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SECRETS OF THE THERAPEUTIC STRATEGY FOR OESOPHAGEAL AND GASTRIC CANCER

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CONTENTS

Dear Colleagues,

The present and the next issue of the official journal of the Hellenic Society of Surgical Oncology, Hellenic Surgical Oncology, are dedicated to the first special congress entitled "Secrets of the therapeutic strategy for oesophageal and gastric cancer", which will take place the 26th and 27th of February 2016 in Thessaloniki, Greece. It is beyond any doubt that the Organizing Committee of the Congress under the Presidency of Professor Ioannis Kanellos and Assistant Professor Konstantinos Sapalidis is the guarantee of a successful meeting.

This issue of Hellenic Surgical Oncology contains manuscripts submitted by speakers who responded to the call for papers. In each manuscript the distinguished speakers discuss the topic of their presentation at the congress. While this issue contains the manuscripts pertaining to oesophageal cancer, those regarding gastric cancer have been collected in the next issue of the Journal.

Moreover, it is my pleasure to announce that the manuscripts of the present issue, as well as the past and coming issues of the Journal will be soon accessible on the Journal's own website in order to further facilitate its accessibility.

It is probably unnecessary to mention that it will be our great pleasure to receive interesting papers from you for publication in the official journal of the Society. Our aim is a high quality Journal which features superior clinical studies (from Greece and abroad), substantial observational data and interesting cases, discusses points of view and updates our readers on recent advances by publishing outstanding reviews and relevant breaking news in the various fields of Surgical Oncology.

Sincerely yours,

Eelco de Bree
Editor-in-Chief

HELLENIC SURGICAL ONCOLOGY 2016; 7(1): 5-8

REVIEW

Advances in the endoscopic diagnosis of early esophageal adenocarcinoma

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ABSTRACT

Barrett's esophagus (BE) is the only known pre-malignant precursor of esophageal adenocarcinoma (EAC), a tumor that is rapidly increasing in the developed world. Over the last few years, there have been major advances in our understanding of epidemiology, pathogenesis and endoscopic management of BE. These developments focus on early recognition of advanced histology and endoscopic treatment of high-grade dysplasia with advanced resection endoscopic techniques. At present, endoscopic surveillance with white-light endoscopy (WLE) biopsies is considered the standard of care for detecting high-grade dysplasia (HGD) in BE. However, current recommended guidelines for surveying patients with BE are time consuming and poorly adhered to. Theoretically, screening and treating early BE should help prevent EAC but the exact incidence of BE and its progression to EAC is not entirely known and cost-effectiveness studies for Barrett's screening are lacking. Over the last decade, new endoscopic imaging technologies, during visual inspection, are being studied to identify high-risk lesions.

KEY WORDS: Barrett's esophagus, early esophageal adenocarcinoma, endoscopy

INTRODUCTION

The incidence of esophageal EAC has increased six to seven-fold from 1975 to 2006.[1] Barrett's esophagus is the most significant known risk factor for EAC. The prevalence of BE has been an issue for debate, with various studies showing a percentage of 0.5-2% in asymptomatic patients and a slightly higher one of 5-10% in patients with symptomatic reflux.[2] Screening for BE is a controversial issue, given the fact that the prevalence of BE in the general population is low despite that the incidence of EAC in patients with BE is 0.1-0.3% per year.

Furthermore adenocarcinoma in patients with HGD approaches 6%. Since these patients should undergo eradication therapy to prevent progression to cancer, efforts are being focused on improving the diagnostic yield for HGD.[3]

Patients with non-dysplastic BE and low-grade

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dysplasia (LGD) should undergo regular surveillance to detect advanced histology that would benefit from eradication/definitive therapy. In these patients, the recommended intervals for surveillance are 3-5 years and 0.5-1 year, respectively. The American Gastroenterological Association (AGA) recommends that screening be considered in adults above 50 years of age with multiple risk factors.[4]

Recent advances in screening for Barrett's esophagus have now led to an expanding role for endoscopy with the focus on early detection and endoscopic treatment of HGD and early neoplasia.

Studies have failed to show that conventional endoscopy is cost-effective in BE screening, due to the requirement for sedation and longer procedure times. Thus, various modalities including chromoendoscopy, narrow-band imaging (NBI) with magnification, confocal laser endomicroscopy or optical coherence tomography (OCT)/ volumetric laser endomicroscopy (VLE) have shown great promise in detecting dysplasia and early neoplasia in BE.

TRANSNASAL ENDOSCOPY

Transnasal endoscopy (TNE) is performed without sedation, using ultra-thin endoscopes advanced through the nose. In 2002, Saeian et al. showed for the first time that unsedated TNE was comparable to standard upper endoscopy in its ability to diagnose BE, as well as dysplasia, with good inter-observer agreement.[5]

ESOPHAGEAL CAPSULE ENDOSCOPY

The Pill Cam ESO capsule endoscope (Given Imaging Ltd., Yoqneam, Israel) is a dual-camera capsule endoscope specially designed for obtaining images of the esophagus.

A meta-analysis, which included 618 patients, evaluated the diagnostic accuracy of esophageal capsule endoscopy (ECE) for BE.[6] Using histological confirmation of intestinal metaplasia as the reference standard for BE diagnosis, the pooled sensitivity and specificity of ECE for BE diagnosis were 78% and 73%, respectively.

WHITE-LIGHT ENDOSCOPY

High-definition endoscopes are available that capture images with up to 2.1 million pixels, compared with the standard-definition endoscopes that have up to 400,000 pixels. These newer high-definition endoscopes allow better resolution of the surface mucosa and can also magnify images 70–140 times, compared with 30–35 times magnification with standard-definition endoscopes.[7] Only around 40% of HGD and esophageal adenocarcinomas were identified as endoscopically suspicious lesions locations during initial *high-definition white-light endoscopy (WLE)*.[8] Given the poor adherence to BE surveillance and the inability to identify dysplasia, other markers of dysplasia as well as endoscopic imaging techniques are being studied.

The consensus statement published in 2012 recommended against the use of standard-definition endoscopes and suggested that high-definition scopes should be used for surveillance of Barrett's epithelium.[9]

CHROMOENDOSCOPY

Dye-based chromoendoscopy involves spraying a chemical solution on the mucosa to enhance visualization of the mucosal surface and vascular pattern by differential absorption. Various dyes that have been studied for enhanced imaging of BE include methylene blue, acetic acid and indigo carmine.

Optical chromoendoscopy: Optical chromoendoscopy involves detailed examination of the mucosal surface and vascular pattern by using filters of different wavelengths, image processing and magnification. As mentioned above, with the availability of high-definition endoscopes, high-resolution WLE is the bare minimum for

evaluation of BE and is recommended by different gastroenterology societies.

Narrow-Band Imaging Magnifying Endoscopy: Narrow-Band Imaging (NBI) endoscopy is the most commonly available and most-studied optical chromoendoscopy modality. Studies have shown that NBI is superior to standard definition WLE in detecting dysplasia in BE[10] but studies comparing high-resolution WLE with NBI have not shown superiority of NBI for surveillance purposes.[11] Studies using *NBI with magnification* have also reported great success in diagnosing advanced histology and a simplified classification of various surface patterns, to diagnose different histological grades of BE.[12]

To conclude, NBI with magnification-targeted biopsies should be obtained when available, in addition to the high-resolution WLE examination.

CONFOCAL LASER ENDOMICROSCOPY

Confocal laser endomicroscopy (CLE) is based on the illumination of a fluorescent target by a low-powered argon ion laser (488 nm wavelength) and detection of light emanating from that target by a photodetection device after it passes through a pinhole, followed by image processing.[13] It allows the highly detailed evaluation of surface epithelium, as well as the vascular pattern of serial sections of thick in vivo specimens. CLE can be performed either by using endoscopes with an integrated confocal imaging capability (Pentax, Tokyo, Japan) or by using a CLE probe advanced through the accessory channel of endoscope (p CLE) (CellVizio, Mauna Kea Technologies, Paris, France).

Multiple studies evaluated p CLE for the diagnosis of BE and advanced histology in BE, but were limited either by sample size or by low diagnostic accuracy, although some showed promising results as well.[14] In a meta-analysis involving seven studies (345 patients and 3080 lesions), it was shown that CLE might have a role in selected patients who *have advanced histology on random biopsies* but no identifiable lesions on high-resolution WLE.[15]

OPTICAL COHERENCE TOMOGRAPHY / VOLUMETRIC LASER ENDOMICROSCOPY

Optical coherence tomography (OCT) is a relatively new imaging modality based on interferometry. It involves the use of a light signal to obtain cross-sectional images in high resolution, by measuring the path length of reflected light followed by image processing. It offers very high spatial resolution of the order of 1–15 μm.[16]

REFERENCES

1. Pera M, Manterola C, Vidal O, et al. Epidemiology of Esophageal Adenocarcinoma. *J Surg Oncol* 2005; 92: 151-159.
2. Ward EM, Wolfsen HC, Achem SR, et al. Barrett's esophagus is common in older men and women undergoing screening colonoscopy regardless of reflux symptoms. *Am J Gastroenterol* 2006; 101: 12-17.
3. Hvid-Jensen F, Pedersen L, Drewes AM, et al. Incidence of adenocarcinoma among patients with Barrett's esophagus. *N Engl J Med* 2011; 365: 1375-1383.
4. Evans JA, Early DS, Fukami N, et al. The role of endoscopy in Barrett's esophagus and other premalignant conditions of the esophagus. *Gastrointest Endosc* 2012; 76: 1087-1094.
5. Saeian K, Staff DM, Vasilopoulos S, et al. Unsedated transnasal endoscopy accurately detects Barrett's metaplasia and dysplasia. *Gastrointest Endosc* 2002; 56: 472-478.
6. Bhardwaj A, Hollenbeak CS, Pooran N, et al. A meta-analysis of the diagnostic accuracy of esophageal capsule endoscopy for Barrett's esophagus in patients with gastroesophageal reflux disease. *Am J Gastroenterol* 2009; 104: 1533-1539.
7. ASGE Technology Committee Kwon RS, Adler DG, Chand B, et al. High-resolution and high-magnification endoscopes. *Gastrointest Endosc* 2009; 69: 399-407.
8. Peters FP, Curvers WL, Rosmolen WD, et al. Surveillance history of endoscopically treated patients with early Barrett's neoplasia: non-adherence to the

Seattle biopsy protocol leads to sampling error. *Dis Esophagus* 2008; 21: 475-479.
9. Bennett C, Vakil N, Bergman J, et al. Consensus statements for management of Barrett's dysplasia and early-Stage esophageal adenocarcinoma, based on a Delphi process. *Gastroenterology* 2012; 143: 336-346.
10. Wolfsen HC, Crook JE, Krishna M, et al. Prospective, controlled tandem endoscopy study of narrow band imaging for dysplasia detection in Barrett's Esophagus. *Gastroenterology* 2008; 135: 24-31.
11. Curvers W, Baak L, Kiesslich R, et al. Chromoendoscopy and narrow-band imaging compared with high-resolution magnification endoscopy in Barrett's esophagus. *Gastroenterology* 2008; 134: 670-679.
12. Singh R, Anagnostopoulos GK, Yao K, et al. Narrow-band imaging with magnification in Barrett's esophagus: validation of a simplified grading system of mucosal morphology patterns against histology. *Endoscopy* 2008; 40: 457-463.
13. De Palma GD. Confocal laser endomicroscopy in the *in vivo* histological diagnosis of the gastrointestinal tract. *World J Gastroenterol* 2009; 15: 5770-5775.
14. Wallace MB, Sharma P, Lightdale C, et al. Preliminary accuracy and interobserver agreement for the detection of intraepithelial neoplasia in Barrett's esophagus with probe-based confocal laser endomicroscopy. *Gastrointest Endosc* 2010; 72: 19-24.
15. Gupta A, Attar BM, Koduru P, et al. Utility of confocal laser endomicroscopy in identifying high-grade dysplasia and adenocarcinoma in Barrett's esophagus: a systematic review and meta-analysis. *Eur J Gastroenterol Hepatol* 2014; 26: 369-377.
16. Jackle S, Gladkova N, Feldchtein F, et al. In vivo endoscopic optical coherence tomography of esophagitis, Barrett's esophagus and adenocarcinoma of the esophagus. *Endoscopy* 2000; 32: 750-755.

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REVIEW

Risk factors and current classification of oesophageal cancer

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ABSTRACT

Oesophageal cancer includes squamous cell carcinoma (SCC) and adenocarcinoma (AC). Despite recent advances it is characterised by poor prognosis. Oesophageal cancer incidence is increasing,[1] causing approximately 406,000 annual deaths worldwide.[2] Oesophageal SCC is more common than AC. During the 70s the majority of cancers were SCC but the incidence of AC has been steadily rising. Smoking and alcohol use are the main carcinogen sources for development of SCC.[3] Other predisposing factors are red meat consumption, water pipe or chewing tobacco use, opium consumption, hot tea drinking, poor oral hygiene, low intake of fresh fruit and vegetables, and low socioeconomic status. Barrett's oesophagus is a confirmed risk factor for the development of AC. One of the strongest emerging risk factors is obesity. Classification of oesophageal cancer in stages is commonly used, aimed at prognostication, delivery of effective stage determined therapy, and quality of care assessment. In 2010 the 7th edition of the Cancer Staging Manual was published. An evidence driven, machine learning analysis based on the global cancer experience was applied for formulation of the current 7th edition.

