRP positive patients (7). In patients with locally advanced bladder cancer treated with neo adjuvant therapy, BCRP did not show any prognostic impact (8),

although p-glycoprotein expression correlated with shorter progression-free survival and high lung resistance related protein/major vault protein expression was associated with a worse response to neo adjuvant chemotherapy. Photofrin, a photosensitizer used in photodynamic therapy, is also a substrate for BCRP and early lung cancer patients with BCRP expression had decreased antitumor responses compared with those who received a photosensitizer which was not a BCRP substrate (9).

Esophageal carcinoma is an aggressive malignancy and is the eighth most common cancer worldwide (10). In the United States, an estimated 17,990 people will be diagnosed with esophageal cancer in 2013 and 15,210 will eventually die of their disease (11). Most patients have non resectable or metastatic disease on diagnosis and there is currently, no standard first line chemotherapy for patients with locally advanced or metastatic disease, although historically platinum and 5-fluorouracil based regimens have been utilized upfront. More recently, irinotecan has been added to the armamentarium of drugs used for this disease, usually in combination with cisplatin. Response rates with this combination have ranged between 30% and 50% (12,13). Despite the addition of newer drugs, no significant strides have been made and five-year survival remains less than 20% (14). Tumor mediated drug resistance may be one of the mechanisms that lead to decreased response to chemotherapy. If therapy could be individualized based on tumor biology, chemotherapy with a higher likelihood of response rates could be selected, thereby prolonging survival.

Irinotecan is one of the substrates for BCRP. In the current study, we explored if BCRP expression is present in esophageal cancers and if this expression correlates with worse prognosis in patients treated with irinotecan chemotherapy. Based on evidence from earlier studies that excision repair cross complement-1 (ERCC1) overexpression can be associated with poor response to cisplatin in non-small cell lung adenocarcinoma, urothelial carcinoma, gastric carcinoma, head and neck squamous cell carcinoma and biliary tract adenocarcinoma (15-19), we further explored ERCC1 expression in esophageal cancers and correlated survival with cisplatin based chemotherapy.

Methods

Institution Review Board approval was obtained to examine medical records and specimens of patients with locally advanced esophageal carcinoma that had been treated at our institution between January 2000 and November 2007. The

primary objective was to examine expression of BCRP in esophageal carcinoma. The secondary objectives included correlation of BCRP expression to survival in those patients treated with irinotecan based chemotherapy and examination of expression of ERCC1 and correlation with survival in patients treated with platinum based therapy.

Paraffin-embedded esophageal cancer specimens were evaluated for BCRP expression by immunohistochemistry using specific anti-BCRP monoclonal antibody BXP-21 (Kamiya Biomed Corp). Sections (5-10 μm) were de-paraffinized, rehydrated, and incubated in 3% H_2O_2 (15 min) to block endogenous peroxidase activity. Antigen retrieval was performed using citrate buffer and non-specific staining was blocked with 0.03% casein. Primary anti-BCRP antibody was applied at a 1:30 dilution in PBS/Tween (PBST) buffer. Following washes in PBST, sections were incubated in biotinylated goat anti-mouse antibody (Jackson ImmunoResearch Laboratories) at a 1:200 dilution, followed by streptavidin horseradish peroxidase conjugate (Zymed Laboratories, Inc, San Francisco, USA) at a 1:20 dilution and DAKO DAB chromogen solution (K3466). Counterstaining was performed with hematoxylin. Controls for staining specificity involved omission of primary antibody or replacement of the primary antibody with normal goat serum. ERCC1 staining was done using Paraffin sections cut at 4 μm , placed on charged slides, and dried at 60 $^\circ\text{C}$ for one hour. Slides were cooled to room temperature, de-paraffinized in three changes of xylene, and rehydrated using graded alcohols. For antigen retrieval, slides were heated in the microwave for 20 minutes in TRS buffer (Dako catalog # S1699), followed by a 15-minute cool down. Endogenous peroxidase was quenched with aqueous 3% H_2O_2 for 10 minutes and washed with PBS/T. Slides were loaded on a DAKO auto stainer and serum free protein block (Dako catalog # X0909) was applied for 5 minutes, blown off, and ERCC1 antibody was applied for one hour. Labeled polymer HRP anti-Mouse Envision reagent (Dako, catalog # K4007) was applied for 30 minutes, followed by the DAB chromogen (Dako) for 10 minutes. Slides were then counterstained with Hematoxylin, dehydrated, cleared and cover slipped.

Scoring was performed by the pathologist who was blinded to the clinical data. For BCRP staining, BCRP score, membrane or cytoplasm of greater than or equal to 30 was considered positive (calculated by multiplying BCRP intensity and % staining). For ERCC1 staining, a proportion score and H score was determined. Proportion score was 0 if 0% staining, 0.1 if 1% to 9%, 0.5 if 10% to

49%, and 1.0 if 50% or more. This proportion score was multiplied by the staining intensity of nuclei to obtain a final semi quantitative H score. Tumors with an H score exceeding 1.0 (i.e., tumors with a staining intensity score of 2 and with 50% or more positive nuclei or with a staining intensity score of 3 and 10% or more positive nuclei) were deemed to be ERCC1-positive (15).

Fisher's exact test was used to determine association between BCRP and ERCC1 expression and gender, type of chemotherapy, and histology. Cox proportional hazards model was used for association of BCRP or ERCC1 and OS. To test the association between ERCC1 and stage, the Wilcoxon test was used. Categorical variables were summarized using frequencies and relative frequencies. A 0.05 nominal significance level was used in all testing.

Results

Demographic distribution

Forty patients were included in the study of which 35 were male and 5 were female. Median age at diagnosis was 66.5 years with a range of 40 to 90 years. Thirty-eight patients belonged to white ethnicity and one patient each was of African American and native Indian background.

Clinical & treatment characteristics and histopathology

The clinical characteristics of the patients included in the study, are described in *Table 1*. Most patients had advanced stage at diagnosis, 2 patients had stage I, 7 patients had stage II, 17 patients had stage III and 10 patients had stage IV disease. In 4 patients, stage was not known. There were 4 squamous cell carcinomas and 36 adenocarcinomas. Of these, 4 originated from the middle third of the esophagus and 36 from the lower third part of the esophagus. Median OS was 19 months. Sixteen patients were treated with cisplatin and irinotecan, eight with oxaliplatin and fluoropyrimidine and sixteen received other first line chemotherapy regimens.

Breast cancer resistance protein (BCRP)

On immunohistochemistry 30 of 40 cancers (75%) expressed BCRP. The distribution was membranous in 17; cytoplasmic in 27 and 14 patients had both cytoplasmic and membranous distribution. Down-regulation of BCRP expression in tumor compared to normal cells was seen

Table 1 Patient demographics and clinical characteristics	
Demographics	N [%]
Age	
Median (years)	66.5
Range (years)	40-90
Gender	
Male	35 [87.5]
Female	5 [12.5]
Ethnicity	
White	38 [95]
Other	2 [5]
Stage	
Stage 1	2 [5]
Stage 2	7 [17.5]
Stage 3	17 [42.5]
Stage 4	10 [25]
Unknown	4 [10]
Pathology	
Adenocarcinoma	36 [90]
Squamous cell carcinoma	4 [10]

in 40% of patients. Median OS was 19 months with no difference in survival between BCRP positive and negative patients (P=0.13). Estimated hazard ratio (HR) of death for BCRP positive patients was 2.29 (95% CI: 0.79-6.64). There was no association between BCRP expression, stage, age, gender or histology. For patients who received cisplatin and irinotecan as first line chemotherapy there was no difference in OS (P=0.39) of BCRP negative versus positive patients.

Excision repair cross complement-1 (ERCC1)

Thirty patients had sufficient sample for ERCC1 staining. Of these, fifteen (50%) were positive for ERCC1. There was no association between ERCC1 expression and gender or histology. There was no significant difference in survival distributions between ERCC1 positive and negative patients (P=0.85). The estimated hazard of death for ERCC1 positive patients is 1.09 (95% CI: 0.46-2.56) times that for ERCC1 negative. For patients who received cisplatin and irinotecan as first line chemotherapy there was no difference in OS (P=0.6299) of ERCC1 positive versus negative patients.

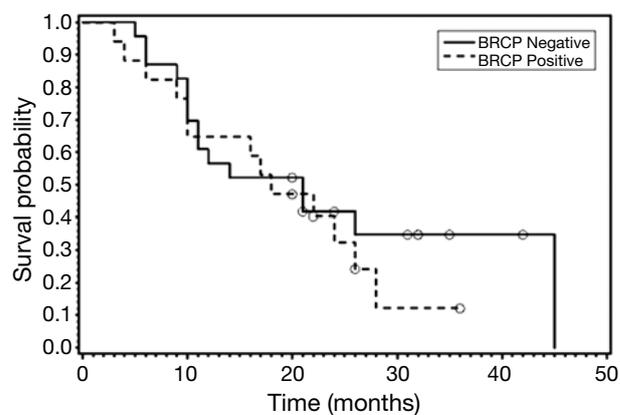


Figure 1 Kaplan Meier curves showing overall survival in BCRP positive vs. BCRP negative patients. BCRP, breast cancer resistance protein.

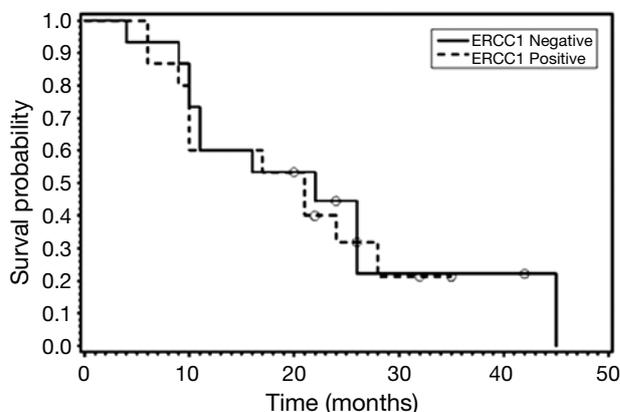


Figure 2 Kaplan Meier curves showing overall survival in ERCC1 positive vs. ERCC1 negative patients. ERCC1, excision repair cross complement-1.

BCRP and ERCC1 expression and co-relation with survival

We also examined the association between BCRP and ERCC1 co-expression and OS (Figures 1-3). Seven patients were positive for both BCRP and ERCC1, nine were negative for both, six had positive BCRP and negative ERCC1 expression and eight had negative BCRP and positive ERCC1 expression. There was no association between combined BCRP and ERCC1 overexpression and gender, stage, histology, type of chemotherapy given and OS.

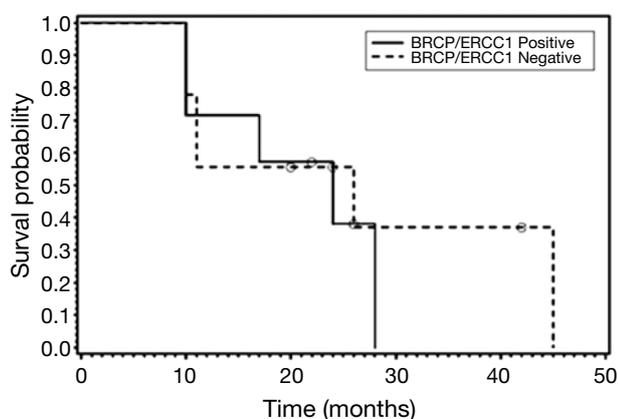


Figure 3 Kaplan Meier curves showing overall survival in both BCRP/ERCC1 positive *vs.* BCRP/ERCC1 negative patients. BCRP, breast cancer resistance protein; ERCC1, excision repair cross complement-1; BCRP, breast cancer resistance protein.