KEY WORDS: oesophageal cancer, squamous cell carcinoma, adenocarcinoma

RISK FACTORS OF OESOPHAGEAL CANCER

The chance of developing oesophageal cancer increases with age. Median age at diagnosis is 55 to60 with a strong male predominance (4:1).[4] Oesophageal cancer is 20 to 30 times more prevalent in China than in USA. A "cancer belt" extending across north India, Iran, the Soviet Union, Mongolia, and northern China on the southern side, describes areas of very high oesophageal SCC incidence.[5] In white USA men AC rates are four times higher than African, Asian, and Native Americans. Female incidence is considerably smaller.

Gastroesophageal reflux disease (GERD), affects 20% to 30% of the population. It is the most important predisposing factor for development of oesophageal AC.[6] The risk is higher than fortyfold for patients with long-standing, severe disease.[7] In Barrett's oesophagus the normal squamous epithelium of the distal oesophagus undergoes

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metaplasia to intestinal-type columnar epithelium. It affects up to 8% of patients with GOR, Overall, the risk increases 50 to 100 times compared to the general population. Patients with Barrett's should be followed-up closely for early cancer detection. However, most patients with Barrett's do not progress to cancer. The annual risk is estimated 0.12%.[8]

Use of tobacco in all forms, is a strong and independent risk factor for the development of oesophageal SCC. Cancer risk is proportional to the duration and amount used.[9] Alcohol is also linked to increased risk of oesophageal SCC. Combination of smoking and alcohol consumption multiplies the risk of developing oesophageal SCC.[10] Regarding oesophageal ACC, smoking constitutes only a moderate risk factor and alcohol consumption does not appear to be linked to increased risk.

Overweight or obese individuals have a threefold increased risk of developing AC. Adipose tissue itself influences tumour development.[11] Secretion of adipokines and cytokines by adipocytes and inflammatory cells has been linked to carcinogenesis. The high incidence of oesophageal AC in certain countries may be linked to a diet high in carbohydrates and processed meat. A diet rich in fruits and vegetables is linked to a lower risk of both subtypes of oesophageal cancer through increased antioxidant effect of vitamins C and E.[12] A protective effect was documented in patients with Barrett's oesophagus with regular multivitamin supplementation.[13] Excessive hot liquid consumption increases the risk for SCC, due to long term damage and inflammation of the oesophageal mucosa.

Achalasia is a rare motility disorder resulting in weak oesophageal peristalsis and lower oesophageal sphincter spasm. SCC is the commonest oesophageal cancer in patients with achalasia, and is thought to result from the carcinogenic effect of large amounts of nitrosamines produced by bacterial overgrowth due to food stasis in the oesophagus.[14] The reported prevalence of oesophageal cancer in patients with achalasia is 3–7%, 50 times higher than in general population.[15] However, recent studies find only a tenfold increased risk for both ESCC and EA.[16] On average, the cancers develop decades after achalasia diagnosis (15 to 20 years).

Tylosis is a rare disease, affecting one in a million people. It is characterised by focal thickening of the skin of the hands and feet. People with this condition also develop oral leukokeratosis and small papillomas of the oesophagus, and have a very high lifetime risk (95% at the age of 65) of developing SCC. Oesophageal SCC develops after 50, earlier than the sporadic form of the disease. Tylosis is inherited by the autosomal dominant trait and shows complete penetrance of the cutaneous features, evident by childhood.[17]

People with Plummer-Vinson or sideropenic dysphagia syndrome have webs in the upper part of the oesophagus, typically along with low iron levels, glossitis, brittle fingernails, and sometimes autoimmune thyroiditis or splenomegaly. A British eponym for this is Paterson-Brown Kelly. The exact cause of PVS is speculated to lie between iron and nutritional deficiencies, genetic predisposition, and autoimmunity.[18] It typically affects middle aged women.[19] The incidence of SCC in patients with PVS is reported to range between 4% to 16%.[20]

Occupational exposure to welding dust, lead fumes and steel may lead to an increased risk of oesophageal cancer. Evidence suggests a relation between silica dust and oesophageal cancer but this is not consistent.[21,22] Occupational exposure to chemicals used in textile industry has been also linked to oesophageal cancer.

Corrosive agents contained in industrial and household drain cleaners (lye) can burn and destroy cells. When accidentally ingested by children they cause severe chemical burns of the oesophagus. With healing, the scar tissue produced can cause a stricture. Both AC and SCC of the oesophagus can develop as a late complication. The reported incidence ranges from 2% to 30%, up to

3000 times higher than in general population.[23]

HPV represents a group of more than 140 recognised genotypes, subdivided into cutaneous and mucosal HPV types. Infection with certain types of HPV is linked to a number of cancers, including head and neck, anal and cervical cancer. HPV infection has been long hypothesised as a possible cause of oesophageal cancer. Reported prevalence of HPV infection in oesophageal carcinomas varies in different studies.[24] Recent research confirms a two to fourfold increased risk for SCC in patients with HPV infection.[25]

CLASSIFICATION OF OESOPHAGEAL CANCER

The extent of primary tumour invasion is classified into different T stages (Table 1). The

Table 1. 7th Edition of AJCC TNM Classification. TNM staging, Histologic Grade and Tumour Location of oesophageal cancer

T: Primary tumour	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	High-grade dysplasia
T1	Tumour invades lamina propria, muscularis mucosa, or submucosa
T1a	Tumour invades lamina propria or muscularis mucosa
T1b	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3	Tumour invades adventitia
T4	Tumour invades the adjacent structure
T4a	Resectable tumour invading pleura, pericardium, or diaphragm
T4b	Unresectable tumour invading other adjacent structures, such as aorta,vertebral body, trachea, etc.
N: Regional lymph nodes	
NX	Regional nodal status cannot be assessed
N0	No regional lymph node involvement
N1	Regional lymph node metastases involving 1 to 2 nodes
N2	Regional lymph node metastases involving 3 to 6 nodes
N3	Regional lymph node metastases involving 7 or more nodes
M: Distant metastases	
M0	No distant metastasis
M1	Distant metastases
Histologic grade of tumour	
GX	Grade cannot be assessed, stage grouping as G1
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated, stage grouping as G3
Tumour location	
Upper or Middle	Cancers above lower border of inferior pulmonary vein
Lower	Cancers below lower border of inferior pulmonary vein

previously used term *carcinoma in situ* has been replaced by *high grade dysplasia*, describing all non-invasive neoplastic epithelium. T1 lesions are subdivided to T1a and T1b. T1b lesions carry a worse prognosis as they are frequently associated with lymph node disease. Classification of nodal metastatic spread has been extended to include lymph nodes in the neck and abdomen, considered metastatic in previous editions. Stage stratification is harmonised with gastric cancer. For mapping purposes, the system used for the classification of non-small cell lung cancer has been adopted. Distant metastatic spread is classified to include M0 (no disease) and M1 (metastasis to distant organs). There has been no agreement on the recommended minimal number of resected lymph nodes necessary for adequate nodal staging. Studies generally show that survival is better the more nodes are removed.[26] This could be related to more accurate staging and the therapeutic result of extended lymphadenectomy. Apart from lymphadenectomy extent, survival is also linked to the lymph node ratio (infiltrated versus totally removed lymph nodes). Non-anatomic features such as tumour grade and approximate location (in upper, middle or lower oesophageal third), are also included in the current version of TNM staging. Oesophageal SCC and AC are grouped differently to stages (Tables 2 and 3). For lower stage SCC, tumour grade and approximate location are also used to assign stage.

Cancers of the cardio-oesophageal junction are principally AC related to Barrett's oesophagus in the West. A classification proposed by Siewert and Stein is commonly used to classify adenocarcinomas located within 5 cm proximal and distal to the COJ.[27] This system classifies tumours as Type I to Type III (oesophageal, cardiac and sub-cardiac) taking into account the relative extent of involvement of either the oesophagus or stomach. These three types of cancers differ regarding causation, demographics, histology and prognosis. Different treatment strategies are therefore necessary to achieve best results.[28] Siewert classification is

Table 2. 7th Edition of AJCC TNM Classification. Stage Groupings for Squamous Cell Oesophageal Carcinoma

Stage	T	N	M	Grade	Tumour location
Stage 0	Tis (HGD)	N0	M0	1	Any
Stage IA	T1	N0	M0	1, X	Any
Stage IB	T1	N0	M0	2-3	Any
	T2-3	N0	M0	1, X	Lower, X
Stage IIA	T2-3	N0	M0	1, X	Upper, Middle
	T2-3	N0	M0	2-3	Lower, X
Stage IIB	T2-3	N0	M0	2-3	Upper, Middle
	T1-2	N1	M0	Any	Any
Stage IIIA	T1-2	N2	M0	Any	Any
	T3	N1	M0	Any	Any
	T4a	N0	M0	Any	Any
Stage IIIB	T3	N2	M0	Any	Any
Stage IIIC	T4a	N1-2	M0	Any	Any
	T4b	Any	M0	Any	Any
	Any	N3	M0	Any	Any
Stage IV	Any	Any	M1	Any	Any

Table 3. 7th Edition of AJCC TNM Classification. Stage Groupings for Oesophageal Adenocarcinoma

Stage	T	N	M	Grade
Stage 0	Tis (HGD)	N0	M0	1, X
Stage IA	T1	N0	M0	1-2, X
Stage IB	T1	N0	M0	3
	T2	N0	M0	1-2, X
Stage IIA	T2	N0	M0	3
Stage IIB	T3	N0	M0	Any
	T1-2	N1	M0	Any
Stage IIIA	T1-2	N2	M0	Any
	T3	N1	M0	Any
	T4a	N0	M0	Any
Stage IIIB	T3	N2	M0	Any
Stage IIIC	T4a	N1-2	M0	Any
	T4b	Any	M0	Any
	Any	N3	M0	Any
Stage IV	Any	Any	M1	Any

less relevant in the East, where lower oesophageal cancers are commonly SCC. The current AJCC classification stages as oesophageal cancer all tumours involving the COJ and extending anywhere between the distal 5 cm of the oesophagus to the proximal 5 cm of the stomach. Further data is awaited to determine the prognostic superiority of this approach.

DISCUSSION

The 7th edition of the TNM staging manual for oesophageal cancer is based on data from the Worldwide Esophageal Cancer Collaboration, a patient database including patients from 13 institutions in Europe, USA and Asia.[29] All 5000 patients studied had surgery but no form of adjuvant or neoadjuvant treatment. Despite worldwide representation and consistent surgical treatment, utility of this database in staging classification is questionable due to the increasing use of preoperative therapies in modern day practice. Furthermore, patients with T4, M1 and cervical oesophageal cancer are not represented adequately as they seldom undergo curatively intended surgery.

An important point for accurate staging of patients with oesophageal cancer is identification of the exact number of metastatic lymph nodes. In the preoperative setting this is possible using a combination of percutaneous cervical and endoscopic ultrasound.[30] Extensive and detailed examination of the resected specimen is necessary for correct identification of the involved nodes. The total number of nodes resected is a surrogate marker of lymphadenectomy quality. Correct handling of the resected specimen, care in the dissection and correct labelling of all excised nodes is of paramount importance and necessitates the presence of a specialised pathologist.

Assignment of the cervical and celiac lymph nodes as regional disease rather than distant metastases is an improvement of the current classification. Designation of cervical or celiac lymphatic involvement as metastatic disease prevented patients from receiving curative surgery, although it was evident that after three field oesophagectomy they enjoyed much better survival compared to others with truly visceral metastases.[31] Likewise, neoadjuvant treatment of cervical nodal disease with chemoradiation produces improved long term survival, better than that with visceral disease.[32]

Residual disease within the TNM system is stratified using the R classification, indicating absence or presence of residual tumour after treatment and quantifying residual disease as microscopic and macroscopic in amount. It applies to residual tumour at the primary site, regional lymph nodes and distant sites and can be used after surgical resection alone or in combination with other forms of treatment. The R stages are defined as; RX when the presence of residual tumour cannot be assessed, R0 when there is no residual tumour, R1 for microscopic residual tumour and R2 for macroscopic residual tumour.

Examination of the resected specimen should include proximal, distal and lateral margin assessment by the pathologist. Curative intent surgery with microscopic involvement of any margin is assigned as R1 resection and in the case of proximal and distant margins associated with worse prognosis. However, microscopic circumferential margin involvement has been shown to not affect long term survival.[33] R category is probably the strongest prognostic indicator after stage of the disease. If applied consistentlyit allows for comparison of treatment results. This treatment variable should be carefully audited and used to guide resource allocation.