Conclusions

BCRP expression is seen in a majority of esophageal cancers and normal esophageal mucosa. ERCC1 expression is also seen in at least half of esophageal cancers. Response rates to most chemotherapy regimens used in frontline therapy ranges 30% to 50% (20-22). The factors for non-responsiveness to chemotherapy remain to be ascertained. Ours was an exploratory analysis which was hypothesis driven with the intention to translate the results into an effective algorithm for treatment strategy. As we move towards the era of individualized medicine, it would be useful to know upfront, the effectiveness of the proposed chemotherapy in a particular patient. This is crucial in patients with esophageal cancer where the need for predictive markers for adjuvant and neo adjuvant chemotherapy is most felt. In this disease where there is high surgical morbidity and mortality with limited success, there is a demand not only for better chemotherapy drugs but also markers to help predict outcome and better utilization of limited resources.

While BCRP and ERCC1 overexpression in other cancers has been shown to be associated with decreased response to chemotherapy, we could not prove the same in our subset of patients. One of the strengths of our study was that it utilized a validated and reproducible method for examination of BCRP and ERCC1 expression. As we select biomarkers for application into clinical practice, we need to ensure that the methods are standard and easily reproducible. Our study fulfilled these criteria; however,

due to our limited sample size we were unable to refute our hypothesis. Furthermore, there may be other genetic and clinical factors that we did not account for which may have affected the results of our study.

Several questions have emerged from this study. To our knowledge, we are the first to demonstrate expression of BCRP in esophageal cancer patients and evidence for down-regulation of BCRP expression in 40% of patients with esophageal cancer as compared with their normal esophageal tissue. It remains to be determined if this down-regulation positively impacts response, and whether the patients that respond to irinotecan based chemotherapy are the ones who show this down-regulation. Most of our specimens had received neoadjuvant therapy and we do not know the effect of chemotherapy on either BCRP or ERCC1 expression; whether there is up or down-regulation on exposure to chemotherapy remains to be determined. With the increasing use of cisplatin and other BCRP substrates such as irinotecan for esophageal cancers, these questions merit further evaluation of BCRP and ERCC1 expression in a larger subset of patients as part of a prospective trial for correlation with response to chemotherapies that may be substrates or modulators of BCRP and ERCC1. Furthermore, BCRP expression can be decreased by epidermal growth factor receptor (EGFR) inhibitors, raising the question if treatment with an EGFR inhibitor could improve clinical outcomes by sensitizing BCRP-positive cancers to therapeutic agents that are BCRP substrates. Successful correlation would allow rational selection of chemotherapies and photosensitizers and individualization of treatments for patients, and would help us to tailor regimens for best clinical outcome.

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HER2 status in Barrett's esophagus & esophageal cancer: a meta analysis

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Background: The oncogenic potential of the Human Epidermal Growth Factor Receptor 2 (HER2) is well known in the context of breast cancer however; its relationship with the development of Barrett's Esophagus (BE) and Esophageal Cancer (EC) is unclear. The aim of this meta-analysis was to determine the overall prevalence and survival of HER2+ in BE & EC.

Patients and methods: Several databases were searched including article reference lists. Inclusion criteria required that studies measured HER2 positivity in subjects with BE or EC.

Results: 33 studies were included in the meta-analysis (10 BE & 23 EC studies). The prevalence of HER2+ was found to be 24% (95% CI: 15-36%) in BE and 26% (95% CI: 19-34%) in EC. Squamous cell carcinoma (SCC) had a higher ER of 32% (95% CI: 20-48%) in comparison with adenocarcinoma (ADC) with an ER of 21% (95% CI: 14-32%). Sub group analyses showed a high geographical variance, Asia was found to be the highest prevalent area with an ER 42% (95% CI: 22-64%). The difference in survival rate between groups HER2- & HER2+ was found to be 7 months.

Conclusions: Our results highlight a high prevalence of HER2+ in subjects with adenocarcinoma. HER2+ appears to decrease the survival time of EC patients.

Keywords: Human epidermal growth factor receptor 2 (HER2); Barrett's esophagus (BE); esophageal cancer (EC); meta-analysis

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Introduction

The incidence of oesophageal adenocarcinoma (ADC) has increased more quickly than for any other malignancy in many western countries (1,2) and the rate of ADC is expected to rise in the coming decades (3). Barrett's Esophagus (BE) is a major risk factor for the development of Esophageal Cancer (EC) (4-6). Understanding the role and prevalence of biomarkers such as human epidermal growth factor receptor 2 (HER2) in BE can possibly prevent the progression of this condition to its most lethal form, ADC, which is known for having an extremely poor prognosis, with an overall 5-year survival of around 10% (7) and potentially allow for early intervention for EC.

HER2 positivity status is thought to play a critical role in the development, progression and metastasis of many malignancies such as breast cancer & gastric cancer (8,9). HER2 is over-expressed by at least one fourth of human breast cancers and correlates with poor clinical outcome in women with node-positive and node-negative disease (10). HER2 targeted therapy (trastuzumab) has improved the outcomes of patients with breast cancer that over-expresses HER2 (11,12). A combination of the monoclonal antibody against HER2 (trastuzumab) with standard chemotherapy improved survival significantly in patients with HER2 positive advanced gastric cancer in the Trastuzumab for Gastric Cancer (ToGA) trial (13). However, the role of HER2 in the development and prognosis of BE & EC is yet

to be clarified.

A meta-analysis of the prevalence of HER2 in both BE & EC has to date not been published. Our aim was to perform a meta-analysis combining the results of studies reporting HER2 status in BE & EC, and thus provide a quantitative estimate of the prevalence of HER2+ in BE & EC, and subsequently patient survival. We hypothesized that there will be an increased rate of HER2+ in patients with BE and EC. We also hypothesize that HER2+ will decrease survival time in subjects with EC.

Methods

Literature search strategy

We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. A systematic search of the databases MEDLINE (from 1950), PubMed (from 1946), EMBASE (from 1949), PubMed (from 1950), and Current Contents Connect (from 1980) through to 2013, to identify relevant articles. The search used the terms 'EC' OR 'BE' AND 'HER2' OR 'c-erbB2', which were searched as text word and as exploded medical subject headings where possible. The reference lists of relevant articles were also searched for appropriate studies. No language restrictions were used in either the search or study selection. A search for unpublished literature was not performed.

Study selection

We included studies that met the following inclusion criteria: (I) HER2 positivity was measured in subjects with BE; (II) HER2 positivity was measured in subjects with EC; (III) Diagnostic method was reported; (IV) Prevalence of HER2 in BE or EC was reported. We excluded studies that did not meet the inclusion criteria.

Data extraction

The data extraction was performed using a standardized data extraction form, collecting information on the publication year, study design, number of cases, number of controls (if any), total sample size, temporal direction, population type, country, continent, mean age, number of adjusted variables, the risk estimates or data used to calculate the risk estimates, confidence intervals (CI) or data used to calculate CIs, the rate of HER2 expression & amplification. Quality of the studies was not assessed and

authors were not contacted for missing data.

Statistical analysis

Pooled event rates (ER) and 95% confidence intervals were calculated for the prevalence of HER2 in subjects with BE or EC (14). We tested heterogeneity with Cochran's Q statistic, with $P < 0.10$ indicating heterogeneity, and quantified the degree of heterogeneity using the I^2 statistic, which represents the percentage of the total variability across studies which is due to heterogeneity. I^2 values of 25%, 50% and 75% corresponded to low, moderate and high degrees of heterogeneity respectively (15). The quantified publication bias using the Egger's regression model (16), with the effect of bias assessed using the fail-safe number method. The fail-safe number was the number of studies that we would need to have missed for our observed result to be nullified to statistical non-significance at the $P < 0.05$ level. Publication bias is generally regarded as a concern if the fail-safe number is less than $5n+10$, with n being the number of studies included in the meta-analysis (17). All analyses were performed with Comprehensive Meta-analysis (version 2.0), Biostat, Englewood NJ (2005).

Results

Study characteristics

From 1,403 studies initially identified, 33 met our inclusion criteria (*Figure 1*). Selected characteristic of the included studies are presented in *Tables 1,2*. The studies represented a variety of geographical regions. Sample sizes ranged from 6 to 124 in BE studies and 14 to 713 in EC studies.

BE

Ten studies with 493 subjects in total were included in the meta-analysis for BE. The mean age was 63.85. The average percentage of males with Barrett's associated ADC was 85.06%. The average percentage of females with BE was 12.82%. Only two studies reported percentage of HER2 positivity among male & females.

BE & IHC

Seven studies examined the status of HER2 through IHC, with an ER of 0.24 (95% CI: 0.15-0.36) (*Figure 2*). There was statically significant heterogeneity ($I^2=69.14\%$,

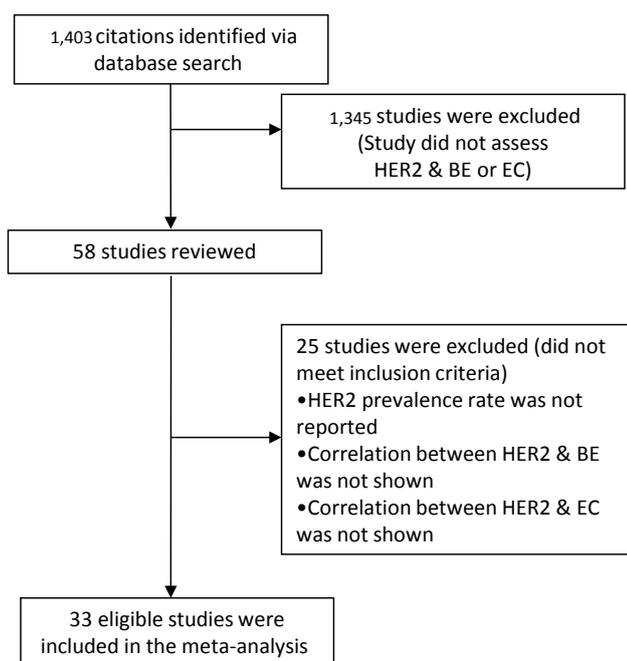


Figure 1 Study selection flowchart.

$P=0.006$). The Egger test for publication bias was not significant ($P=0.43$). A regional comparison was not carried out for BE as 6 out of 7 studies were conducted in Europe.

BE & FISH

Five studies evaluated the prevalence of HER2 positivity through FISH, with an ER of 0.15 (95% CI: 0.06–0.33) (Figure 3). There was statically significant heterogeneity ($I^2=80.00\%$, $P<0.001$). The Egger test for publication bias was not significant ($P=0.89$). A regional comparison was not carried out for BE as 4 out of 5 studies were conducted in Europe.

EC

Twenty three studies with 3,032 were included in the meta-analysis for EC and HER2. The mean age was 63. The average percentage of males with EC was 85.0%, of these an average of 25.14% were HER2 positive. The average percentage of females with EC was 15.0% of these an average of 28.14% were HER2 positive.