REFERENCES

1. Pennathur A, Gibson MK, Jobe BA, et al. Oesophageal carcinoma. *Lancet* 2013; 381: 400-412.
2. Mao WM, Zheng WH, Ling ZQ. Epidemiologic risk factors for oesophageal cancer development. *Asian Pac J Cancer Prev* 2011; 12: 2461-2466.
3. Blot WJ. More evidence of increased risks of cancer among alcohol drinkers. *Am J Epidemiol* 1999; 150:

1138-1140.
4. DeMeester SR. Epidemiology and biology of oesophageal cancer. *Gastrointest Cancer Res* 2009; 3(Suppl 2): 2-5.
5. Rasool S, Ganai AB, Syed Sameer A, Masood A. Oesophageal cancer: associated factors with special reference to the Kashmir Valley. *Tumori* 2012; 98: 191-203.
6. Lordick F, Ebert M, Stein HJ. Current treatment approach to locally advanced oesophageal cancer: is resection mandatory? *Future Oncol* 2006; 2: 717-721.
7. Lagergren J, Bergstrom R, Lindgren A, et al. Symptomatic gastro-oesophageal reflux as a risk factor for oesophageal adenocarcinoma. *N Engl J Med* 1999; 340: 825-831.
8. Hvid-Jensen F, Pedersen L, Drewes AM, Sørensen HT, Funch-Jensen P. Incidence of adenocarcinoma among patients with Barrett's oesophagus. *N Engl J Med* 2011; 365: 1375-1383.
9. Pandeya N, Williams GM, Sadhegi S, et al. Associations of duration, intensity, and quantity of smoking with adenocarcinoma and squamous cell carcinoma of the oesophagus. *Am J Epidemiol* 2008; 168: 105-114.
10. Lagergren J, Bergström R, Lindgren A, et al. The role of tobacco, snuff and alcohol use in the aetiology of cancer of the oesophagus and gastric cardia. *Int J Cancer* 2000; 85: 340-346.
11. Löfdahl HE, Lu Y, Lagergren P, Lagergren J. Risk factors for oesophageal adenocarcinoma after antireflux surgery. *Ann Surg* 2013; 257: 579-582.
12. Navarro Silvera SA, Mayne ST, Risch H, et al. Food group intake and risk of subtypes of oesophageal and gastric cancer. *Int J Cancer* 2008; 123: 852-860.
13. Dong LM, Kristal AR, Peters U, et al. Dietary supplement use and risk of neoplastic progression in oesophageal adenocarcinoma: A prospective study. *Nutr Cancer* 2008; 60: 39-48.
14. Eckardt AJ, Eckardt VF. Current clinical approach to achalasia. *World J Gastroenterol* 2009; 15: 3969-75.
15. Carter R, Brewer LA. Achalasia and oesophageal carcinoma. Studies in early diagnosis for improved surgical management. *Am J Surg* 1975; 130: 114-120.
16. Zendehdel K, Nyren O, Edberg A, et al. Risk of oesophageal adenocarcinoma in achalasia patients, a retrospective cohort study in Sweden. *Am J Gastroenterol* 2011; 106: 57-61.
17. Blaydon DC, Etheridge SL, Risk JM, et al. RHBDF2 mutations are associated with tylosis, a familial oesophageal cancer syndrome. *Am J Hum Genet* 2012; 90: 340-346.
18. Geerlings SE, Statius van Eps LW. Pathogenesis and consequences of Plummer-Vinson syndrome. *Clin Investing* 1992; 70: 629-630.
19. Chen TS, Chen PS. Rise and fall of the Plummer-Vinson syndrome. *J Gastroenterol Hepatol* 1994; 9: 654-658.
20. Rashid Z, Kumar A, Komar M. Plummer-Vinson syndrome and postcricoid carcinoma: late complications of unrecognized celiac disease. *Am J Gastroenterol* 1999; 94: 1991.
21. Pan G, Takahashi K, Feng Y, et al. Nested case-control study of oesophageal cancer in relation to occupational exposure to silica and other dusts. *Am J Ind Med* 1999; 35: 272-280.
22. Calvert GM, Rice FL, Boiano JM, et al. Occupational silica exposure and risk of various diseases: an analysis using death certificates from 27 states of the United States. *Occup Environ Med* 2003; 60: 122-129.
23. Kiviranta NK. Corrosive carcinoma of the oesophagus. *Acta Otolaryngol* 1952; 102: 1-9.
24. Syrjänen KJ. HPV infections and oesophageal cancer. *J Clin Pathol* 2002; 55: 721-728.
25. Hardefeldt HA, Cox MR, Eslick GD, et al. Association between human papillomavirus (HPV) and oesophageal squamous cell carcinoma: a meta-analysis. *Epidemiol Infect* 2014; 142: 1119-1137.
26. Tachimori Y, Ozawa S, Numasaki H, et al. Efficacy of lymph node dissection by node zones according to tumor location for esophageal squamous cell carcinoma. *Esophagus* 2016; 13: 1-7.
27. Siewert JR, Stein HJ. Classification of adenocarcinoma of the oesophagogastric junction. *Br J Surg* 1988; 85: 1457-1459.
28. Curtis NJ, Noble F, Bailey IS, et al. The relevance of the Siewert classification in the era of multimodal therapy for adenocarcinoma of the gastro-oesophageal junction. *J Surg Oncol* 2014; 109: 202-207.
29. Rice TW, Rusch VW, Apperson-Hansen C, et al. Worldwide esophageal cancer collaboration. *Dis Esophagus* 2009; 22: 1-8.
30. Rösch T. Endoscopic ultrasonography: imaging and beyond. *Gut* 2003; 52: 1220-1226.
31. Igaki H, Tachimori Y, Kato H. Improved survival for patients with upper and/or middle mediastinal lymph node metastasis of squamous cell carcinoma of the lower thoracic esophagus treated with 3-field dissection. *Ann Surg* 2004; 239: 483-490.
32. Zhang P, Xi M, Zhao L, et al. Efficacy and prognostic

analysis of chemoradiotherapy in patients with thoracic esophageal squamous carcinoma with cervical lymph nodal metastasis alone. *Radiat Oncol* 2014; 9: 256-259.

33. Theologou T, Diaba M, Kyawa PA, et al. The impact of positive circumferential margin on survival following oesophagectomy using the new 7th TNM classification. *Eur J Cardiothorac Surg* 2013; 44: 855-859.

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REVIEW

Perioperative nutritional support protocols in esophageal cancer patients

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INTRODUCTION

Esophageal cancer is commonly associated with malnutrition in the vast majority of patients undergoing esophagectomy. This phenomenon is partly attributed to the disease process itself, the location of the tumor and other factors, such as dysphagia which is often accentuated due to chemotherapy/radiotherapy treatment.[1] Malnutrition occurs in 60–85% of esophageal cancers, which is one of the highest reported rates when compared to other malignancies, such as lung, head and neck, stomach, and pancreatic cancers.[2] According to recent publications, 32% of patients who had an esophagectomy witnessed more than 10% weight loss preoperatively,[3] whilst 90% of patients have a 5% weight loss at 3 months postoperatively.[4] Malnutrition in these patients is often related to the presence of cancer cachexia. Cancer cachexia is a complex syndrome which combines anorexia, early satiety, weakness, anemia, inflammation, excessive weight loss, and loss of muscle mass with or without loss of fat mass[5] and is present in 60–80% of these patients.[6] Taking all the aforementioned factors into account, current literature suggests that nutritional assessment in the preoperative phase, as well as perioperative nutritional interventions might prevent, to a certain extent, or attenuate the manifestation of malnutrition related consequences.

NUTRITIONAL ASSESSMENT

Perioperative nutritional assessment of esophageal cancer patients is of great significance, since the clinician can detect changes in nutritional status at an early stage which, in turn aids the interdisciplinary team in evaluating patient's nutritional risk and determining the nutritional interventions required.

One commonly used criterion of malnutrition is the percentage of weight loss in a certain period of time. More specifically, weight loss of more than 5% in the previous month or more than 10% in the last 3–6 months is considered significant malnutrition.[7,8]

Moreover, there are many tools used in the clinical setting, that assist in identifying malnourished cancer patients.[9] The Subjective Global

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Assessment, a questionnaire based on four parameters of the patient's history (percentage of weight loss, changes in habitual diet, presence of significant gastrointestinal symptoms, changes in patient's functional capacity) and three elements of their physical examination (loss of subcutaneous fat, muscle wasting, and presence of edema or ascites), is the most commonly used tool for nutritional screening in malnourished hospital patients with cancer in order to receive nutritional support.[10] Other tools that have been studied in gastrectomy and esophagectomy patients is the Prognostic Nutritional Index and the Nutritional Risk Screening 2002.[11,12] Patients with a high Prognostic Nutritional Index -a tool which includes serum albumin and absolute peripheral lymphocyte count- had a higher prevalence of postoperative complications.[13]

Albumin is an independent risk factor for complications after esophagectomy, since patients with hypoalbuminemia have twice the risk of postoperative infection and increased incidence of acute respiratory distress syndrome (ARDS).[14]

Hand Grip Strength is another method used to measure muscle strength, which is directly related to the physiologic status of the individual and reflects patient's nutritional condition. It could be used in patient's perioperative assessment due to the fact that is an inexpensive, not time-consuming method, with a high predictive value.[15] Reduction in muscle mass is a prognostic parameter for complications in the postoperative period and the loss of functional capacity of skeletal muscle is a predictor of morbidity and mortality. More specifically, patients with weak hand grip strength have higher risk of complications and mortality after elective esophagectomy with reconstruction.[16]

Furthermore, assessment of sarcopenia plays an emerging role in cancer patients owing to the fact that CT scanning is a gold standard imaging method of body composition analysis at the tissue-organ level.[17] CT scans can identify reduced muscle mass and predict negative cancer outcomes in people with abdominal malignancies, where traditional methods of assessment are less effective.[18]

NUTRITIONAL SUPPORT

The proper type of feeding (i.e. enteral/parenteral nutrition, immunonutrition, oral supplements etc.) as well as the right time of feeding is a matter of controversy due to lack of consistent evidence for patients undergoing esophagectomy. Enteral feeding is considered the method of choice for the nutritional support of cancer patients with functioning gastrointestinal tract. Enteral nutrition is advantageous over parenteral nutrition for the following reasons: it provides all the necessary micro- and macro-nutrients in a more intact form, is less expensive, maintains gut mucosal integrity, inhibits the cytokine response, has a decreased risk of complications, reduces the secretion of stress hormones, and inhibits bacterial translocation.[19]

Nevertheless, enteral nutrition is often avoided in order to minimize strain to the anastomoses and reduce the inherent risks of post-operatively impaired gastrointestinal motility. Another concern involves the return of gut motility or peristalsis and the ability of the gut to absorb nutrients. Surgical advances have increased the certainty of esophagoenteric anastomoses, making early oral enteral feeding after surgery feasible.[20]

Gabor et al[21] compared the impact of early enteral nutrition on intensive care unit stay, total hospital stay, peri-operative complications, and mortality after esophagectomy or gastrectomy. The Early Enteral Nutrition (EEN) group was started on tube feeds at 10 mL/hours 6-hour post-operatively, and goal rate was achieved by post-operative day 7 (POD 7). Total Parenteral Nutrition (TPN) was initiated in the control group on POD 1, and enteral feeding was initiated on POD 7. Compared to the TPN group, the EEN patients had significantly fewer ICU and total hospital days and a significantly faster return of bowel function. Mortality rate was not affected.

Fujita et al[22] included 154 patients following

transthoracic esophagectomy, comparing patients receiving parenteral support to those receiving enteral nutrition. The enteral group had significantly fewer life-threatening complications and shorter hospital stays than the parenteral group.

Another study[23] that supports early enteral feeding after esophagectomy, included 208 esophagectomy patients who received Enteral Nutrition postoperatively and were divided into three groups (Group 1, 2 and 3) based on whether they received EN within 48 h, 48 h-72 h or more than 72 h, respectively. Postoperative complications, length of hospital stay (LOH), days for first fecal passage, cost of hospitalization, and difference in serum albumin values between postoperatively were recorded. Group 1 had the lowest thoracic drainage volume, the earliest first fecal passage, and the lowest LOH and hospitalization expenses of all three groups. The incidence of pneumonia was by far the highest in Group 3 (p=0.019). Finally, all postoperative outcomes of nutritional conditions were worst in Group 3. It is therefore safe and valid to start early enteral nutrition within 48 h for esophageal cancer patients.

Results from a recent meta-analysis[24] concerning cancer patients following esophagectomy indicate that early postoperative EN could significantly decrease the pulmonary complications and anastomotic leakage compared with Parenteral Nutrition. On eighth postoperative day, the EN group had higher levels of albumin and prealbumin compared with the PN group. However, there was no difference in digestive complications between these two approaches.

Yin et al[25] implemented a fast track program for esophagectomy patients in order to reduce hospital stays to 7 days after surgery. An algorithm for Fast Track was created and oral nutrition started in the first postoperative day. The results showed that early oral nutrition was safe and tolerable, indicating that Fast Track protocols are a feasible option for patients scheduled for elective esophageal cancer resections without compromising quality.

Other studies suggest that that combination of enteral and parenteral feeding is more beneficial, since Total Parenteral Nutrition could lead to hyperglycemia in stressed patients. A combination of EN and TPN might have some benefits when compared to TPN alone, such as: improvement of intestinal integrity and stimulation of incretin production contributing in improved glucose control in patients undergoing esophagectomy.[26] The European Society for Parenteral and Enteral Nutrition (ESPEN) guidelines for nutritional support suggest that interruption of nutritional intake is unnecessary after surgery in most patients and in patients who require postoperative artificial nutrition, enteral feeding, or a combination of enteral and supplementary parenteral feeding is the first choice. Also this combination should be considered in patients in whom more than 60% of energy needs cannot be met via the enteral route.[27]

More specifically, ESPEN guidelines on Enteral Nutrition and surgery emphasize on the benefits and feasibility of feeding with catheter jejunostomy in esophageal resection.[28] On the other hand, the American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines for critically ill patients establish that if a patient is expected to undergo major upper gastrointestinal surgery and Enteral Nutrition is not feasible, Parenteral Nutrition should be provided under very specific conditions:[29]

1) If the patient is malnourished, PN should be initiated 5–7 days preoperatively and continued into the postoperative period;
2) PN should not be initiated in the immediate postoperative period but should be delayed for 5–7 days (should EN continue not to be feasible); and
3) PN therapy provided for a duration of less than 5–7 days would be expected to have no outcome effect and may result in increased risk to the patient. Thus, PN should be initiated only if the duration of therapy is anticipated to be more than 7 days.

Another aspect should be taken into consideration is the type of enteral feeding administration. There are three possible routes for early enteral nutrition following esophagectomy: via early oral intake, a jejunostomy tube or a nasojejunal tube. In most cases a nasojejunal tube or a jejunostomy tube is used. No significant differences were found between both routes regarding short-term outcome, but information regarding patient satisfaction and long-term outcome were lacking.[30]

The wide variation in the practice of home jejunostomy likely reflects the preferences of individual centres. It has largely been utilised in patients who are malnourished pre-operatively,[31] and those with post-operative complications.[32] A study conducted in esophagectomy patients discharged with a feeding jejunostomy, identified tube placement to be associated with a reduced amount of weight loss in the first six months after surgery and a greater chance of discharge home compared to other destinations.[33]

Immunonutrition is one of the most debated topics in nutritional support of esophageal cancer patients. The term immunonutrition includes formulas that contain immune-modulating substances such as arginine, ribose nucleic acid and omega-3-fatty acids.

A review conducted in 2013, concluded that there is heterogeneity with respect to the types of operations undertaken (two studied patients undergoing oesophagectomy, three studied patients undergoing gastrectomy and one had patients undergoing both operations). Additionally, the included RCTs used different formulations of Enteral Immunonutrition and Standard Enteral Nutrition, further limiting the comparability of the studies. Moreover, not all studies reported the same outcomes as far as inflammatory and immunological markers are concerned. Postoperative enteral immunonutrition could be promising in improving humoral immunity in patients undergoing oesophagogastric resection, but this improvement is not related to a reduced hospital stay, nor does it reduce the rate of infections. Therefore, there is no convincing evidence in terms of routine immunonutrition in patients undergoing oesophageal resection for cancer.[34]

On the other hand, preoperative nutritional supplementation with immune-enhancing formulas was associated with reduced infectious complications, mortality, and duration of hospitalization, and with improved short-term survival in patients with esophageal cancer. These results highlight the possible need to provide immunonutrients before surgery to obtain adequate levels at the time of surgical stress when the need for stimulation of the immune system is maximized.[35]

CONCLUSIONS

Esophageal cancer is associated with malnutrition and impaired nutritional intake. Nutritional screening, early detection of malnourished patients and personalized nutritional support could reduce postoperative complications and ameliorate the quality of life of these patients.

REFERENCES

1. Miller RK, Bozeman CM. Nutrition therapy issues in esophageal cancer. *Curr Gastroenterol Rep* 2012; 14: 356-366.
2. Riccardi D, Allen K. Nutritional management of patients with esophageal and esophagogastric junction cancer. *Cancer Control* 1999; 6: 64–72.
3. Bailey SH, Bull DA, Harpole DH, et al. Outcomes after esophagectomy: a ten-year prospective cohort. *Ann Thorac Surg* 2003; 75: 217–222.
4. Bower MR, Martin RC. Nutritional management during neoadjuvant therapy for esophageal cancer. *J Surg Oncol* 2009; 100: 82-87.
5. Argilés JM, Olivan M, Busquets S, López-Soriano FJ. Optimal management of cancer anorexia–cachexia syndrome. Cancer Manag Res 2010; 2: 27-38
6. Dewys WD, Begg C, Lavin PT, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. *Am J Med* 1980; 69: 491-497.
7. Nitenberg G, Raynard B. Nutritional support of the

cancer patient: Issues and dilemmas. *Crit Rev Oncol Hematol* 2000; 34: 137-168.
8. Baker A, Wooten LA, Malloy M. Nutritional considerations after gastrectomy and esophagectomy for malignancy. *Current Treat Options Oncol* 2011; 12: 85-95.
9. August DA, Huhmann MB. American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors. A.S.P.E.N. clinical guidelines: Nutrition support therapy during adult anticancer treatment and in hematopoietic cell transplantation. *JPEN J Parenter Enteral Nutr* 2009; 33: 472-500.
10. Detsky AS, Smalley PS, Chang J. The rational clinical examination: Is this patient malnourished? *JAMA* 1994; 271: 54-58.
11. Nozoe T, Kimura Y, Ishida M, Saeki H, Korenaga D, Sugimachi K. Correlation of pre-operative nutritional condition with post-operative complications in surgical treatment for oesophageal carcinoma. *Eur J Surg Oncol* 2002; 28: 396-400.
12. Guo W, Ou G, Li X, Huang J, Liu J, Wei H. Screening of the nutritional risk of patients with gastric carcinoma before operation by NRS 2002 and its relationship with postoperative results. *J Gastroenterol Hepatol* 2010; 25: 800-803.
13. Buzby GP, Mullen JL, Mattews DC, et al. Prognostic nutritional index in gastrointestinal surgery. Am J Surg 1980; 139: 160-167.
14. Ryan AM, Hearty A, Prichard RS, et al. Association of hypoalbuminemia on the first postoperative day and complications following esophagectomy. *J Gastrointest Surg* 2007; 11: 1355-1360.
15. Nunes FF, Fernandes SA, Bertolini CM, et al. Avaliação nutricional do paciente cirrótico: comparação entre diversosmétodos. *Scientia Medica* 2012; 22: 12-17.
16. Chen CH, Ho-Chang, Huang YZ, Hung TT. Handgrip strength is a simple and effective outcome predictor in esophageal cancer following esophagectomy with reconstruction: a prospective study. *J Cardiothorac Surgery* 2011; 6: 98.
17. Prado CM, Birdsell LA, Baracos VE. The emerging role of computerized tomography in assessing cancer cachexia. *Curr Opin Support Palliat Care* 2009; 3: 269-275.
18. Gibson DJ, Burden ST, Strauss BJ, Todd C, Lal S. The role of computed tomography in evaluating body composition and the influence of reduced muscle mass on clinical outcome in abdominal malignancy: a systematic review. *Eur J Clin Nutrition* 2015; 69: 1079-1086.
19. Demeyer I, Bataillie K, Baute L. Long-term sedation inthe ICU: Enteral versus parenteral feeding. *Clin Intensive Care* 1994; 5(5 Suppl):13-16.
20. Kamei H, Hachisuka T, Nakao M, Takagi K. Quick recovery of serum diamine oxidase activity in patients undergoing total gastrectomy by oral enteralnutrition. *Am J Surg* 2005; 189: 38-43.
21. Gabor S, Renner H, Matzi V, et al. Early enteral feeding comparedwith parenteral nutrition after oesophageal oroesophagogastric resection and reconstruction. *Br J Nutr* 2005; 93: 509-513.
22. Fujita T, Daiko H, Nishimura M. Early enteral nutrition reduces the rate of life-threatening complications after thoracic esophagectomy in patients with esophageal cancer. *Eur Surg Res* 2012; 48: 79-84.
23. Wang G, Chen H, Liu J, Ma Y, Jia H. A comparison of postoperative early enteral nutrition with delayed enteral nutrition in patients with esophageal cancer. *Nutrients* 2015; 7: 4308-4317.
24. Peng J, Cai J, Niu ZX, Chen LQ. Early enteral nutrition compared with parenteral nutrition for esophageal cancer patients after esophagectomy: a meta-analysis. *Dis Esophagus* 2015, [Epub ahead of print].
25. Jianjun Q, Yin L, Wenqun X, Ming Y, Qingfeng J. Fast track program for esophagectomy patients. *Thoracic Cancer* 2012; 3: 55-59.
26. Lidder P, Flanagan D, Fleming S, et al. Combining enteral with parenteralnutrition to improve postoperative glucose control. *Br J Nutr* 2010; 103: 1635-1641.
27. Braga M, Ljungqvist O, Soeters P, Fearon K, Weimann A, Bozzetti F. ESPEN guidelines on parenteral nutrition: Surgery. *Clin Nutr* 2009; 28: 378-386.
28. Weimann A, Braga M, Harsanyi L, et al. ESPEN guidelines on enteral nutrition: Surgery including organ transplantation. Clin Nutr 2006; 25: 224-244.
29. McClave SA, Taylor BE, Martindale RG, et al. Guidelines for the provision and assessment of nutrition support therapyin the adult critically ill patient. *JPEN* 2009; 33: 277-316.
30. Weijs TJ, Berkelmans GH, Nieuwenhuijzen GA, et al. Routes for early enteral nutrition after esophagectomy. A systematic review. *Clin Nutr* 2015; 34: 1-6.
31. Fenton JR, Bergeron EJ, Coello M, Welsh RJ, Chmielewski GW. Feeding jejunostomy tubes placed during esophagectomy: are they necessary? *Ann Thorac Surg* 2011; 92: 504-512.

32. Gupta V. Benefits versus risks: a prospective audit. Feeding jejunostomy during esophagectomy *World J Surg* 2009; 33: 1432-1438.
33. Martin L, Lagergren J, Jia C, Lindblad M, Rouvelas I, Viklund P. The influence of needle catheter jejunostomy on weight development after oesophageal cancer surgery in a population-based study. *Eur J Surg Oncol* 2007; 33: 713-717.
34. Mabvuure NT, Roman A, Khan OA. Enteral immunonutrition versus standard enteral nutrition for patients undergoing oesophagogastric resection for cancer. *Int J Surg* 2013; 11: 122-127.
35. Kubota K, Kuroda J, Yoshida M, Okada A, Deguchi T, Kitajima M. Preoperative oral supplementation support in patients with esophageal cancer. *J Nutr Health Aging* 2014; 18: 437-440.

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REVIEW

How accurate is staging of oesophageal cancer according to TNM?

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ABSTRACT

Oesophageal cancer is the fifth most common cause of cancer-related deaths in men and the eighth leading cause of cancer mortality in women worldwide. More than 90% of oesophageal cancers are either squamous cell carcinomas (SCCs) or adenocarcinomas. Staging is the most critical parameter for patient care and treatment planning. Accurate staging helps predict recurrence and survival, determines the adjuvant treatment strategy, and allows comparison of oncologic outcomes across different institutions

KEY WORDS: oesophageal cancer, accurate staging, TNM

Oesophageal cancer is the fifth most common cause of cancer-related deaths in men and the eighth leading cause of cancer mortality in women worldwide.[1] More than 90% of oesophageal cancers are either squamous cell carcinomas (SCCs) or adenocarcinomas.[2] During the twentieth century, SCC has predominated. The past two decades, however, the incidence of oesophageal adenocarcinoma has increased dramatically in Western countries. As a result, adenocarcinoma now accounts for >60 percent of all oesophageal cancers in the United States. In contrast, worldwide, SCC still predominates.[3]

SCC is evenly distributed between the middle and lower oesophagus, whereas approximately three-fourths of all adenocarcinomas are found in the distal esophagus.[2] Nearly 50-60% of patients with oesophageal cancer present with incurable locally advanced or metastatic disease. Only a minority can achieve prolonged progression-free survival, while palliative treatment is the aim for the majority. For patients with localized, potentially resectable disease, median survival strongly correlates with disease stage.[4]

Most patients, though, have tumours that invade through oesophageal wall or are node-positive, and long-term survival is poor. Nearly 15% of these patients can be cured using multimodality therapy, which includes surgical resection and preoperative or definitive chemoradiationtherapy.[5] Consequently, accurate staging of cancer is important for stage-specific treatment, thus minimizing inappropriate treatment. Moreover, it allows for

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interinstitutional comparisons and disclosure of prognosis to patients.[6]

Current practice guidelines for preoperative staging of oesophageal cancer include endoscopic ultrasonography (EUS), CT of the chest and abdomen and PET/CT or PET/MR.[7] Several studies show that EUS is the most reliable tool for assessing the depth of tumour and locoregional LN metastases, with an accuracy of 74–89% for tumour depth and 65–79% for LN metastases.[8] CT alone cannot identify the histological layers of the oesophageal wall. Thus, the role of CT is usually limited to exclusion of T4 cancers.[9]

Integrated PET-CT scans, which can evaluate both locoregional and distant spread of tumours, could increase the accuracy of staging for oesophageal cancer when used in combination with EUS.[8] Recently, Lee et al showed that PET/MR imaging demonstrated T-staging accuracy comparable to that of EUS, although not statistically significant. PET/MR posed even higher accuracy than EUS and PET/CT for prediction of N staging.[9]

The current staging of esophageal cancer is assessed with the 7th edition of the TNM system as developed by the American Joint Committee on Cancer (AJCC). This revision is data-driven based on data from the Worldwide Esophageal Cancer Collaboration (WECC), which consisted of 13 countries.[5] According to the new system:

1. The histological types of oesophageal cancer represent two different diseases (Tables 1 and 2).
2. Tumour location is simplified, and esophagogastric junction is added.
3. Reassignment of stage groupings using T, N, M categories as well as histologic grade of differentiation (G), and for SCCs, tumour location. (Table 3)
4. Redefining of Tis (carcinoma in situ) as high-grade dysplasia.
5. T4 disease is subclassified.
6. Nodal (N) status is subclassified according to the number of regional metastatic nodes (Table 4).