EC & IHC

Studies that examined HER2 positivity through IHC had

an ER of 0.26 (95% CI: 0.19–0.34) (Figure 4). There was statistically significant heterogeneity ($I^2=92.45\%$, $P<0.001$). The Egger test for publication bias was not significant ($P=0.25$). The studies evaluating HER2+ in ADC had an ER of 0.21 (95% CI: 0.14–0.32, $P<0.001$). Studies that examined HER2 in squamous cell carcinoma (SCC) had an ER of 0.32 (95% CI: 0.20–0.48). The studies that investigated HER2+ in both ADC & SCC had an ER of 0.30 (95% CI: 0.13–0.55). All three groups, ADC, SCC and the combination had a statistically significant heterogeneity ($P<0.001$), $I^2=91.67\%$, $I^2=88.08$ and $I^2=95.03$ respectively. We also evaluated the regional influence of HER2+ in EC. It was found that Asia had an ER of 0.42 (95% CI: 0.22–0.64) with a statistically significant heterogeneity ($I^2=88.82\%$, $P=0.003$). Europe had an ER of 0.17 (95% CI: 0.10–0.27) with a statistically significant heterogeneity ($I^2=90.79\%$, $P=0.001$). North America had an ER of 0.33 (95% CI: 0.21–0.48). There was statistically significant heterogeneity ($I^2=86.93\%$, $P<0.001$).

EC & ISH

We found an ER of 0.15 (95% CI: 0.10–0.22) (Figure 5). There was statistically significant heterogeneity ($I^2=86.01\%$, $P<0.001$). The Egger test for publication bias was not significant ($P=0.43$). The studies were also evaluated by cancer types (ADC & SCC) (Figure 6). We found an ER of 0.15 (95% CI: 0.09–0.26) for ADC, with a statistically significant heterogeneity ($I^2=91.13\%$, $P<0.001$). The ER for SCC was 0.16 (95% CI: 0.10–0.24), with a statistically non-significant heterogeneity ($I^2=0\%$, $P=0.43$). We also evaluated the regional influence of HER2+ in EC. It was found that Europe had an ER of 0.12 (95% CI: 0.08–0.19). There was statistically non-significant heterogeneity ($I^2=60.17\%$, $P=0.08$). North America had an ER of 0.20 (95% CI: 0.08–0.41). There was statistically significant heterogeneity ($I^2=93.83\%$, $P<0.001$).

EC & survival

The pooled HR is 1.45 (95% CI: 0.85–2.48). It was not statistically significantly ($P=0.17$). Between groups HER2+ & HER2-, a difference of 7 months was noted (95% CI: 6–20 months). This was not statistically significant ($P=0.29$).

Discussion

Our meta-analysis shows that there is a high prevalence rate of HER2+ in both BE and EC populations, 24% and

Table 1 BE studies included in the Systematic Review

No.	Author	Year	Continent	Test Method	Cases
1	Rossi <i>et al.</i> (18)	2010	Europe	IHC, FISH	44
2	Rauser <i>et al.</i> (19)	2007	Europe	IHC, FISH	124
3	Brien <i>et al.</i> (20)	2000	North America	FISH	63
4	Walch <i>et al.</i> (21)	2001	Europe	FISH	23
5	Geddert <i>et al.</i> (22)	2002	Europe	IHC	46
6	Flejou <i>et al.</i> (23)	1994	Europe	IHC	66
7	Hardwick <i>et al.</i> (24)	1995	Europe	IHC	31
8	Nakamura <i>et al.</i> (25)	1994	Europe	IHC	80
9	Kim <i>et al.</i> (26)	1997	North America	IHC	10
10	Walch <i>et al.</i> (27)	2000	Europe	IHC, FISH	6

Table 2 EC studies included in the Systematic Review

No.	Author	Year	Continent	Cases	Test method	Histology
1	Yoon <i>et al.</i> (28)	2012	North America	713	IHC, FISH	EAC
2	Thompson <i>et al.</i> (29)	2011	Australia	89	IHC, SISH	EAC
3	Hu <i>et al.</i> (30)	2011	North America	116	IHC, CISH	EAC
4	Reichelt <i>et al.</i> (31)	2006	Europe	255	IHC, FISH	EAC
5	Hardwick <i>et al.</i> (32)	1997	Europe	127	IHC	EAC & SCC
6	Duhaylongsod <i>et al.</i> (33)	1995	North America	42	IHC	EAC
7	Sauter <i>et al.</i> (34)	1993	North America	14	IHC	EAC
8	Langer <i>et al.</i> (35)	2011	Europe	142	IHC, FISH	EAC
9	Friess <i>et al.</i> (36)	1999	North America	39	IHC	EAC & SCC
10	Mimura <i>et al.</i> (37)	2005	Asia	66	IHC, FISH	SCC
11	Stoecklein <i>et al.</i> (38)	2008	Europe	107	FISH	EAC & SCC
12	Polkowski <i>et al.</i> (39)	1999	Europe	41	IHC	EAC
13	Sato-Kuwabara <i>et al.</i> (40)	2009	South America	185	IHC, FISH	SCC
14	Yamamoto <i>et al.</i> (41)	2012	Asia	142	IHC	SCC
15	Birner <i>et al.</i> (42)	2011	Europe	330	IHC	EAC & SCC
16	Wei <i>et al.</i> (43)	2007	Europe	40	IHC	SCC
17	Sano <i>et al.</i> (44)	1997	North America	32	IHC	EAC & SCC
18	Brien <i>et al.</i> (20)	2000	North America	63	ISH	EAC
19	Nakamura <i>et al.</i> (21)	1994	Europe	62	IHC	EAC
20	Zhan <i>et al.</i> (45)	2012	Asia	145	IHC, FISH	SCC
21	Flejou <i>et al.</i> (23)	1994	Europe	66	IHC	EAC & SCC
22	Bizari <i>et al.</i> (46)	2006	South America	40	IHC, FISH	SCC
23	Schoppmann (47)	2011	Europe	176	IHC, CISH	EAC & SCC

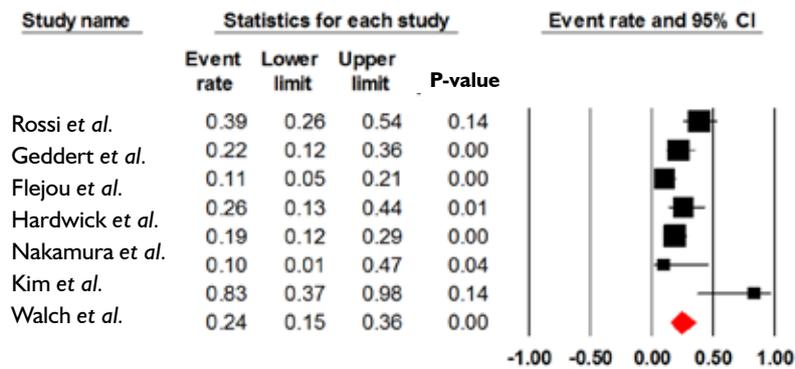


Figure 2 HER2+ event rates in BE studies using IHC.

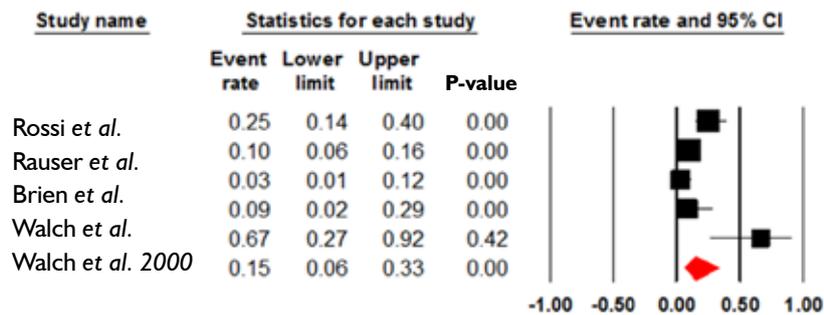


Figure 3 HER2+ event rates in BE studies using FISH.

26%, respectively. The prevalence rate of HER2+ in EC and BE is higher than that of Breast Cancer (12,48). The ratio between male and females in the studies was 5:1 in both BE and EC subjects. From EC studies it was shown that although the proportion of women diagnosed with EC was lower than males, the prevalence of HER2+ was slightly higher. Men had an event rate of 25.14%, while women were 28.14%. On the contrary, analysis of the two studies that had reported HER2+ percentage among males and females in BE studies showed that the prevalence of HER2+ among male was almost double that of women. Both BE and EC studies have shown that Stage III had the highest percentage of patients. The low level of HER2+ in Stage I and II can be explained by the late diagnosis of the disease. The significance of tumour staging in HER2+ is still not clear. Ryu *et al.* (49) has shown that an increase in HER2 in the serum was correlated to tumour staging and histological grading in breast cancer patients. On the other hand, Mahzouni *et al.* (6) has shown that there was no correlation

between HER2+ and tumour staging among meningioma patients.

Studies assessing BE show wide variation in terms of HER2+. Almost half the studies classified the patient groups as having either low or high grade dysplasia, while other studies classified patients as having Barrett's associated ADC. These studies have the potential of misclassification bias and increased heterogeneity due to the mixing of these two groups. Further studies of pure Barrett's oesophagus patients are required. The effect of reflux disease on the HER2+ rate is unknown as no studies have specifically addressed this patient group.

A larger proportion of the included BE studies analysed HER2 status using IHC while a very small number have used FISH. This validates the results as the diagnostic method is of the same nature in the included studies. Another consistent factor noticed in the BE studies was the regional variation. The majority of the studies have conducted the analysis in European patients/region, which

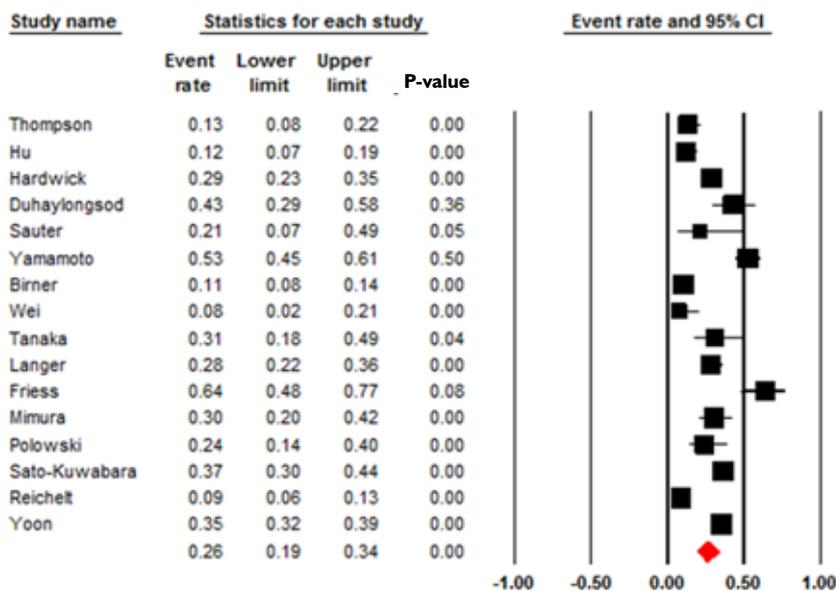


Figure 4 HER2+ event rates in EC studies using IHC.