Table 1. Stage Groupings for Squamous Cell Carcinoma

	Stage				
	N0				
TM Category	G1	G2–G3	N1	N2	N3
T1M0	IA	IB	IIB	IIIA	IIIC
T2M0			IIB	IIIA	IIIC
LE	IB	IIA			
UME	IIA	IIB			
T3M0			IIIA	IIIB	IIIC
LE	IB	IIA			
UME	IIA	IIB			
T4M0			IIIC	IIIC	IIIC
T4a	IIIA	IIIA			
T4b	IIIC	IIIC			
Any T, M1	IV	IV	IV	IV	IV

Table 2. Stage Groupings for Adenocarcinoma

	Stage				
	N0				
TM Category	G1–G2	G3	N1	N2	N3
T1M0	IA	IB	IIB	IIIA	IIIC
T2M0	IB	IIA	IIB	IIIA	IIIC
T3M0	IIB	IIB	IIIA	IIIB	IIIC
T4M0			IIIC	IIIC	IIIC
T4a	IIIA	IIIA			
T4b	IIIC	IIIC			
Any T, M1	IV	IV	IV	IV	IV

The development of separate stage grouping which is provided for SCCs and adenocarcinomas of the oesophagus and oesophagogastric junction represents a major change.[4] This change was based upon an analysis of worldwide data on 4627 patients with cancer of the oesophagus or EGJ who underwent surgery alone, and which showed that among patients with lymph node-negative tumours, prognosis was dependent on T-stage as well as histology, grade, and tumour location.[5] Tumours at the oesophagogastric junction and proximal 5 cm of the stomach that extend into the EGJ or oesophagus are classified and staged as oesophageal cancers.[5] All other tumours that are located in the stomach >5 cm from the EGJ, or those within 5 cm or the EGJ without exten-

Table 3. Comparison of Sixth and Seventh Editions of TNM Staging System for Esophageal Cancer

Category	Sixth Edition	Seventh Edition
Tumor	Tis: carcinoma in situ	Tis: high-grade dysplasia
	T1: invasion of lamina propria, muscularis mucosae, or submucosa	T1: invasion of lamina propria, muscularis mucosae, or or submucosa
	T2: invasion of muscularis propria	T2: invasion of muscularis propria
	T3: invasion of adventitia	T3: invasion of adventitia
	T4: invasion of adjacent structures	T4: invasion of adjacent structures
	…	T4a: resectable (pleura, pericardium, or diaphragm)
	…	T4b: unresectable (aorta, vertebral body, or trachea)
Node	N0: absent	N0: absent
	N1: present	N1: 1–2 regional LNs
	…	N2: 3–6 regional LNs
	…	N3: ≥7 regional LNs
Metastasis	M0: absent	M0: absent
	M1a: cervical LN (in upper esophageal cancer) or celiac LN (in lower esophageal cancer)	M1: present
	M1b: all other distant metastases	…

Table 4. Esophageal Cancer Staging of Lymph Node Metastases in the Sixth and Seventh Editions

Location of Lymph Node Metastases	Sixth Edition	Seventh Edition
Cervical and supraclavicular	N1 (CE), M1a (UE), M1b (ME, LE)	N1–N3
Mediastinal and perigastric	N1 (UE, ME, LE), M1b (CE)	N1–N3
Celiac	M1a (LE), M1b (CE, UE, ME)	N1–N3
Distant	M1b	M1

CE = cervical esophagus, LE = lower esophagus, ME = middle esophagus, UE = upper esophagus.

sion into the oesophagus are staged as gastric cancers. Tumours arising in the cervical, thoracic oesophagus, or abdominal oesophagus, including those that arise within the cardia of the stomach within 5 cm of the EGJ share the same criteria for T stage designation.[5]

As far as the definition of regional lymph nodes is concerned, data suggesting the prognostic importance of the number of involved lymph nodes rather than location in oesophageal cancer led to a change in N stage classification with an emphasis on number of involved nodes rather than location in the 2010 edition.[4] Moreover, only patients with distant metastasis can be categorized as having stage IV disease. Consequently, 87% of the patients with stage IV disease who were assessed according to the 6th edition criteria were reclassified as having stage IIB, IIIA, IIIB, and IIIC disease according to 7th edition criteria. Because these stages all had different survivals the present results support the new concept that it is unnecessary to identify nonregional lymph node metastasis and to label these nodes as M1A or M1B.[6]

On the other hand, some points of the new TNM system are in dispute. When searching the literature, survival roles of histology grade and cancer location in esophageal cancer patient seem controversial.[5,10,11] Histological grade and tumour

location were not shown to be significant prognostic factors in several studies.[12-16] Whether the location of the intrathoracic oesophageal cancer should be regarded as a prognostic factor is also debatable. Some reported studies commented that patients' survival improves as location of oesophageal tumour moves distally. However, these studies are comprised by a heterogeneous group of patients where most of the "distal" tumour were adenocarcinoma in distal oesophagus or gastroesophageal junction.[11,13] To specifically address this issue, Doki et al.[17] demonstrated that patients of upper, middle, or lower intrathoracic squamous cell oesophageal cancer had similar 5- and 10-year disease-free survival.

Furthermore, the current oesophageal cancer staging system was not designed to consider the anatomical and histological structure of gastric cancers. That means that two gastric cancers with different T classification, one with penetration into the subserosal layer and the other with penetration of the serosal layer, would be the same T3 classification in the oesophageal scheme. However, serosal exposure of gastric cancer has such a great implication that it cannot be neglected. In this regard, an anatomical definition of tumour depth in EGJ cancer should be considered to reflect cancer invasion into the gastric wall in addition to the oesophageal wall according to Kim et al.

With respect to the target organ, the 7th AJCC staging system is based on data of Western populations, where adenocarcinoma of the distal esophagus, which requires distal oesophagectomy, is the prevailing type.[18] However, in Eastern countries most of the EGJ cancers are proximally located adenocarcinomas of the stomach and can be treated with total gastrectomy or extended total gastrectomy. Propably, the use of the oesophageal staging system in proximal gastric cancer may result in misclassification of staging and inappropriate planning of treatment for patients in eastern countries.[18]

Controversy, also, exists when examining nodal staging. Two recent studies with ESCC suggested that there were no differences in survival between pN2 and pN3 patients.[19,20] This is caused due to the lack of a well-accepted cut-off for the N-classification in each research centre. Both different surgical approaches used in each hospital and a possible difficulty in counting the exact number of resected lymph nodes can result in varying numbers of lymph nodes harvested from each patient.[19] Yang et al suggested that the nodal categories for SCC should be classified into four groups: N0 (no positive lymph nodes), N1 (1 positive lymph node), N2 (2 to 3 positive lymph nodes), and N3 (>4 positive lymph nodes). This classification indicates that systemic disease might be universally present in SCC patients with more than four positive LNs, and a more extensive operation would likely fail to alter the outcome.[19]

One other parameter is that the current UICC staging does not take into consideration whether or not extracapsular lymph node involvement (EC-LNI) is present in the resectedmetastaticlymph nodes. A systematic review confirmed the poorer overall and disease-free survival in case of EC-LNI.[20] This review quoted four studies reporting the impact of EC-LNI exclusively on adenocarcinoma of the oesophagus and GOJ treated by primary surgery.[20-23] Three of them revealed the incidence of EC-LNI, up to 66%.[20,21,23] The pooled incidence for EC-LNI was 61%. Five-year overall survival ranged from 33 to 53% and from 0 to 23% for patients with IC-LNI and EC-LNI, respectively. These studies furthermore identified EC-LNI as an independent prognostic factor for survival in a multivariate analysis. EC-LNI gives additional information not reflected in the actual UICC/AJCC TNM staging system, especially for the pN1 category and would be helpful in identifying oesophageal cancer patients with better prognosis.

In conclusion, staging is the most critical parameter for patient care and treatment planning. Accurate staging helps predict recurrence and survival, determines the adjuvant treatment strategy, and allows comparison of oncologic outcomes across different institutions

REFERENCES

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; 61: 69-90.
2. Daly JM, Fry WA, Little AG, et al. Esophageal cancer: results of an American College of Surgeons patient care evaluation study. *J Am Coll Surg* 2000; 190: 562-572.
3. Baquet CR, Commiskey P, Mack K, et al. Esophageal cancer epidemiology in blacks and whites: racial and gender disparities in incidence, mortality, survival rates and histology. *J Natl Med Assoc* 2005; 97:1471.
4. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. American Joint Committee on Cancer (AJCC) cancer staging manual. 7th ed. Chicago: Springer, 2010.
5. Rice TW, Rusch VW, Apperson-Hansen C, et al. Worldwide esophageal cancer collaboration. *Dis Esophagus* 2009; 22: 1-8.
6. Talsma K, van Hagen P, Grotenhuis BA, et al. Comparison of the 6th and 7th Editions of the UICC-AJCC TNM Classification for Esophageal Cancer. *Ann Surg Oncol* 2012; 19: 2142-2148.
7. Varghese TK Jr, Hofstetter WL, Rizk NP, et al. The Society of Thoracic Surgeons guidelines on the diagnosis and staging of patients with esophageal cancer. *Ann Thorac Surg* 2013; 96: 346-356.
8. Shin S, Kima HK, Choia YS, Kimb K, Shim YM. Clinical stageT1-T2N0M0 oesophageal cancer: accuracy of clinical staging and predictive factors for lymph node metastasis. *Eur J Card Thoracic Surg* 2014; 46: 274-279.
9. Lee G, Hoseok I, Kim SJ, et al. Clinical implication of PET/MR imaging in preoperative esophageal cancer staging: comparison with PET/CT, endoscopic ultrasonography, and CT. *J Nucl Med* 2014; 55: 1242-1247.
10. Altorki NK, Zhou XK, Stiles B, et al. Total number of resected lymph nodes predicts survival in esophageal cancer. *Ann Surg* 2008; 248: 221-226.
11. Bogoevski D, Onken F, Koenig A, et al. Is it time for a new TNM classification in esophageal carcinoma? *Ann Surg* 2008; 247: 633-641.
12. Hsu PK, Wu YC, Chou TY, Huang CS, Hsu WH. Comparison of the 6th and 7th editions of the American Joint Committee on Cancer tumor-node-metastasis staging system in patients with resected esophageal carcinoma. *Ann Thorac Surg* 2010; 89: 1024-1031.
13. Eloubeidi MA, Desmond R, Arguedas MR, Reed CE, Wilcox CM. Prognostic factors for the survival of patients with esophageal carcinoma in the U.S.: the importance of tumor length and lymph node status. *Cancer* 2002; 95: 1434-1443.
14. Situ D, Wang J, Lin P, et al. Do tumor location and grade affect survival in pT2N0M0 esophageal squamous cell carcinoma? *J Thorac Cardiovasc Surg* 2013; 146: 45-51.
15. Roder JD, Busch R, Stein HJ, Fink U, Siewert JR. Ratio of invaded to removed lymph nodes as a predictor of survival in squamous cell carcinoma of the oesophagus. *Br J Surg* 1994; 81: 410-413.
16. Nomura M, Shitara K, Kodaira T, et al. Prognostic impact of the 6th and 7th American Joint Committee on Cancer TNM staging systems on esophageal cancer patients treated with chemoradiotherapy. *Int J RadiatOncol Biol Phys* 2012; 82: 946-952.
17. Yam PC, Tong D, Law S. Comparisons of sixth and seventh edition of the American Joint Cancer Committee staging systems for esophageal cancer *Ann Surg Oncol* 2014; 21: 583-588.
18. Kim HI, Cheong JI, Song KJ, et al. Staging of adenocarcinoma of the esophagogastric junction: Comparison of AJCC 6th and 7th gastric and 7th esophageal staging systems. *Ann Surg Oncol* 2013;2 0: 2713-2720.
19. Yang HX, Wei JC, Xu Y, et al. Modification of nodal categories in the seventh American Joint Committee on Cancer staging system for esophageal squamous cell carcinoma in Chinese patients. *Ann Thorac Surg* 2011; 92: 216-224.
20. Wind J, Lagarde S, ten Kate F, Ubbink D, Bemelman W, Van Lanschot J. A systematic review on the significance of extracapsular lymph node involvement in gastrointestinal malignancies. *Eur J Surg Oncol* 2007; 33: 401-408.
21. Lerut T, Coosemans W, Decker G, et al. Extracapsular lymph node involvement is a negative prognostic factor in T3 adenocarcinoma of the distal esophagus and gastroesophageal junction. *J Thorac Cardiovasc Surg* 2003; 126: 1121-1128.
22. D'Journo XB, Doddoli C, Michelet P, et al. Transthoracic esophagectomy for adenocarcinoma of the esophagus: standard versus extended two-field mediastinal lymphadenectomy? *Eur J Cardiothorac Surg* 2005; 27: 697-704.
23. Lagarde S, ten Kate F, de Boer D, Busch O, Obertop H, van Lanschot J. Extracapsular lymph node involvement in node-positive patients with adenocarcinoma of the distal esophagus or gastroesophageal junction. *Am J Surg Pathol* 2006; 30: 171-176.