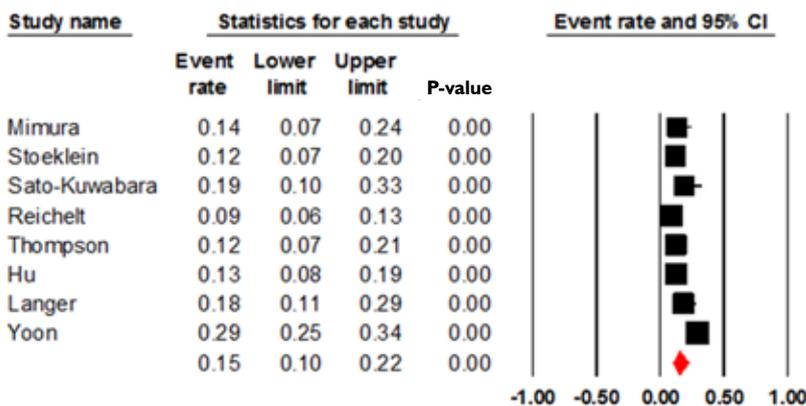


Figure 5 HER2+ event rates in EC studies using FISH.

once again provides accuracy in analysing these data as one. The BE sample size is relatively low, this may decrease the quality and power of the BE analysis. Our findings suggest that the investigation of HER2 might be beneficial in characterizing the progression from BO to dysplasia and ADC. These potential markers might also contribute to deciding alternative therapeutic methods, as advised by some preliminary data (50).

The prevalence rate of HER2+ among patients with

SCC was significantly higher than that of ADC. When comparing studies that have included both ADC and SCC, the reason for this difference of HER2+ between ADC and SCC is unclear. Hardwick *et al.* (32) have analysed HER2+ among ADC and SCC separately and have shown that SCC has a higher HER2+ prevalence than ADC. On the other hand, Birner *et al.* (42) have shown that ADC has a higher HER2+ rate than SCC. The two remaining studies Stoecklein *et al.* (38) and Friess *et al.* (36) have combined

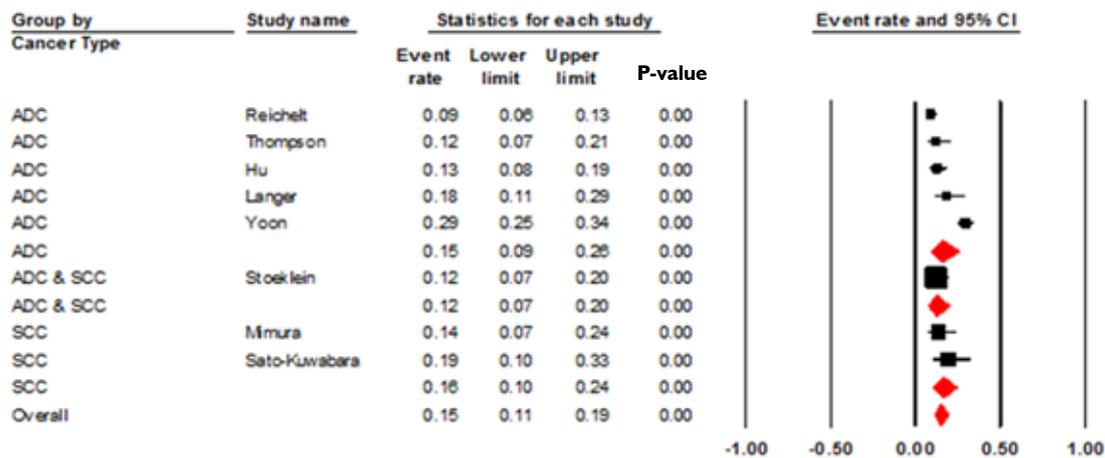


Figure 6 HER2+ event rates in EC studies by cancer types (ADC or SCC).

the prevalence rate of HER2+ among ADC and SCC and therefore prevalence rates between the two groups was not defined. The meta-analysis has shown that an event rate of HER2+ in EC was highest in Asian regions. This is likely due to the fact that Asian regions, especially China have the highest incidence of SCC in the world (51,52). This increased rate of incidence could be due to risk factors such as genetic predisposition (51), high concentrations of nitrate nitrogen in drinking water (53) and other water resources (54).

The survival analysis among the EC studies concluded that subject who are HER2+ have an average decreased survival rate of 7 months. Although the accumulated results conclude that HER2+ leads to poor prognosis compared to HER2-, a handful of the studies that were included such as Duhaylongsod *et al.* (33) and Yoon *et al.* (28) have stated that HER2+ improves survival compared to HER2-. Four studies (29,30,32,36) have concluded that HER2+ does not make a difference in survival rate, while six studies (31,35,37-40) report that HER2+ decreases the survival rate. The discrepancies among results can be due to factors such as, patient definition, diagnostic methods, and classification of HER2+. It has been suggested that poorer survival in HER2-positive patients with squamous cell carcinoma could be due to increased resistance to radiation therapy (55) and cisplatin-based chemotherapy (56). Moreover, the addition of trastuzumab in head and neck squamous cell carcinoma cell lines seemed to enhance the effect of irradiation (57).

The statistically significant heterogeneity and publication bias amongst the included studies may be due to several factors. There is a slight variation in the patient eligibility

for each study. These differences in patient definition can lead to potential bias and could drive the analysis in one direction. Excluding studies that appear to be outliers may have potentially reduced heterogeneity. Due to the limited number of studies available in this area, excluding these studies will reduce sample size and consequently increase heterogeneity once again.

Similarly, the classification system used between each study for HER2+ varies. Studies such as Hu *et al.* (30), Reichelt *et al.* (31), Wei *et al.* (43) and Sato-Kuwabara *et al.* (40) have classified HER2+ as IHC ≥ 2 while Mimura *et al.* (37) have drawn the line at IHC ≥ 1 , and Langer *et al.* (35) have classified HER2+ as IHC 3+. Similarly with FISH, Langer *et al.* (35), Mimura *et al.* (37), Thompson *et al.* (29) and Hu *et al.* (30) have classified HER2+ as FISH 2+, while Sato-Kuwabara *et al.* (40) have classified HER2+ as FISH 3+. A standardized classification system is required in order to determine the full potential of HER2+ in EC. Misclassification of IHC results will consequently affect results of FISH. There was a variation in event rate between the diagnostic methods. The ER of HER2+ was high through IHC, in comparison to the ER of HER2+ through FISH (for both BE & EC). Ahmed *et al.* (58) has stated that in the case of breast cancer results of IHC and FISH require a minimum of 95% concordance, which we have not seen in the current study. Barrett *et al.* (59) has highlighted that IHC 2+ weak positive are often not accompanied by a FISH positive or represent gene amplification in breast cancer tissues. The HercepTest™ is considered valid for the identification of HER2+ in the case of gastric cancer (60), no classification system has been implemented for EC. The

accuracy of the IHC HER2+ results is vital in determining the FISH status. The validity of the results can also be questioned by the diagnostic method each study has used.

Studies such as Reichelt *et al.* (31) provided strong clinical and experimental data and by collaborating these data they have provided survival outcomes of patients, which was vital in the survival analysis. This study also had strong FISH and IHC concordance. The studies that have studied one histology of EC (ADC or SCC) have a higher quality of data in comparison to studies that have combined these data. This is reflective in the homogeneity of the study sample.

Langer *et al.* (35) has stated that the correlation between the biomarker and increase mortality can only be demonstrated through 3D *in situ* hybridization. This raises the question of validity among all other studies that have not carried out this technique but have completed a survival analysis. Studies published prior to 2000 have examined molecular markers such as c-erb2 and p53, while studies post 2000 have focused on HER2. There is evidently a variation in prognostic factors. While Yoon *et al.* (28) has reported that two pathologists were used to examine HER2+, many other studies have failed to mention methods used to analyse HER2+.

The Mayo Clinic (28) has so far published the largest cohort evaluating the relationship between HER2/ErbB2 expression and oesophageal adenocarcinomas out of the 713 patients (17%) of EACs were HER2+, with strong agreement between HER2 amplification and expression ($k=0.83$). HER2+ was significantly associated with lower tumour grade, less invasiveness, fewer malignant nodes, and the presence of adjacent BE. EACs with BE had higher odds of HER2 positivity than EACs without BE, independent of pathologic features [OR=1.8 (95% CI: 1.1-2.8)]. Among all cases, HER2 positivity was significantly associated with disease-specific survival (DSS) in a manner that differed by the presence or absence of BE ($P_{\text{interaction}}=0.0047$). In EACs with BE, HER2 positivity was significantly associated with improved DSS [HR=0.54 (95% CI: 0.35-0.84), $P=0.0065$] and overall survival ($P=0.0022$) independent of pathologic features, but was not prognostic among EACs without BE.

In the recently published ToGA trial (13), which was the first randomized, controlled, Phase III trial for gauging the effectiveness of trastuzumab in gastric cancer, A total of 594 with locally advanced or metastatic HER2-overexpressing adenocarcinoma of the stomach or gastroesophageal junction (GEJ) were randomized to receive trastuzumab plus chemotherapy or chemotherapy alone. Twenty-two

per cent of patients out of more than 3,800 cases screened in 24 countries showed HER2 expression, with a good concordance rate between IHC staining and FISH. The tumours were confirmed to be either HER2 gene amplified by FISH or protein overexpressing via IHC. The patients were included in the study only if the tumour was scored as 3+ on IHC or if it was 2+ on IHC and FISH positive

Among the patients that entered the study, 82% had primary gastric cancer and 18% had primary GEJ adenocarcinoma. Ninety-seven per cent had metastatic disease. The median age was 60 years (range, 21-83 years) and 76% were male. Previous therapies included gastrectomy (23%), previous neoadjuvant and/or adjuvant therapy (7%) and previous radiotherapy (2%). Trastuzumab was administered at an initial dose of 8 mg/kg intravenously followed by 6 mg/kg every 3 weeks until disease progression or significant toxicity. The chemotherapy regimen comprised of cisplatin 80 mg/m² intravenously every 3 weeks for six cycles and a fluoropyrimidine (either capecitabine 1,000 mg/m² orally twice daily for 14 days or 5-fluorouracil 800 mg/m²/day continuous intravenous infusion for 5 days every 3 weeks for six cycles).

The trial was sealed after the second interim analysis when 167 deaths had occurred on the trastuzumab arm and 184 deaths on the control arm. In the final analysis, the median survival was 13.8 months in patients allocated to trastuzumab plus chemotherapy compared with 11.1 months in chemotherapy group alone ($P=0.0046$). Overall tumour response, complete or partial, was significantly increased (47% *vs.* 35%) in trastuzumab plus chemotherapy arm versus chemotherapy alone. The hazard ratio (HR) was 0.74 (95% CI: 0.60-0.91; $P=0.0036$, two sided) in favour of the trastuzumab arm. Exploratory survival analyses in subgroups defined by IHC testing indicated that trastuzumab was most effective in prolonging survival in the IHC 3+ tumours and less effective in IHC 2+ tumours. However, the final exploratory survival analyses included only the HER2/neu FISH positive patients.