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REVIEW

Staging accuracy of esophageal cancer by endoscopic ultrasound: A systematic review

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ABSTRACT

Endoscopic ultrasound (EUS) is the most accurate method for locoregional staging of esophageal carcinoma and should be performed in patients being considered for surgery once distant metastases have been excluded by computed tomography and/or positron emission tomography. The accuracy of EUS is operator-dependent, and interobserver reliability is influenced by experience and tumor stage. EUS-guided fine needle aspiration improves further lymph node staging accuracy and should be performed when confirmation of metastatic lymphadenopathy will alter patient therapy. Limitations caused by stenotic tumors, precluding echoendoscope passage and complete staging, are being overcome by smaller caliber instruments and dilation of the lumen. The additional information that may be obtained must be balanced by the risk of perforation when dilation is undertaken. EUS has a limited role in restaging patient after chemotherapy and/or radiation therapy, but is the most sensitive technique for detecting locoregional tumor recurrence.

KEY WORDS: esophageal cancer, endoscopic ultrasound, staging, imaging modalities

INTRODUCTION

The incidence of esophageal adenocarcinoma has been rising in western countries over the past decades.[1,2] Esophageal carcinoma is an aggressive disease associated with poor prognosis due to the fact that most patients have an advanced tumor stage at the time of diagnosis.[3-6] Differences in survival between patients with early and advanced stage tumors correlates with tumor extension through the esophageal wall into the adventitia (T3), and/or with the presence of metastatic lymph nodes (N1).[5-10] Surgical intervention is generally advised for fit patients with stage IIa or lower.[8-10]

Preoperative adjuvant therapy (chemotherapy and radiotherapy) may increase survival of patients with advanced stage disease.[11,12] In such patients palliative measures seem to be as effective as more aggressive treatments. These reports reinforce the importance of accurately staging esophageal carcinoma prior to undertaking therapy.

EUS is the most accurate method for assessing the loco regional spread of tumor in these patients. We will summarize data pertaining to the role of EUS in preoperative staging of esophageal carcinoma, the role of EUS FNA in sampling lymph nodes to improve staging accuracy of EUS and

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the role of EUS to predict treatment response after neoadjuvant therapy.

PREOPERATIVE STAGING OF ESOPHAGEAL CARCINOMA

Initial evaluation of the patients diagnosed with esophageal carcinoma centers on assessing patients' operative risk and staging the tumor. If the patient is a surgical candidate, preoperative tumor staging is warranted because their disease extent will influence treatment planning. Initial efforts are directed to exclude the presence of distant metastases CT scan or Positron Emission Tomography (PET) scanning have been used for this purpose. PET scanning may be more accurate for the diagnosis of stage IV disease than CT scan or EUS (82% vs 64% vs 71% accuracy, respectively), but not for differentiation of N0 vs N1 (59% vs 45% vs 74% accuracy, respectively).[13]

A more detailed evaluation of locoregional disease staging (T and N stage) should be obtained if distant metastases are not demonstrated. EUS has been proven to be more accurate than transabdominal ultrasound, CT scan, magnetic resonance imaging (MRI), or PET scanning for locoregional scanning of esophageal carcinoma.[14-25]

HISTOLOGIC CORRELATES OF THE ENDOSCOPIC IMAGE

Currently available echoendoscopes operate at different ultrasound frequencies (5, 7.5, 12 and 20MHz), allowing one to visualize the esophageal wall as a 5-layer structure (first hyper echoic layer: superficial mucosa, second hypoechoic layer: deep mucosa, third hyperechoic layer: submucosa, fourth hypo echoic layer: muscularis propria, fifth hyper echoic layer: adventitia).[26] The ability to visualize the five layers permits a detailed understanding of the degree of tumor infiltration into the wall layers, and determination of the tumor stage (T stage).[26]

A limitation of standard echoendoscopes is that they cannot visualize the muscular mucosa. High frequency mini probes (20 MHz) provide a more detailed visualization permitting delineation of nine layers in the esophageal wall (first and second layer: superficial mucosa [hyper and hypo echoic respectively], third layer: lamina propria [hyperechoic], fifth layer: submucosa [hyperechoic] sixth, seventh and eighth layer: inner circular muscle and outer longitudinal muscle of the muscularis propria with intermuscular connective tissue [hypo, hyper, hypo echoic respectively], ninth layer: adventitia [hyperechoic]).[27,28] This may have particular importance when evaluating superficial lesions for which nonsurgical therapy is being considered (endoscopic mucosal resection, photodynamic therapy).

EUS FOR T STAGING OF SUPERFICIAL TUMORS

EUS is the most accurate technique for locoregional staging of esophageal cancer, with an overall accuracy of EUS for T and N staging of 80 to 90 percent (Table 1).[25,27]

An accurate tumor stage is essential for treatment decision in early tumors, mainly when nonsurgical therapies are considered as an alternative for cure (endoscopic mucosal resection EMR or photodynamic therapy PTD). Large meta-analysis found that EUS was accurate for staging T1a and T2b tumors, with an area under the receiver operating characteristic curve of 0.93 to 0.96.[29] If the tumor does not invade the muscular mucosa,

Table 1. Preoperative TN staging accuracy of CT and EUS in esophageal carcinoma

	Patients	T Stage (range)	N Stage (range)
	(n)	(%)	(%)
CT	1154	45	54
		(40-50)	(48-71)
EUS	1035	85	77
		(59-92)	(50-90)

lymph node metastases are unlikely to be present and EMR may be curative.[30] By contrast, lymph node metastases may be present in up to 10% of patients of patients with invasion into the muscular mucosa.[30,31]

If the EUS identifies esophageal cancer that invades the muscular mucosa, or if there is evidence of lymph node involvement, then surgical therapy is frequently recommended. On the other, if the EUS only mucosal disease, EMR can be considered to remove the tumor and precisely define the depth of invasion. The pathology result from the EMR can then be used to guide the final decision as to whether endoscopic therapy alone is sufficient or if surgery should be recommended.

High frequency ultrasound catheters (20-30 MHz) allow one to assess if tumor invades muscular mucosa with an accuracy of 84%, improving T staging accuracy in superficial carcinomas (T1 vs T2) from 76 to 92%.[27,28] However, their limited depth of penetration into the surrounding tissues (approximately 3cm) precludes adequate assessment of N stage.[32]

EUS FOR T STAGING OF ADVANCED TUMORS

In patients with advanced tumors of the esophagus, the presence of a tight stenosis may preclude a complete EUS exam with the dedicated echoendoscopes (12.7mm in diameter). This was illustrated in a series of 113 patients who underwent esophagectomy in whom the accuracy of EUS for T and N staging was much higher for traversable (81 and 86% respectively) as compared with non-traversable tumors (28 and 72% respectively).[30] EUS staging mistakes are due to incomplete tumor traversal leading to T and N understating, and oblique scanning resulting in T staging errors.[32,33]

Several options are possible to enhance tumor staging in these settings:

a. Dilation of the lumen to a diameter of 14 to 16mm with either a Savary dilator or a pneumatic balloon appears sufficient to allow traversal for stenotic lesions.[33] However, a perforation frequency as high as 24% has been described with this practice. The high perforation rate may be in part due to the blunt tips of the older instruments. The newer echoendoscopes are built with a smaller tip that allows for easier passage of the echoendoscope through the stenotic tumor.[32] In patients with severely stenotic tumors, a progressive dilation strategy over several days rather than a single dilation is advised. In one report, Savary dilation to 14 to 16mm permitted passage of the echoendoscope in 85 to 100% of patients without complications; two additional dilators of incremental diameter were passed once resistance was encountered, and the dilation was limited to <13mm in one third of patients.[34]
b. High frequency ultrasound catheters introduced through the biopsy channel of the echoendoscope, due to their small caliber (3mm in diameter) may allow traversing tight strictures. Although this may improve the accuracy of T and N staging, the limited depth of penetration of mini probes may lead to incomplete assessment of loco regional spread (understaging of lymph node spread).
c. A wire-guided blind echoendoscope is available for staging stenotic tumors (Olympus R MH-908). This probe measures 7mm in diameter and can be advanced over a guide wire. However, this dedicated probe is not widely available and celiac axis cannot be adequately assessed with this probe.

The additional information that may be obtained from a complete EUS exam must be balanced by the risk of perforation when dilation is undertaken. A direct comparison of these techniques to determine their comparative accuracy has not been performed. Based on clinical practice, the performance of upper gastrointestinal endoscopy with a standard gastroscope initially at the time of EUS to assess the degree of stenosis is recommended. If the gastroscope evidences a

severely tight stenosis that cannot be traversed with a slim endoscope, dilation is not advised as the risk of perforation is elevated, and the passage of the echoendoscope, even with this intervention, infrequent. In patients with circumferential stenosis permitting passage of a gastroscope but not the echoendoscope, judicious dilation is undertaken.

ACCURACY OF EUS FOR DETERMINING UNRESECTABILITY

The accuracy of EUS for determination of T4 stage is approximately 86%.[14]

The presence of an advanced tumor at EUS typically results in palliative treatment of chemoradiation followed by restaging and surgical resection possible.

Unresectability is also suggested in patients with tumor arising above the level of carina, with extension through the esophageal wall into the mediastinum. Below the carina, extension into adjacent structures such as the pleura, aorta, diaphragm, and liver represents T4 disease, precluding surgical resection with a curative intent without neoadjuvant chemoradiation.

EUS FOR PREOPERATIVE LYMPH NODE STAGING

Endosonographic criteria that are suggestive of malignancy in the lymph nodes include a width greater than 10mm, round shape, smooth border, and echopoor pattern.[35] Although none of these criteria is diagnostic of malignancy alone, the presence of an echo poor pattern and a width >10mm have been found to be the most specific EUS criteria for malignancy. When all four suspicious features are present, there is an 80 to 100% chance of metastatic involvement (Table 2).[36]

Unfortunately only 25% of malignant nodes will have all four diagnostic criteria for malignancy. These results demonstrate the limitations of EUS criteria for preoperative determination of lymph node staging. However, greater number of malignant appearing periesophageal lymph nodes detected by EUS predicted worse survival.[37] The demonstration of clinically suspicious lymph nodes may support the selection of induction chemoradiotherapy over surgery alone, particularly in patient with T2 disease.

Table 2. Endoscopic ultrasound (EUS) criteria for assessment of lymph nodes

	Benign	Malignant
Size (width)	<10mm	>10mm
Shape	Elongated	Round
Border	Irregular	Smooth
Echogenity	Echorich	Echopoor

Some investigators have proposed that EUS-FNA may help improvement of providing cytologic confirmation of malignant disease spread as long as the primary tumor is not in the pathway of the aspiration needle.

Sensitivity, specificity and accuracy of EUS for locoregional lymph nodes are all over 85% when surgical resection specimen or cytology results are considered as the gold standard.[38-40]

EUS FNA appears to improve the nodal staging beyond that achieved by EUS alone. These results were confirmed by a prospective study conducted at the Mayo Clinic comparing the performance characteristics of helical CT, EUS and EUS FNA for preoperative lymph node staging of esophageal carcinoma. The endosonographers were blinded to CT findings, and committed to an N stage prior to perform performing the EUS-FNA part. Table demonstrates the superior accuracy of EUS FNA over EUS and helical CT (Table 3).

Optimal criteria for identifying malignant lymph nodes based upon EUS features and selecting patients for whom EUS FNA is required continue to evolve. The modified EUS criteria (four standard criteria plus EUS-identified celiac lymph nodes, >5lymph nodes, or EUS T3/T4 tumor) were more accurate than standard criteria at identifying malignant lymph nodes.

Table 3. Prospective lymph node staging of esophageal carcinoma: CT vs EUS vs EUS FNA

	Sensitivity	Specificity	Accuracy
	n % (95% C.I.)		
CT	14/48, 29% (17%, 44%)	25/28, 89% (72%, 98%)	39/76, 51% (40%, 63%)
EUS	34/48, 71% (56%, 83%)	22/28, 79% (59%, 92%)	56/76, 74% (62%, 83%)
EUS FNA	40/48, 83% (70%, 93%)	26/28, 93% (77%, 99%)	66/76, 87% (77%, 94%)
	p-value		
CT vs EUS	<0.001	0.257	0.003
CT vs EUS FNA	<0.001	0.655	<0.001
EUS vs EUS FNA	0.058	0.102	0.012

INTEROBSERVER VARIATION FOR ESOPHAGEAL CARCINOMA STAGING

The accuracy of EUS and EUS-FNA is operator-dependent. The available evidence suggests that inter observer reliability is influenced by experience and tumor stage.[41-44]

Experienced endosonografers (>50-75 EUS exams in esophageal cancer cases) have good agreement for T and N stage, except for T2 tumors in which agreement was poor. When inexperienced endosonografers were tested (<20 EUS exams in patients with esophageal cancer), degree of accuracy and consistency on tumor stage assessment was significantly lower. Technical factors (ballon overinflation, oblique scanning, and inadequate use of higher scanning frequencies) may be responsible for staging errors among inexperienced endosonografers.[41,44,45]

Expert endosonografers tend to overstage esophageal carcinomas (8-14% of cases), typically in T2 lesions and may be attributed to peritumoral inflammation leading to an overestimation of mural penetration[44]. Understaging occurs in 3-15% of esophageal carcinomas and has been associated with microscopic infiltration of the tumor into the deeper layer that is beyond the resolution capabilities of the echoendoscopes.[42]

RESTAGING AFTER CHEMORADIATION

One of the most controversial areas in oncology is the optimal treatment of potentially resectable esophageal cancer. Patients with advanced tumor stage may benefit from preoperative chemoradiation therapy. Surgeons desire an evaluation of response to treatment prior to advising the patients on tumor resection. Unfortunately, the accuracy of EUS is poor in the setting (44% for T stage and 58% for N stage) (Table 4).

To explain such differences, it has been suggested that EUS may not be able to differentiate between post treatment inflammation/fibrosis and tumor residual. Despite the low level of accuracy

Table 4. Accuracy of endoscopic ultrasound (EUS) post-chemoradiotherapy in patients with esophageal carcinoma

	N	T stage*	N stage*
Isenberg G, et al 1998	31	43	-
Zuccaro G, et al 1999	59	37	38
Laterza E, et al 1999	87	47	71
Bowrey DJ, et al 1999	17	59	59
Kalha I, et al 2004	83	29	49
OVERALL (mean)	277	(43)	(44)

* Data shown represent percentages.

of EUS after chemotherapy and radiotherapy, it has been reported that a reduction in maximal cross-sectional area of tumor after adjuvant therapy correlates with tumor response to treatment and signals a better prognosis.[45,46]

EUS FOR DETECTION OF LOCOREGIONAL RECURRENCE

In certain clinical situations patients present with symptoms of signs worrisome for locoregional recurrence with negative endoscopy and radiographic evaluation. In this setting EUS is extremely accurate (sensitivity >92% and specificity >96%) for detecting loco regional relapse, and it should be considered in the work up of such patients.[46,47]

In one series of 45 patients who had undergone resection for localized esophageal carcinoma, EUS examination was performed every six months for a period of two years. The positive predictive value of an abnormal EUS for tumor recurrence was 92%, and two thirds of patients with tumor relapse on us were asymptomatic. In patients with signs or symptoms suspicious for recurrence, EUS and FNA should be performed to establish a diagnosis, although, it is un clear if early detection of tumor recurrence may help improve survival in these patients.[47,48]

The author declares that he has no conflict of interest.

REFERENCES

1. Pera M, Cameron AJ, Trastek VF, et al. Increasing incidence of adenocarcinoma of the esophagus and esophagogastric junction. *Gastroenterology* 1993; 104: 510-513.
2. Blot WJ, Devesa SS, Kneller RW, Fraumeni JF. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. *JAMA* 1991; 265: 1287-1289.
3. Forastiere AA, Heitmiller RF, Kleinberg L. Multimodality therapy for esophageal cancer. *Chest* 1997; 112: 195S-200S.
4. Pommier RF, Vetto JT, Ferris BL, Wilmarth TJ. Relationships between operative approaches and outcomes in esophageal cancer. *Am J Surg* 1998; 175: 422-425.
5. Siewert JR, Fink U, Beckurts KTE, Roder JD. Surgery of squamous cell carcinoma of the esophagus. *Ann Oncol* 1994; 5: 1-7.
6. Roder Jd, Busch R, Stein HJ, Siewert JR. Ratio of invaded to removed lymph nodes as a predictor of survival in squamous cell carcinoma of the esophagus. *Br J Surg* 1994; 81: 410-413.
7. Fleming Id, Cooper JS, Henson DE, et al. In: AJCC Cancer Staging Manual. Lippincott-raven (Eds), Philadelphia, 1997 P.
8. Edwards JM, Hillier VF, Lawson RA, et al. Squamous carcinoma of the esophagus: histological criteria and their prognostic significance. *Br J Cancer* 1989; 59: 429-433.
9. Hagen JA, Peters JH, DeMeester TR. Superiority of extended en bloc esophagogastrectomy for carcinoma of the lower esophagus and cardia. *J Thorac Cardiovasc Surg* 1993; 106: 850-858.
10. DeMeester TR, Zaninotto G, Johansson KE. Selective therapeutic approach to cancer of the lower esophagus and cardia. *J Thorac Cardiovasc Surg* 1988; 95: 42-54.
11. Walsh TN, Noonan N, Hollywood D, et al. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. *N Engl J Med* 1996; 335: 462-467.
12. Ando N, Ozawa S, Miki H, Suwa T, Kitajima M. Neoadjuvant chemotherapy and chemoradiotherapy in the treatment of esophageal cancer. *Jap J Cancer Chemother* 1995; 22: 1878-1885.
13. Flamen P, Lerut A, Van Cutsem E, et al. Utility of positron emission tomography for the staging of patients with potentially operable esophageal carcinoma. *J Clin Oncol* 2000; 18: 3202-3210.
14. Murata Y, Suzuki S, Hashimoto H. Endoscopic ultrasonography of the upper gastrointestinal tract. *Surg Endosc* 1988; 2: 180–183.
15. Tio TL, Coene PP, Den Hartog Jager FC, Tytgat GN. Preoperative TNM classification of esophageal carcinoma by endosonography. *Hepatogastroenterology* 1990; 37: 376-81.
16. Vilgrain V, Mompoint D, Palazzo L, et al. Staging of oesophageal carcinoma: comparison of results with endoscopic sonography and CT. *Am J Radiol* 1990; 155: 277-281.
17. Botet JF, Lightdale CJ, Zauber G, et al. Preoperative staging of esophageal cancer: Comparison of endoscopic US and dynamic CT. *Radiology* 1991; 181:419-425.

18. Grimm H, Binmoeller KF, Hamper K, et al. Endosonography for preoperative locoregional staging of esophageal and gastric cancer. *Endoscopy* 1993; 25: 224-30.
19. Rosch T, Lorenz R, Zenker K, et al. Local staging and assessment of resectability in carcinoma of the esophagus, stomach and duodenum by endoscopic ultrasonography. *Gastrointest Endosc* 1992; 38: 460-467.
20. Quint LE, Glazer GM, Orringer MB. Esophageal imaging by MR and CT: study of normal anatomy and neoplasms. *Radiology* 1985, 156: 727-731.
21. Petrilo R, Balzarini L, Bidoli P. Esophageal squamous cell carcinoma: MRI evaluation of the mediastinum. *Gastrointest Radiol* 1990, 15: 275-278.
22. Takasima S, Takeuchi N, Shiozaki H. Carcinoma of the esophagus: CT vs. MR imaging in determining resectability. *Am J Radiol* 1991; 156: 297-302.
23. Lehr L, Rupp N, Siewert JR. Assessment of resectability of esophageal cancer by computed tomography and magnetic resonance imaging. *Surgery* 1988; 103: 344-350.
24. Koch J, Robert AH Jr. Staging of esophageal cancer: Computed tomography, magnetic resonance imaging and endoscopic ultrasound. *Semin Roentgenol* 1994; 29: 364.
25. Rosch T. Endoscopic staging of esophageal cancer: a review of literature results. *Gastrointest Endosc Clin North Am* 1995; 5:53.
26. Kimmey MB, Martin EW, Haggitt RC, et al. Histological correlates of gastrointestinal endoscopic ultrasound images. *Gastroenterology* 1989; 96: 433-441.
27. Hasegawa N, Niwa Y, Arisawa T, et al. Preoperative staging of superficial esophageal carcinoma: comparison of an ultrasound probe and standard endoscopic ultrasonography. *Gastrointest Endosc* 1996; 44: 388-393.
28. Murata Y, Suzuki S, Ohta M, et al. Small ultrasonic probes for determination of depth of superficial esophageal cancer. *Gastrointest Endosc* 1996; 44: 23-28.
29. Thosani N, Singh H, Kapadia A, et al. Diagnostic accuracy of EUS in differentiating mucosal versus submucosal invasion of superficial esophageal cancers: a systematic review and meta analysis. *Gastrointest Endosc* 2012; 75: 242-253.
30. Tajima Y, Nakanishi Y, Ochiai A, et al. Histopathologic findings predicting lymph node metastasis and prognosis of patients with superficial esophageal carcinoma: analysis of 240 surgically resected tumors. *Cancer* 2000; 88: 1285-1293.
31. Tio L. Diagnosis and staging of esophageal carcinoma by endoscopic ultrasonography. *Endoscopy* 1998; 30 (Suppl 1): A33-A40.
32. Rosch T, Classen M. Pitfalls in endosonographic imaging. In: Gastrointestinal endosonography, Van Dam/Sivak, WB Saunders Company 1999. p. 123.
33. Catalano MF, Van Dam J, Sivak MV. Malignant esophageal strictures: staging accuracy of endoscopic ultrasonography. *Gastrointest Endosc* 1995; 41: 535-539.
34. Wallace MB, Hoffman BJ, Sahai AS, et al. Imaging of esophageal tumors with a water-filled condom and a catheter US probe. *Gastrointest Endosc* 2000; 51: 597-600.
35. Van dam J, Rice TW, Catalano MF, et al. High-grade malignant stricture is predictive of esophageal tumor stage. Risks of endosonographic evaluation. *Cancer* 1993; 71: 2910-2917.
36. Menzel J, Hoepffner N, Nottberg H, et al. Preoperative staging of esophageal carcinoma: miniprobe sonography versus conventional endoscopic ultrasound in a prospective histopathologically verified study. *Endoscopy* 1999; 31: 291-297.
37. Mallery S, Van Dam J. Increased rate of complete EUS staging of patients with esophageal cancer using the non- optical, wire-guided echoendoscope. *Gastrointest Endosc* 1999; 50: 53-57.
38. Bhutani MS, Hawes RH, Hoffman BJ. A comparison of the accuracy of echo features during endoscopic ultrasound (EUS) and EUS-guided fine needle aspiration for diagnosis of malignant lymph node invasion. *Gastrointest Endosc* 1997; 45: 474-479.
39. Wiersema MJ, Vilmann P, Giovannini M, et al. Endosonography-guided fine-needle aspiration biopsy: diagnostic accuracy and complication assessment. *Gastroenterology* 1997; 112: 1087-1095.
40. Giovannini M, Seitz JF, Monges G, et al. Fine-needle aspiration cytology guided by endoscopic ultrasonography: results in 141 patients. *Endoscopy* 1995; 27: 171-177.
41. Burtin P, Berg P, Bour B, et al. Evaluation of the teaching of echo-endoscopy. Application to the assessment of invasiveness of cancer of the esophagus and the cardia. *Gastroenterol Clin Biol* 1995; 19: 15-19.
42. Catalano MF, Sivak MV Jr, Bedford RA, et al. Observer variation and reproducibility of endoscopic ultrasonography. *Gastrointest Endosc* 1995; 41: 115-120.
43. Palazzo l, Burtin P. Interobserver variation in tumor

staging. *Gastrointest Endosc Clin North Am* 1995; 5: 559.
44. Fockens PF, Van den Brande J, van Dullemen HM, et al. Endosonographic T-staging of esophageal carcinoma: a learning curve. *Gastrointest Endosc* 1996; 44: 58-62.
45. Massari M, Cioffi U, de Simone M, et al. Endoscopic ultrasonography for preoperative staging of esophageal carcinoma. *Surg Laparosc Endosc* 1997; 7: 162-165.
46. Catalano MF, Sivak MV, Rice TW, van Dam J. Postoperative screening for anastomotic recurrence of esophageal carcinoma by endoscopic ultrasonography. *Gastrointest Endosc* 1995; 42: 540-544.
47. Fockens P, Manshanden CG, Van Lanschot JJ, et al. Prospective study on the value of endosonographic follow-up after surgery for esophageal carcinoma. *Gastrointest Endosc* 1997; 46: 487-491.
48. Muller C, Kahler G, Scheele J. Endosonographic examination of gastrointestinal anastomoses with suspected locoregional tumor recurrence. *Surg Endosc* 2000; 14: 45-50.

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REVIEW

Siewert's classification of gastroesophageal junction cancer: New trends

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ABSTRACT

There is an increasing trend in the incidence of gastroesophageal junction (EGJ) cancer in the western world during the last 30 years, reflecting overall an important increase of adenocarcinoma (AC) against a decrease of squamous cell carcinoma (SCC) cases. Siewert's classification (2000) which was based on pathological topography has now been changed to a more dynamic classification introduced by the American Joint Committe on Cancer (AJCC) on their 7th Edition of AJCC Cancer Staging Manual. The important change refers to cancers whose epicenter is in the lower thoracic esophagus, EGJ, or within the proximal 5 cm of the stomach that extend into the EGJ or esophagus (Siewert III), which are now stage grouped similar to AC of the esophagus. The revised staging system includes separate stage groupings for SCC and AC and gives attention to the optimum number of resected lymph nodes according to T stage in order to maximize survival. This approach remains a subject of disagreement, some confusion and debates.