In October 2010, the FDA granted approval for trastuzumab in combination with cisplatin and a fluoropyrimidine (capecitabine or 5-fluorouracil) for the treatment of patients with HER2-overexpressing metastatic gastric or GEJ adenocarcinoma who have not received previous treatment for metastatic disease (13). Several ongoing trials have the goal of evaluating trastuzumab in oesophagogastric and/or gastric cancer in the first line in combination with chemotherapy or as a salvage agent in

recurrent cancer.

In conclusion, it was seen that HER2+ prevalence in both BE and EC was relatively high with approximately a fourth of patients indicating HER2+. HER2+ in EC has been shown to decrease survival. HER2+ targeted therapy for eligible patients should be considered and carried out in a clinical trial. Further studies looking at HER2+ effect on survival should also be carried out with all relevant diagnostic methods and classification systems used.

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Forthcoming prognostic markers for esophageal cancer: a systematic review and meta-analysis

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Background: The incidence of esophageal cancer is rising, and survival rates remain poor. This meta-analysis summarizes five molecular mechanisms of disease progression, which are related to prognosis.

Patients and methods: A systematic search was conducted using MEDLINE, PubMed, EMBASE, Current Contents Connect, Cochrane library, Google Scholar, Science Direct, and Web of Science. Original data was abstracted from each study and used to calculate a pooled event rate and 95% confidence interval (95% CI).

Results: Our analysis included five octamer-binding transcription factor 4 (OCT4) studies (564 patients), six sex determining region Y-box 2 (SOX2) studies (336 patients), five oestrogen receptor (ER) studies (367 patients), seven MET or MNNG HOS Transforming gene (c-Met) studies (1,015 patients) and six insulin like growth factor receptor studies (764 patients). Incidence of OCT4 in SCC was 53.60% (95% CI: 0.182-0.857) and the overall hazard ratio for poor clinic outcome was 2.9 (95% CI: 1.843-4.565). The incidence of SOX2 in SCC was 69.2% (95% CI: 0.361-0.899) however, was associated with significant heterogeneity of 90.94%. The prevalence of Oestrogen receptor α and β in SCC were 37.90% (95% CI: 0.317-0.444) and 67.20% (95% CI: 0.314-0.901) respectively. The prevalence of MET in EAC was 33.20% (95% CI: 0.031-0.884) and the incidence of insulin-like growth factor-1 receptor (IGF-1R) in EAC was 67.70% (95% CI: 0.333-0.898).

Conclusions: Our results show that the status of ER, OCT4 and SOX2 expression correlates with the unfavourable prognosis in patients with esophageal squamous cell carcinoma (ESCC). This study also highlights the potential impact of the IGF-1R on the biology of EAC and the expression of Met was recognised as a significant prognostic factor. Our data supports the concept of IGF axis, ER, Met, OCT4 and SOX2 inhibition as (neo-) adjuvant treatment.

Keywords: Esophageal cancer; insulin-like growth factor axis (IGF axis); oestrogen receptors (ER); MET or MNNG HOS Transforming gene (c-Met); octamer-binding transcription factor 4 (OCT4); sex determining region Y-box 2 (SOX2)

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Introduction

The incidence and mortality from cancer of all types in the United States has decreased during the 1991–2006 timeframe (1). However, the opposite is true for esophageal cancer. Its incidence and mortality continue to rise. In 2010, estimated new cases of esophageal cancer number 16,640 in the United States, while deaths total 14,500 (1). The United States has seen an average increase of 20.6% per year in the incidence of adenocarcinoma of the esophagus

since that time (2). It is projected that there will be 16,470 new patients diagnosed with esophageal cancer and 14,280 deaths from it in 2008 (1).

Esophageal cancer is a highly lethal disease in which only one-third of patients present with resectable disease. Of this select group, the average 5-year survival is only 35–45% (3). Another consideration is our less-than-satisfactory ability to predict particular tumour's response to neoadjuvant therapy. Targeted molecular therapy in upper gastrointestinal cancer has become an increasingly popular topic over the past few

years. In part, this is due to rapid advances in our capability to characterize tumour biology. In esophageal cancer, VEGF (4), E-cadherin (5), COX2 (6), Survivin (7), EGFR (8) and HER2 (9) have been thoroughly investigated in the past with the help of a meta-analysis. However, insulin-like growth factor axis (IGF axis), oestrogen receptors (ER), MET or MNNG HOS Transforming gene (c-Met), octamer-binding transcription factor 4 (OCT4) and sex determining region Y-box 2 (SOX2) have not been examined.

Current concepts suggest that centrally deposited fat, so-called visceral adipose tissue, is more metabolically active than peripheral subcutaneous fat, and a more significant fuel for the association with dysmetabolism and related problems, including cancer (10). The IGF axis is thought to play a role in the link between obesity and cancer (11). The observation that insulin resistance is associated with an increased risk of cancer has led to the hypothesis that this may be mediated through the IGF axis (12,13).

One promising subset may include tumours with MET gene amplification resulting in overexpression and constitutive activation of the encoded receptor tyrosine kinase MET (14,15). In a large-scale preclinical screening approach, previously MET amplification in approximately 20% of gastric cancer cell lines and have demonstrated that this amplification confers extraordinary susceptibility to apoptosis induction by the selective MET inhibitor PHA-665752 (Pfizer, La Jolla, CA) (16). Recently, crizotinib (PF-02341066, Pfizer) was identified as an orally bioavailable, potent, ATP-competitive small-molecular inhibitor of the catalytic activity of MET kinase (17,18).

Sox2 is an important member of the Sox gene family. Sox (SRY box) genes have been identified through their homology to the high mobility group (HMG) box (79 amino acids) of sex-determining factor SRY (19-22). The Sox genes encode transcription factors that interact with DNA through their highly conserved HMG domain (23,24). The Sox genes are expressed in a wide variety of tissues, and play important roles in the regulation of organ development and cell type specification (20,22). It has been found that amplification at the chromosomal region 3q26 occurs frequently in esophageal squamous cell carcinoma (ESCC) and that SOX2 within the 3q26 amplicon is amplified and overexpressed (25).

OCT4, also known as OCT3, belongs to the POU (Pit-Oct-Unc) transcription factor family (26). The POU family of transcription factors can activate the expression of their target genes through binding the octameric sequence motif with an AGTCAAAT consensus sequence (27,28). The

expression of this gene is necessary for the maintenance of pluripotentiality in embryonic stem cells (ESCs) and primordial germ cells and is down-regulated in all differentiated cells *in vitro* as well as *in vivo* (28).

The striking 3-4: one male predominance of ESCC has been observed in areas (29,30). The molecular mechanisms for such distinct gender difference in term of mortality rate and prognosis are not clear. Sex hormones, especially the typical type of oestradiol/oestrogen, and their respective receptors have been speculated to be crucial determinants for sex-related susceptibility to cancer. Oestrogen and progesterone receptors (ER and PR) are over-expressed in EC tissue whereas absent in mature normal esophageal mucosa of the foetus (31). Inhibitory effect by oestrogen on ESCC growth and development has been observed in mouse ESCC model (32). Studies on breast and endometrial cancers have shown that there are two different isoforms of human ER, i.e., ER α and ER β , both of which are receptors for oestradiol. Recent studies have indicated that ER α expression is an unfavourable prognostic indicator in ESCC (33).

The aim of this meta-analysis was to summarize these five molecular mechanisms of disease progression, which are related to prognosis.

Methods

Study protocol

We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses PRISMA guidelines where possible in performing our systematic review (34). We performed a systematic search through MEDLINE (from 1950), PubMed (from 1946), EMBASE (from 1949), Current Contents Connect (from 1998), Cochrane library, Google scholar, Science Direct, and Web of Science to May 2013. The search terms included “esophageal cancer”, “SOX2, OCT4, MET, IGF and oestrogen”, which were searched as text word and as exploded medical subject headings where possible. No language restrictions were used in either the search or study selection. The reference lists of relevant articles were also searched for appropriate studies. A search for unpublished literature was not performed.

Study selection

We included studies that met the following inclusion criteria:

- Studies identifying the population of patients with

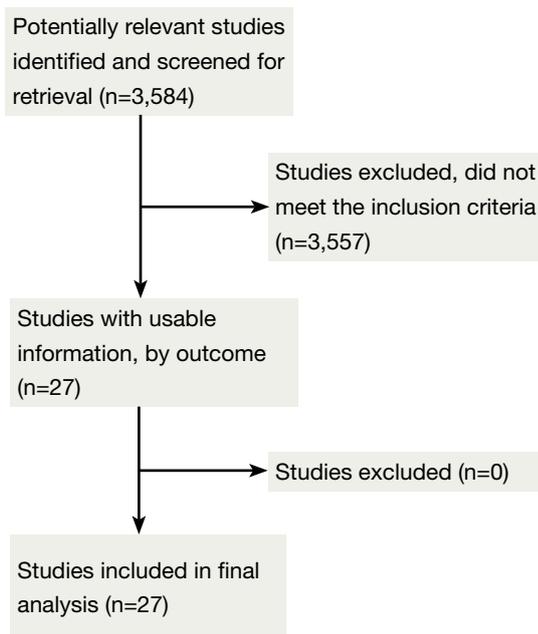


Figure 1 Flow of included studies.

esophageal cancer;

- Studies dealing with the association between SOX2, OCT4, MET, insulin like growth factor receptor and oestrogen with esophageal cancer.

Data extraction

We performed the data extraction using a standardized data extraction form, collecting information on the publication year, study design, number of cases, total sample size, population type, country, continent, mean age and clinical data. The event rate and confidence intervals were calculated.

Statistical analysis

Pooled event rate and 95% confidence intervals were using a random effects model (35). We tested heterogeneity with Cochran's Q statistic, with $P < 0.10$ indicating heterogeneity, and quantified the degree of heterogeneity using the I^2 statistic, which represents the percentage of the total variability across studies which is due to heterogeneity. I^2 values of 25%, 50% and 75% corresponded to low, moderate and high degrees of heterogeneity respectively (36). The quantified publication bias using the Egger's regression model (37), with the effect of bias assessed using the fail-safe number method. The fail-safe number was the number of

studies that we would need to have missed for our observed result to be nullified to statistical non-significance at the $P < 0.05$ level. Publication bias is generally regarded as a concern if the fail-safe number is less than $5n + 10$, with n being the number of studies included in the meta-analysis (38). All analyses were performed with Comprehensive Meta-analysis (version 2.0).

Results

The original search strategy 3,584 retrieved studies (Figure 1). The abstracts were reviewed and articles were selected for full-text evaluation. Of the articles selected, only 27 studies (12,484 patients) met full criteria for analysis and are summarised in Table 1. This included five OCT4 studies (564 patients), six SOX2 studies (336 patients), five oestrogen receptor studies (367 patients), seven MET studies (1,015 patients) and 6 Insulin like growth factor receptor studies (764 patients). The years of publication ranged from 1990 to 2012.

The incidence of OCT4 in SCC was 53.60% (95% CI: 0.182-0.857) and the overall hazard ratio for poor clinic outcome was 2.9 (95% CI: 1.843-4.565). The incidence of SOX2 in SCC was 69.2% (95% CI: 0.361-0.899) however, was associated with significant heterogeneity of 90.94%. The prevalence of ER α and β in SCC were 37.90% (95% CI: 0.317-0.444) and 67.20% (95% CI: 0.314-0.901) respectively. The prevalence of MET in EAC was 33.20% (95% CI: 0.031-0.884) and the incidence of insulin-like growth factor-1 receptor (IGF-1R) in EAC was 67.70% (95% CI: 0.333-0.898).

Heterogeneity and publication bias

The heterogeneity of outcomes has been summarized in Table 2. The reason for significant heterogeneity may be attributed to different population groups. No publication bias was detected using the Egger's regression model.

Discussion

Esophageal cancer is one of the most aggressive neoplasms and the overall prognosis for esophageal cancer patients is poor (64). One of the reasons for the low survival rate is the tumour's intrinsic resistance to many clinical therapies, especially chemotherapy. Chemotherapy often removes the bulk of a tumour mass without preventing tumour recurrence, suggesting the

Table 1 Characteristic of the studies included in the systematic review

Author	Biomarker	Tumour type	Country	Year	Patients
Li <i>et al.</i> (39)	OCT4	ESCC	China	2012	50
Wang <i>et al.</i> (40)	SOX2 and OCT4	ESCC	Norway	2009	162
He W <i>et al.</i> (41)	OCT4	ESCC	China	2012	153
Zhou Xi <i>et al.</i> (42)	OCT4	ESCC	China	2011	174
Bass <i>et al.</i> (43)	SOX2	ESCC	U.S.A	2009	40
Bahl <i>et al.</i> (44)	SOX2 and OCT4	ESCC	India	2012	25
Saigusa <i>et al.</i> (45)	SOX2	ESCC	Japan	2011	20
Gen <i>et al.</i> (25)	SOX2	ESCC	Japan	2010	40
Long <i>et al.</i> (46)	SOX2	ESCC and EAC	USA	2009	49
Nozoe <i>et al.</i> (33)	Oestrogen receptors α and β	ESCC	Japan	2007	73
Liu <i>et al.</i> (47)	Oestrogen receptor β	EAC	USA	2004	27
Wang <i>et al.</i> (48)	Oestrogen receptor β	ESCC	China	2011	132
Kalayarasan <i>et al.</i> (49)	Oestrogen and progesterone receptors	ESCC and EAC	India	2008	45
Zuguchi <i>et al.</i> (50)	Oestrogen receptors α and β	ESCC	Japan	2012	90
Saeki <i>et al.</i> (51)	C-MET	ESCC	Japan	2002	76
Tuynman <i>et al.</i> (52)	C-MET	EAC	The Netherlands	2008	145
Houldsworth <i>et al.</i> (53)	C-MET	EAC	USA	1990	1
Porte <i>et al.</i> (54)	C-MET	ESCC and EAC	Italy	1998	36
Anderson <i>et al.</i> (55)	C-MET	EAC	UK	2006	72
Lennerz <i>et al.</i> (56)	C-MET	EAC	USA	2011	489
Kato <i>et al.</i> (57)	C-MET	ESCC	Japan	2013	196
Imsumran <i>et al.</i> (58)	IGF-Ir	ESCC	USA	2007	100
Donohoe <i>et al.</i> (59)	IGF-Ir	EAC	Ireland	2012	220
Doyle <i>et al.</i> (60)	IGF-Ir	EAC	Ireland	2012	124
Kalinina <i>et al.</i> (61)	IGF-Ir	EAC	Germany	2010	234
Iravani <i>et al.</i> (62)	IGF-Ir	EAC	USA	2003	34
Zhao <i>et al.</i> (63)	IGF-Ir	EAC	Canada	2009	52

Table 2 Overall odds ratio and 95% CI for patient outcomes

Outcome	Event rate (%)	95% CI	I ²	P value
Incidence of OCT4 in SCC	53.6	0.182-0.857	97.65	<0.001
OCT4 pooled hazard ratio	2.9	1.843-4.565	0.00	0.51
Incidence of SOX2 in SCC	69.2	0.361-0.899	94.37	<0.001
Incidence of oestrogen receptor β in SCC	67.2	0.314-0.901	94.88	<0.001
Incidence of oestrogen receptors α in SCC	37.9	0.317-0.444	0.00	0.41
Incidence of MET in EAC	33.2	0.031-0.884	98.81	<0.001
Incidence of IGF-1R in EAC	67.7	0.333-0.898	89.87	<0.001

survival of a subset of cancer stem cells. Studies have provided experimental evidence for the concept that human tumour growth may depend on a small portion cancer stem cells (65).

SOX2 and OCT4

The expressions of Oct3/4 and Sox2 were firstly discovered in human esophageal squamous cancer cell lines with the

antibody AF1759 and MAB2018 from R&D System for immunocytochemistry. Among 153 specimens from the department of Oncology at Zhengzhou University (66), 105 (68.7%) were negative or weakly positive for OCT4 staining; 21 (13.7%) were moderately positive and 27 (17.6%) were strongly positive. Higher expression level of OCT4 was significantly associated with higher histological grade ($P<0.001$), indicating its correlation with dedifferentiation of these tumours. The median follow-up time for the 56 patients still alive was 124 months (range, 118-155 months) and for the remaining 97 patients who died during the follow-up period was 61 months (range, 1-139 months). In univariate analysis, patients with low OCT4 expression level in tumours had a better overall survival than patients with tumour showing moderate or high OCT4 expression level ($P=0.002$ and $P<0.001$), respectively. Zhou *et al.* (42) Oct4 protein was expressed in most (93.7%) ESCC samples but it was not observed in esophageal mucosa. The over-expression of Oct4 in ESCCs suggests that it is a potential target for ESCC therapy. Oct4 could be a useful tumour marker in an immunohistochemical panel designed to differentiate between ESCC and esophageal mucosa. Expression of Oct4 in tumorspheres might indicate the presence of a population of ECSCs and its expression in xenograft tumours suggests that Oct4 is also associated with tumour metastasis. SOX2 gene is an amplification target of 3q26.3 in ESCC, and that SOX2 promotes ESCC cell proliferation *in vitro* (25). LY294002, an inhibitor of phosphatidylinositol 3-kinase, and rapamycin, an inhibitor of mTORC1, suppressed the ability of SOX2 to enhance proliferation of ESCC cells *in vitro*. Effects of SOX2 knockdown, including reduced levels of phosphorylated AKT and decreased ESCC cell proliferation, were reversed with constitutive activation of AKT with knockdown of phosphatase and tensin homolog. In mouse xenografts, SOX2 promoted *in vivo* tumor growth of ESCC, which was dependent on AKT/mTORC1 activation. LY294002 suppressed the ability of SOX2 to enhance tumor growth of ESCC by reducing cell proliferation, but not by enhancing apoptosis. These findings suggest that SOX2 promotes *in vivo* tumor growth of ESCC through activation of the AKT/mTORC1 signaling pathway, which enhances cell proliferation (67).

Wang *et al.* (40) established that Sox2 expressions were significantly associated with higher histological grade ($P<0.001$ for both factors), indicating their correlation to dedifferentiation in these tumours and a significant correlation between increasing levels of

Sox2 immunostaining and decreasing survival for the patients ($P<0.001$) was observed. After being stratified by histological grade, Sox2 expressions were still significantly associated with unfavourable overall survival ($P=0.008$ and $P=0.003$, respectively).

The role of OCT4 & Sox2 in esophageal carcinogenesis evidences further studies.

Oestrogen receptor

Oestrogens, the primary female sex hormones, are mechanistically linked to aspects of cancer risk and cancer development. A connection between oestrogen-activated signalling and carcinogenesis in many organs, including mammary glands (68), ovaries and colon (69) has been clearly defined, although it is unclear whether a similar connection exists for the esophagus, and esophageal adenocarcinoma in particular. Furthermore, oestrogen is actively involved in the regulation of metabolism in adipose tissues (70), and it can be synthesized locally by activated aromatase in adipocytes in both men and women (71). Therefore it seems reasonable to consider that oestrogens might contribute towards the gender difference for esophageal adenocarcinoma. Involvement of oestrogen signalling in regulation of adipose tissue metabolism indicates a possible connection between the effects of oestrogen and male obesity-one of the main risk factors for esophageal adenocarcinoma.

A recent article from Japan (50) ER α immunoreactivity was detected in the nuclei of carcinoma cells in 38/90 ESCC ER β immunoreactivity was detected in the nuclei of carcinoma cells with a variety of immunointensity in 88/90 ESCC. Correlation between the status of ER β immunoreactivity and clinicopathological variables in 90 ESCC patients There was a statistically significant positive association between ER β H score and tumor differentiation ($P=0.0403$) and TNM-pM (LYM) ($P=0.0164$). There was also a weak but statistically significant positive correlation between the ER β H score and Ki67/MIB1 LI ($P=0.0497$, $r=0.207$). No significant association was detected between ER β immunoreactivity and age, gender, tumor size, depth of tumor invasion, presence of lymph node metastasis, TNM stage, lymphatic invasion, venous invasion or infiltrative growth pattern of the patients examined in the present study.

The patients with positive nuclear ER α immunoreactivity in carcinoma cells were by no means associated with better survival or favorable clinical outcome (log-rank test: OS,

P=0.4660; DFS, P=0.3468). In the present study, the patients with high nuclear ER β immunoreactivity were significantly associated with shorter survival or adverse clinical outcome (log-rank test: OS, P=0.0017; DFS, P=0.0005). Results of univariate analysis (Table 2) demonstrated that pathological stage (OS, P=0.0003; DFS, P=0.0006), ER β status in the nucleus of carcinoma cells (OS, P=0.0025; DFS, P=0.0010), tumor size (OS, P=0.0485; DFS, P=0.0366) and infiltration type (OS, P=0.0200; DFS, P=0.0416) were all significant prognostic factors for OS and/or DFS in 90 ESCC examined in our study. A subsequent multivariate analysis did reveal that ER β status (OS, P=0.0010; DFS, P=0.0007) was an independent prognostic factor for OS and DFS of these patients, as well as pathological stage (OS, P=0.0019; DFS, P=0.0091) and infiltration type (OS, P=0.0185; DFS, P=0.0328).

Future perspective would be if a confirmed link might provide support for ER β to be used as a target for therapy, or as a prognostic marker.

Met expression and esophageal adenocarcinoma

The Met receptor is a tyrosine kinase receptor, the product of a proto-oncogene (72). It acts as a receptor for hepatocyte growth factor (HGF), a potent mitogen and pro-motility agent for epithelial cells (73,74). HGF is primarily produced by mesenchymal cells to act on Met-expressing epithelial cells in a paracrine fashion (75).

The predominant adhesion protein of epithelial tissue is E-cadherin (13), and this is down-regulated in esophageal cancer (76). E-cadherin binds to β -catenin at the cell membrane and is linked to the control of β -catenin—regulated transcription (77,78). The β -catenin protein is found in three cellular pools: membranous, cytoplasmic, and nuclear. The translocation among these is tightly regulated (79), and the dynamic equilibrium determines the signaling role (80). Nuclear β -catenin is seen in esophageal tumorigenesis (81), and many catenin target genes show increased expression (82,83). Studies have shown an association between HGF/Met stimulation and increased phosphorylation of β -catenin in cell lines (84-86).

Studies of the expression of Met in esophageal malignancy showed increased expression in tumors compared with normal mucosa (51,77,87). Met activation in esophageal cancer induces changes consistent with early invasion, such as down-regulation of E-cadherin, increased nuclear TCF/ β -catenin signaling, and anchorage-independent growth. The expression of Met in esophageal adenocarcinoma is

associated with a poorer prognosis *in vivo* (55).

The crizotinib expanded phase I cohort study was performed by Massachusetts General Hospital/Harvard Medical School (56). Ten (2%) of 489 patients screened harbored MET amplification; 23 (4.7%) harbored EGFR amplification; 45 (8.9%) harbored HER2 amplification; and 411 (84%) were wild type for all three genes (i.e., negative). MET-amplified tumors were typically high-grade adenocarcinomas that presented at advanced stages (5%; n=4 of 80). EGFR-amplified tumors showed the highest fraction of squamous cell carcinoma (17%; n=4 of 23). HER2, MET, and EGFR amplification were, with one exception (MET and EGFR positive), mutually exclusive events. Survival analysis in patients with stages III and IV disease showed substantially shorter median survival in MET/EGFR-amplified groups, with a rank order for all groups by median survival (from most to least aggressive): MET (7.1 months; P<0.001) less than EGFR (11.2 months; P=0.16) less than HER2 (16.9 months; P=0.89) when compared with the negative group (16.2 months). Two of four patients with MET-amplified tumors treated with crizotinib experienced tumor shrinkage (-30% and -16%) and experienced progression after 3.7 and 3.5 months. MET amplification defines a small and aggressive subset of GEC with indications of transient sensitivity to the targeted MET inhibitor crizotinib (PF-02341066).

These efforts suggest that implementation of larger-scale, genome-wide assays—which would include assessment of MET copy number as well as other infrequent gene amplifications—may be an effective approach to identify multiple rare subgroups that might benefit from targeted therapies.

Insulin like growth factor axis and esophageal adenocarcinoma

Insulin resistance leads to reduced levels of IGF binding proteins and results in a subsequent increase in free IGF-1 (88). Prospective studies have shown a relationship between circulating IGF-1 and the risk of developing prostate, breast, colorectal and other cancers (12). The IGF-1R plays a role in the establishment and maintenance of cellular transformation (89), and the receptor or its ligands may be overexpressed in human tumours (90,91). Its action may protect against apoptosis, and favours invasion and metastasis (92,93).

Howard *et al.* (94) stated that 91% of patients with esophageal adenocarcinoma expressed leptin receptor (ObR), 95% expressed adiponectin receptors 1 (AdipR1)

and 100% expressed adiponectin receptors 2 (AdipR2). Relative expression of ObR was upregulated in 67%, and AdipR1 and AdipR2 were downregulated in 55% and 68% respectively, relative to the calibrator sample. Upregulated ObR and AdipR2 expression was significantly associated with anthropometric and radiological measures of obesity. Upregulated ObR was associated with advanced tumour and node category ($P=0.036$ and $P=0.025$, respectively), and upregulated AdipR2 with nodal involvement ($P=0.037$).

Studies *in vitro* support a role for the IGF axis in esophageal adenocarcinoma progression. Blockade of the IGF-1R leads to apoptosis (95) and IGF-1 stimulates proliferation (62). In esophageal cancer, overexpression of IGF-1R has been associated with the malignant progression of Barrett's esophagus to adenocarcinoma (96).

Trinity College (60) reported that higher IGF-1R protein expressions were observed in SCC cells compared with esophageal adenocarcinoma cells however only adenocarcinoma cell lines significantly increased proliferation in response to IGF-1 ($P<0.01$). Serum IGF-1 levels were highest in esophageal adenocarcinoma patients ($P<0.01$) and higher in viscerally obese vs. nonobese ($P<0.05$) patients. In resected esophageal cancer, increased expression of IGF-1R was observed in the tumor and invasive edge compared with tumor associated stroma ($P<0.05$), which coincided with increased CD68+ cells in stromal tissue surrounding invasive tumor edge ($P<0.01$).

A total of 220 patients were studied by Donohoe *et al.* (59). Total and free IGF-1 levels were significantly increased in the serum of viscerally obese patients. Gene expression analysis revealed a significant association between obesity status and both IGF-1R ($P=0.021$) and IGF-1 ($P=0.031$) in tumours. TMA analysis demonstrated that IGF-1R expression in resected tumours was significantly higher in viscerally obese patients than in those of normal weight ($P=0.023$). Disease-specific survival was longer in patients with negative IGF-1R expression than in those with IGF-1R-positive tumours (median 60.0 versus 23.4 months; $P=0.027$). This highlights the relationship between IGF axis with visceral obesity, and a probable impact on the biology of esophageal adenocarcinoma through its receptor.

Studies are ongoing with other novel agents targeting insulin like growth factor receptor, its ligand IGF-1, and telomerase enzyme (97).

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Clinical tools to predict outcomes in patients with esophageal cancer treated with definitive chemoradiation: are we there yet?

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Abstract: Definitive chemoradiation (CRT) is a well-established treatment for esophageal cancer, but disease recurrence is common and many patients do not achieve initial remission with CRT alone. Predictors of outcome with CRT are needed to guide prognosis and further treatment decisions, in particular the need for post-CRT surgery. We review the role of baseline clinical factors, such as histology and tumor bulk, in predicting response to CRT. Post-CRT assessments, particularly PET imaging, may provide further information about the likelihood of complete response and survival, but the predictive power of clinical assessments remains limited. Emerging research on biomarkers holds promise for more tailored and accurate prediction of outcome with definitive CRT.

Keywords: Esophageal cancer; radiotherapy; chemoradiation (CRT); response prediction

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Introduction

Radiotherapy, when delivered with concurrent radiosensitizing chemotherapy, is a potentially curative treatment for nonmetastatic esophageal cancer. The seminal RTOG 8501 trial demonstrated that approximately one in four patients treated with concurrent chemoradiation (CRT) become long-term survivors. This was in contrast to patients treated with radiation alone, among whom there were no long-term survivors (1,2). Unfortunately, most patients treated with definitive CRT still experience disease recurrence, prompting many efforts to improve outcomes by intensifying CRT or adding additional treatment modalities, particularly surgery.

In many cases, the pattern of failure is local. The local progression rate in RTOG 8501 exceeded 50%, reflecting not only local relapse but also local persistence of disease in many patients. Efforts to improve the local control rate by increasing radiation dose have so far been unsuccessful (3,4). Higher radiation doses may not improve the therapeutic ratio in definitive CRT, given that acute toxicities of CRT are significant even with the moderate doses of RT

currently used. Nonetheless, the optimal radiotherapy dose for patients treated with CRT alone is still unknown and depending on the primary tumor site and histology, patients may be treated with doses ranging from 5,000 to 6,600 cGy. Improved predictors of outcome after definitive CRT are urgently needed to better individualize therapy and identify patients who may benefit from dose intensification and those in whom moderate doses are adequate.

For patients with resectable disease, trimodality therapy with surgery after CRT is often favored. Since CRT achieves pathologic complete response (pCR) in only 20-30% of patients, surgery mitigates against the possibility of persistent tumor leading to local progression or distant metastatic spread (5). Two randomized trials of CRT with or without surgery demonstrated reduced local recurrence with trimodality therapy (6,7). However, these trials failed to demonstrate an improvement in survival with surgery, likely due to an increase in treatment-related mortality.

Despite the lack of a demonstrable survival advantage, it stands to reason that some patients with esophageal cancer benefit from surgery after CRT. Non-responders to CRT have residual viable malignancy that would be eradicated by

surgical resection, making surgery a curative intervention if occult systemic spread has not yet occurred. Conversely, for the substantial minority of patients who achieve complete pathologic response to CRT, surgical resection likely adds nothing to the probability of cure, while exposing the patient to the significant risks and morbidities of a major operation. For these reasons, the ability to predict whether CRT alone will be curative for a given patient would be immensely valuable.

Many factors have been examined as potential predictors of CRT response, which can be broadly divided into two categories: (I) potential predictors based on pre-treatment patient or tumor characteristics; and (II) potential predictors based on diagnostic tests or tumor characteristics during or immediately after CRT.

Pre-CRT predictors

Besides stage, the most important differentiating factor in the treatment and prognostication of esophageal cancer is histology. The literature establishing efficacy of definitive CRT is almost entirely limited to squamous cell carcinoma (SCC), which comprised the vast majority of patients in the RTOG 8501 trial, as well as the two major trials of CRT with or without surgical resection referenced above. There are few prospective data on definitive CRT for AC, which now represents the predominant form in the Western world. Multiple lines of evidence suggest that SCC is more likely to respond to definitive CRT than AC. For example, a matched-pair analysis of CRT in SCC *vs.* AC showed significantly greater rates of clinical complete response (cCR) in SCC (8).

pCR rates have been shown to correlate with outcome (9), and pCR rates in studies of preoperative CRT are a reasonable proxy for the expected outcome of definitive CRT in these patients. In the landmark CROSS trial, which compared pre-operative carboplatin and paclitaxel with concurrent radiotherapy to a dose of 4,140 cGy versus surgery alone, the rate of pCR was significantly greater for SCC than for AC (49% *vs.* 23%, $P=0.008$), though preoperative CRT proved beneficial for both subtypes (5). Investigators at Memorial Sloan-Kettering Cancer Center (MSKCC) have also shown, based on analysis of post-CRT esophagectomy specimens, that the pCR rate is significantly greater in SCC than AC (10). The presence of signet ring cell features and high tumor grade may further diminish the probability of response to CRT in AC (11-13).

Because outcomes with definitive CRT are better

established in SCC, some clinicians are more likely to defer surgery after CRT for SCC than for AC, when a cCR has been achieved. It is reasoned that SCC patients with cCR are more likely to have a pCR and therefore, potentially be cured without requiring surgery. Among patients with cCR to CRT, SCC histology was independently associated with improved disease-free survival in an analysis by MD Anderson Cancer Center (MDACC) (13). However, a significant number of SCC patients with cCR may have microscopic residual disease, leaving open the question of whether surgery should nevertheless be pursued in cCR patients who can safely undergo resection (14).

One option that has been evaluated to balance the potential risks of surgery after definitive CRT with the need to address residual disease is the use of surgical salvage. This approach allows the opportunity to improve locoregional control while reserving surgical resection only for patients with residual or recurrent locoregional disease. The RTOG reported reasonably good results with definitive CRT in a small single-arm trial of selective surgical salvage in a cohort with mostly adenocarcinoma (AC) (15). Nonetheless, this option relies on the ability to distinguish between responders and non-responders to CRT.

Besides histology, baseline tumor bulk and extent is commonly hypothesized to predict outcome with definitive CRT. Indeed, the MDACC group found that node-positive status and T3/T4 disease correlated with worse disease-free survival after definitive CRT (13). Investigators from Taiwan reported that increasing pre-treatment tumor depth, as well as increased length, predicted for local recurrence after CRT (16). Along with T and N stage, lymph node size was found to be independently prognostic in SCC patients undergoing definitive CRT by Japanese investigators (17). It is logical that patients with a greater baseline disease burden remain at higher risk for relapse even if cCR to CRT is achieved, but a validated threshold for recommending further treatment such as surgery has not yet been established.

FDG-PET imaging, which has proven value in detecting occult metastatic disease in esophageal cancer, has also been investigated as a predictor for CRT efficacy. The intensity of FDG uptake correlates with tumor metabolic activity and may therefore predict biologic behavior and treatment responsiveness. Numerous studies have examined the prognostic value of baseline maximum standardized uptake value (SUV_{max}) in patients with esophageal cancer, with most showing a correlation between SUV_{max} and outcome (18). However, whether baseline SUV_{max} is an independent

prognostic factor in the context of treatment with CRT is less clear. For example, Rizk *et al.* identified a lower baseline SUV_{max} as a positive prognostic factor for patients undergoing surgery alone, but SUV_{max} no longer predicted survival when applied to patients undergoing preoperative CRT (19,20). In fact, patients with $SUV_{max} > 4.5$ were more likely to achieve pCR after CRT, suggesting that higher baseline FDG avidity is actually a positive predictive factor for success with definitive CRT. However, an analysis by Suzuki *et al.* in definitive CRT patients reached the opposite conclusion, in that higher baseline SUV_{max} correlated with worse overall survival (21). A more recent analysis from this group indicated that patients with baseline $SUV_{max} < 6$ fare equally well with CRT alone as with trimodality therapy, and this finding awaits validation in other cohorts and in the prospective setting (22).

Post-CRT predictors

Even if narrowly defined in terms of stage, histology, and metabolic activity as described above, it seems unlikely that pre-treatment clinical categorization alone can identify a population of esophageal cancer patients with reliably predictable outcome after CRT. Post-CRT assessments of tumor burden, since they attempt to measure CRT effectiveness directly, may be a more robust predictor of long-term outcome in a given patient. Positive identification of viable malignancy after CRT (such as with biopsy) essentially proves that definitive CRT will not be curative for that patient. However, it is much more difficult to show that the absence of detectable malignancy after CRT translates to cure, because of the inherent challenge of ruling out microscopic disease. The only way to prove that pCR has been achieved is to resect the tumor and subject the specimen to histologic analysis, but this obviously defeats the purpose of determining whether surgery is therapeutically beneficial in the first place.

The most commonly accepted method of establishing CRT response is endoscopic biopsy. Unsurprisingly, a negative post-CRT biopsy is correlated with a significantly better outcome than a positive biopsy, since the negative result at least holds some promise of an actual pCR (23). However, multiple studies have shown that most patients with a negative post-CRT biopsy have residual tumor cells in the esophagectomy specimen. As a result, the negative predictive value of endoscopic biopsy is only on the order of 30% (23-26). Whether surgery improves aggregate survival in such patients by removing persistent foci of disease

remains unproven, based on the randomized studies of CRT with or without surgery discussed earlier. Regardless, it is clear that sampling error significantly limits the predictive power of post-CRT biopsy. The accuracy of restaging endoscopic ultrasound in the post-CRT setting is also quite poor (27).

Whether post-CRT PET can distinguish complete from incomplete responders has been extensively investigated. In a provocative study from Wake Forest University, investigators found that a complete metabolic response was the strongest prognostic factor for survival in patients treated with definitive CRT, and suggested that surgery may only be necessary for metabolic nonresponders (28). Investigators at MDACC reported that definitive CRT achieved equivalent survival to trimodality therapy only if a significant post-CRT metabolic response had been achieved similarly suggesting that persistent FDG-avidity is a useful determinant of whether surgery is needed (29).

Multiple groups have now reported strong correlation between post-CRT metabolic response and outcomes, both with respect to pCR and survival (30-34). However, some groups have also reported no significant or clinically useful association between residual FDG avidity and pCR (35,36). A review of multiple studies of PET response after induction chemotherapy or CRT attempted to synthesize these disparate results. Drawing overall conclusions from these retrospective studies was limited by inherent differences in patient characteristics and FDG-PET techniques, but it was concluded that residual FDG avidity likely has predictive value (18). Assessment of PET response after CRT appears to be less reliable than after chemotherapy alone, as persistent FDG-avidity from radiation esophagitis is typically indistinguishable from active malignancy.

FDG-PET has particular promise in evaluating response to chemotherapy in patients with esophageal AC. A seminal prospective trial from Germany showed that after starting induction chemotherapy, early response assessment with PET could predict whether significant pathologic response would be achieved (37). Reduction in the SUV_{max} of $> 35\%$ from baseline to the scan performed 2 weeks into chemotherapy was associated with improved disease-free survival. A prospective trial at MSKCC of induction chemotherapy followed by preoperative CRT indicated that PET response after the induction chemotherapy phase correlated with pCR after CRT (38). Because it is clear (from RTOG 8501) that definitive radiotherapy can achieve cure only with effective chemotherapy, PET

response after induction chemotherapy may be a useful predictor of outcome with definitive CRT. A strategy of utilizing post-induction chemotherapy PET to direct the choice of radiosensitizing chemotherapy is now being tested prospectively in the CALGB 80803 trial, and may further validate post-induction chemotherapy PET response as a useful predictor of outcome with CRT.

Combining multiple clinical factors could improve predictive power compared to any single factor. Ajani *et al.* constructed a model to predict pCR after CRT, based on multivariate analysis of multiple demographic and clinical factors (12). They found that gender, tumor grade, baseline T-stage, post-treatment SUV_{max}, and post-treatment biopsy status were independently associated with pCR and incorporated these factors into a nomogram. A high nomogram score after CRT would predict a >60% chance of pCR upon surgery. The authors acknowledged that this model requires validation before clinical use. Even if validated, it is debatable whether a model that accurately predicts pCR in approximately two out of three patients would be sufficient to make a significant treatment decision such as surgery.

Biomarkers and future directions

Though clinical parameters and PET assessments have value in predicting response to definitive CRT, it is unlikely that any of those tools will be reliable enough to ensure that CRT alone maximizes survival for a given patient, or that surgery would definitely improve outcome. An alternative, potentially more promising approach is to identify biomarkers to predict the likelihood of response to CRT.

Numerous genetic biomarkers have been reported to have association with CRT response, including NF- κ B (39), p53 (40), ERCC1 (41), BRCA1 (42), and ALDH-1 (43), among others. DNA-repair (44) and apoptosis-related protein expression levels (45) have also been proposed as predictors of CRT response. Several groups have constructed multiple-gene expression profiles to discriminate CRT responders from non-responders (46,47).

Other areas of recent investigation include the correlation of micro-RNA expression and CRT outcomes. Ko *et al.* reported that complete responders to CRT had different miRNA expression profiles than nonresponders (48). Skinner *et al.* have subsequently developed an miRNA expression model to predict pCR after neoadjuvant CRT (49). Serum biomarkers such as protein complement levels (50), and interleukin-6 levels (51), have also been correlated with CRT

response. A Dutch group recently reported that cancer stem cell markers might have predictive value in the treatment of esophageal cancer with radiotherapy (52).

Whether any of these or other candidate biomarkers will be validated in a larger population remains to be seen, and much translational work remains to be done before any such biomarker is shown to be sufficiently robust to enter routine clinical use and direct treatment decisions. However, significant improvements in the ability to predict CRT response will likely come from these avenues of investigation.

Conclusions

At this time, available clinical tools do not permit the clinician to predict confidently whether definitive CRT will lead to cure, or even to a pCR. However, significant though imperfect correlations between numerous factors and CRT outcome have been identified. Baseline clinical factors, most notably histologic subtype and possibly SUV_{max}, correlate with the probability of pCR. Additional predictive value may be obtained by incorporating post-CRT assessments, such as biopsy and PET. Positive post-CRT biopsy is an indication that CRT alone has been insufficient and surgery likely beneficial. A negative post-CRT PET combined with negative biopsy suggests that favorable outcome may be achieved without surgery, but whether surgery should routinely be omitted in this circumstance remains debatable due to the substantial risk of persistent microscopic disease. Even if biopsy and PET imaging are not sensitive enough at this time to identify residual microscopic disease after CRT, they have added value for many patients with esophageal cancer in whom surgery may be a high-risk procedure, by helping to guide expectant management and follow-up recommendations. Emerging data on molecular biomarkers are likely to improve predictive ability, but it is uncertain which biomarkers will prove most helpful, and when such tools will be available and validated for clinical decision-making.

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Skin metastases from esophageal and esophagogastric junction cancer

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Introduction

A large proportion of esophageal cancers present initially in an advanced stage (1). Extra-nodal metastases are seen in 20% of the patients (2,3), the liver and lungs are the more common places (2,3). Cutaneous metastases (CM) are rarely reported (4-12).

We report two cases of skin metastases from esophageal cancer.

Case report

Case 1

A 68-year-old male patient presented with dysphagia for 3 months. Upper endoscopy and computerized tomography disclosed a mid-thoracic esophageal squamous cell

carcinoma with extension to the airway rendering the tumor inoperable. No extra-nodal metastasis was noticed. The patient presented concomitantly with two red nonpainful fast-growing nodules with ulceration in the nose and neck (*Figure 1*). Biopsy disclosed a squamous cell carcinoma considered a metastasis due to the atypical and rapid grow for a primary skin lesion since histology cannot differentiate both conditions. The patient was sent to oncologic clinical treatment.

Case 2

A 73- year-old male patient presented with skin lesion 2 years after a total gastrectomy and distal esophagectomy for esophagogastric junction cancer followed by adjuvant chemotherapy (T3N1M0). Physical examination revealed



Figure 1 Cutaneous metastases from an esophageal squamous cell carcinoma.



Figure 2 Cutaneous metastases from an esophagogastric junction adenocarcinoma.

an extensive area of the abdomen covered by red plaques (*Figure 2*). Biopsy disclosed an adenocarcinoma. No other site of recurrence was detected. Patient was referred to clinical oncologic treatment.

Discussion

The skin is an uncommon site of metastases. CM was found in only 10% of a large series with over 4000 cases of metastatic cancer (4). Skin metastases from esophageal cancer affect less than 1% of the cases (9,13). It may originate from squamous cell carcinoma as well as from adenocarcinoma (4-12). Skin metastases from esophagogastric junction tumors with similar characteristics to gastric cancer have also been described (7) as for that matter skin metastases from gastric tumors have also been rarely reported (9,14,15). A myriad of presentations may be seen, however, nodules are the most common form (5,8,10). Any location in the body may be affected (4).

The presence of CM denotes an advanced disease. Survival is dismal with an average of 4 months (4). Surgeons must be aware that cutaneous lesions may represent the first sign of systemic spreading of esophageal carcinoma (4,9).

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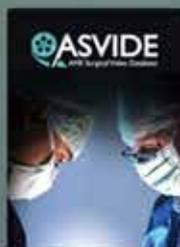
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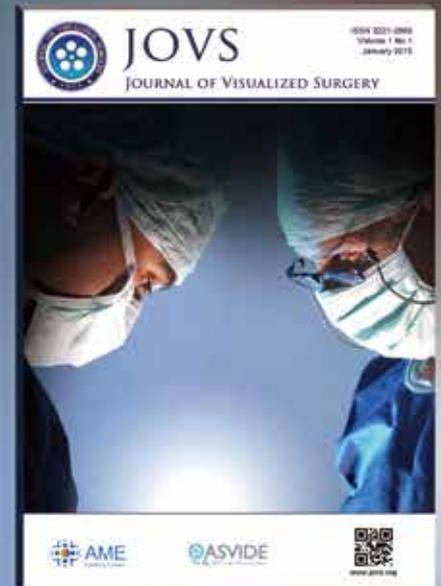
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