KEY WORDS: gastroesophageal junction cancer, adenocarcinoma, squamous cell carcinoma, classification, staging, lymph nodes

INTRODUCTION

There is an increasing trend in the incidence of gastroesophageal junction (GEJ) cancer in the last 30 years in the western world, which reflects an important increase of adenocarcinoma (AC) against a decrease of squamous cell carcinoma (SCC) cases. Gastroesophageal reflux disease and Barrett's esophagus are the two major risk factors for AC, and others include obesity and high body mass index. The TNM classification developed by the American Joint Committe on Cancer (AJCC) in 2002 was based on the pathological review of the surgical specimen in patients who had surgery as primary care.[1] The topography had been described by Siewert in 2000.[2] In 2010 the AJCC introduced a more dynamic classification on their 7th Edition of AJCC Cancer Staging Manual.[1] The revised classification was based on the risk-adjusted random forest analysis of the data generated by the Worldwide Esophageal Cancer Collaboration in 4,627 patients who were treated with primary esophagectomy without preoperative

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therapy. Survival worsening parameters which were incorporated in the new classification were depth of invasion, presence of regional lymph node metastases except distant metastases, submucosal or intramucosal invasion, and histology of the cancer. The staging system was revised for the esophageal and EGJ cancers, including the cancer within the first 5 cm of the stomach that extend into the EGJ or distal thoracic esophagus. However, this new classification may not work well for baseline clinical staging or in patients who received preoperative therapy. This new classification has several other shortcomings including: inclusion of proximal 5 cm of stomach lack of guidance for regional resectable and unresectable cancer, and the emphasis on the number of nodes rather than their anatomic locations and significance. Size of the lymph node is also not addressed.

SIEWERT'S CLASSIFICATION

Siewert[2] classified the AC of the EGJ into three types based purely on the anatomic location of the epicenter of the tumor or the location of the tumor mass in relation to the anatomic EGJ. The anatomic EGJ is denoted by the "Z" line formed as the esophageal mucosa gives place to the gastric mucosal folds. Although this line is not always visible endoscopically, the identification of palisate vessels on the gastric mucosa help to speculate the spot where the "Z" line should appear, just above them. The original Siewert classification was the following: if the epicenter of the tumor or more than 66% of the tumor mass was located more than 1 cm above the anatomic EGJ, then the tumor was classified as an AC of the distal esophagus, or carcinoma Siewert type I; if the epicenter of the tumor or tumor mass was located within 1 cm proximal and 2 cm distal to the anatomic EGJ, this AC was classified as Siewert type II; if the epicenter of the tumor or more than 66% of the tumor mass was located more than 2 cm below the anatomic EGJ, the tumor was classified as Siewert type III.

In 2000, the Siewert classification was changed slightly incorporating definitions.[3] Siewert Type I tumors were defined as "AC of the distal esophagus" with the tumor center located within 1-5 above the anatomic EGJ. Siewert Type II tumors were defined as "the true carcinoma of the cardia" with the tumor center within 1 cm above and 2 cm below the EGJ. Siewert Type III was defined as "the subcardial carcinoma" with the tumor center between 2-5 cm below the EGJ, infiltrating the EGJ and the distal esophagus from below.

In the revised AJCC staging system [1], tumors whose midpoint is in the lower thoracic esophagus, EGJ, or within the proximal 5 cm of the stomach that extend into the RGJ or esophagus (Siewert types I and II, and Types III invading RGJ) are classified as AC of the esophagus for the purposes of staging. All other cancers with a midpoint in the stomach lying more than 5 cm distal to the EGJ, or those within 5 cm of the EGJ but not extending into the EGJ or esophagus (Siewert Type III not invading RGJ) are staged using the gastric cancer staging system.

WHAT HAS CHANGED

Therefore, in the new classification, Siewert Type III tumors invading the GEJ are classified as AC of the esophagus, and this has raised many reactions and debates by gastric cancer surgeons including the Japanese Gastric Cancer Group.

Table 1 summarizes the revised TNM definitions. Tumors *in situ* are now defined as "high grade dysplasia (HGD)". T4 is subclassified according to respectability. The previous locoregional lymph node stage N0 or N1 is suspended and N is subclassified according to the number of infiltrated nodes. M is redefined and further simplified. The degree of differentiation (G) is taken into account along with TNM classification for the final decision on the tumor stage. Separate charts for tumor stage are introduced for AC and SCC (Tables 2a and 2b).

Table 1

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence or primary tumor
Tis	High-grade dysplasia (HGD)
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades lamina propria, or muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Resectable tumor invading pleura, pericardium or diaphragm
T4b	Unresectable tumor invading other adjacent structures, such as aorta, vertebral body, trachea, etc
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1-2 regional lymph nodes
N2	Metastasis in 3-6 regional lymph nodes
N3	Metastasis in seven or more regional lymph nodes
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
Histologic Grade (G)	
GX	Grade cannot be assessed-stage grouping as G1
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated-stage grouping as G3 squamous

THE IMPORTANCE OF LYMPH NODE METASTASIS

Lymphatic drainage is intramural and longitudinal, with channels starting already at the lamina propria and forming a submucosal plexus that communicates through longitudinal channels piercing the muscularis propria with regional lymph nodes in the periesophageal fat. Additionally, almost half of the channels from the submucosal plexus drain directly into the thoracic duct.[4] Regional lymph nodes extend from periesophageal cervical to celiac nodes. Data have demonstrated that the number of infiltrated regional lymph nodes is the most important prognostic factor, and that lymph node ratio is not useful in staging.[5] One should keep in mind that lymph node infiltration occurs very early in the course of the disease. T1a intramucosal tumors are expected to give up to 5% lymph node infiltrations, whereas the percentage incrases up to 25% in T1b submucosal tumors.[6] Therefore, the more lymph nodes resected the better the survival is. Optimum lymphadenectomy depends on T classification: For pT1 ten nodes

Table 2a. Squamous cell carcinoma

Stage	T	N	M	Grade	Tumor Location
0	Tin (HGD)	N0	M0	G1, GX	Any
IA	T1	N0	M0	G1, GX	Any
IB	T1	N0	M0	G2-3	Any
	T2-3	N0	M0	G1, GX	Lower, X
IIA	T2-3	N0	M0	G1, GX	Upper, Middle
	T2-3	N0	M0	G2-3	Lower, X
IIB	T2-3	N0	M0	G2-3	Upper, Middle
	T1-2	N1	M0	Any	Any
IIIA	T1-2	N2	M0	Any	Any
	T3	N1	M0	Any	Any
	T4a	N0	M0	Any	Any
IIIB	T3	N2	M0	Any	Any
IIIC	T4a	N1-2	M0	Any	Any
	T4b	Any	M0	Any	Any
	Any	N3	M0	Any	Any
IV	Any	Any	M1	Any	Any

must be resected, for pT2 20 nodes and for pT3 or pT4 30 nodes or more. This is the main implication on the usefulness of the new edition of the AJCC classification. The guidelines recommend that at least 15 lymph nodes should be removed for adequate nodal staging.

Table 2b. Adenocarcinoma

Stage	T	N	M	Grade
0	Tin (HGD)	N0	M0	G1, GX
IA	T1	N0	M0	G1-2, GX
IB	T1	N0	M0	G3
	T2	N0	M0	G1-2, GX
IIA	T2	N0	M0	G3
IIB	T3	N0	M0	Any
	T1-2	N1	M0	Any
IIIA	T1-2	N2	M0	Any
	T3	N1	M0	Any
	T4a	N0	M0	Any
IIIB	T3	N2	M0	Any
IIIC	T4a	N1-2	M0	Any
	T4b	Any	M0	Any
	Any	N3	M0	Any
IV	Any	Any	M1	Any

CLINICAL CLASSIFICATION – TUMOR EXTENTION EVALUATION - RESECTABILITY

Clinical classification (c) involves endoscopy with biopsy, endoscopic ultrasound with fine needle aspiration for tumor and nodes, CT and PET/CT for assessment of TNM and G classifications. These maybe supplemented by cervical lymph node biopsies to assess M, as well as by bronchoscopy, endoscopic bronchial ultrasound with fine needle aspiration, mediastinoscopy, thoracoscopy, laparotoscopy with lavage cytology and CT-directed percutaneous biopsies to assess stage and respectability.[7]

Laparoscopy may be useful in selected patients in detecting radiographically occult metastatic disease, especially in patients with Siewert II and III tumors. Positive peritoneal cytology (performed in the absence of visible peritoneal impants) is as-

sociated with poor prognosis and is defined as M1.[7]

Prior to starting therapy all patients should be assessed by an esophageal surgeon for physiologic ability to undergo esophageal resection. Esophageal resection should be considered for all physiologically fit patients with resectable esophageal cancer (>5cm from cricopharyngeus). Siewert tumor type should be assessed in all patients with adenocarcinomas involving the EGJ. Siewert types I and II are treated as described in the guidelines for esophageal and EGJ cancers and a variety of surgical approaches may be employed.[7] Siewert type III lesions are considered gastric cancers and thus the relative guidelines should be followed.[8] In some cases additional esophageal resection may be needed in order to abtain adequate margins.

Endoscopic mucosal resection (EMR) is indicated for HGD or Tis tumors, as well as T1a moderately differentiated lesions without evidence of lymphovascular invasion or suspicious lymph nodes, and should be supplemented with esophagectomy in case of deep positive margins or unsuccessful procedure. T1-T3 tumors (stage I and II) are considered to be potentially resectable, regardless of lymphatic disease spread in locoregional lymph nodes, although patients with bulky, multi-station nodal involvement have poor overall survival, and should be assessed for their physiologic ability to undergo major operations. Selected patients with stage III disease may have resectable tumor as well. Certain T4 tumors infiltrating non critical structures such as pericardium, pleura or diaphragm are considered resectable (T4a).

EGJ tumors with supraclavicular lymph node involvement, stage IV tumors with distant metastases including non regional lymph node involvement and T4b tumors with involvement of heart, great vessels, trachea, lung, liver, pancreas and spleen are considered unresectable.

DISCUSSION – DEBATES

Many aspects of attempting GEJ tumor classification have attracted criticism. The GEJ is an artificial division between two organs that remains difficult to accurately localize at endoscopy, radiologically or by laparoscopic assessment and inter-observer divergence has been shown. The presence of Barrett's esophagus, hiatus hernia or the tumor itself may distort the anatomical findings. Also, large tumors may straddle two Siewert groups and the epicentre may be hard to define. Patterns of lymph node spread have been shown by some to be similar for GEJ and distal esophageal tumors. However, when major treatment decisions are based on Siewert group, such as surgical approach, the risk of incomplete resection through inadequate lymphadenectomy exists if the tumor is incorrectly classified.[9] Some groups advocate a transthoracic two-field resection for GEJ adenocarcinoma irrespective of Siewert group and have demonstrated similar tumor biology and patient survival between tumors of the distal esophagus and GEJ. Others would advocate a tailored approach to GEJ tumors with the belief that Siewert III tumors represent true gastric cancer and are better treated with total gastrectomy and D2 lymphadenectomy.

On the other hand, there has been a lot of criticism against the 7th edition of the AJCC Cancer Staging Manual, mainly because of staging Siewert types II and III as esophageal cancer. Especially the Japanese community has raised many reactions by publishing in 2011 their criticism against the new classification[10] declaring that "although we basically comply with the staging system, the Japanese Gastric Cancer Association Committee firmly denied the new definition of GEJ tumors. We remain more confortable to consider adenocarcinomas of the subcardia (Siewert type III) as gastric cancer and believe that these should be classified and staged using the gastric scheme; not the esophageal scheme as in the AJCC 7th Edition. In the new Japanese Classification we adopt the definition of the EGJ area proposed by the Japan Esophageal Society, i.e., the area extending 2 cm above to 2 cm below the EGJ." Ever Possibly there are many other factors that we should take into

account in order to classify properly GEJ tumors, such as existence or not of atrophy and H. Pylori infection.[11]

Conclusively, the 7th edition of the AJCC Cancer Staging Manual has certainly improved harmonization of gastric and distal esophageal/GEJ-type adenocarcinomas, although debates and other more serious issues persist, particularly regarding the optimal neoadjuvant treatment for the management of GEJ carcinomas.

REFERENCES

1. Edge SB, Byrd DR, Compton CC, et al. AJCC Cancer Staging manual (ed 7). New York, NY: Springer; 2010: pp 103-115.
2. Siewert JR. Carcinoma of the cardia: carcinoma of the gastroesophageal junction classification, pathology and extend of resection. *Dis Esophagus* 1996; 9: 173-182.
3. Siewert JR, Feith M, Werner M, Stein HJ. Adenocarcinoma of the esophagogastric junction: results of surgical therapy based on anatomical/topographic classification in 1,002 consecutive patients. *Ann Surg* 2000; 232: 353-361.
4. Kuge K, Murakami G, Mizobushi S, et al. Submucosal territory of the direct lymphatic drainage system to the thoracic duct in the human esophagus. *J Thorac Cardiovasc Surg* 2003; 125: 1343-1349.
5. Peyre CG, Hagen JA, DeMeedter SR, et al. The number of lymph nodes removed predicts survival in esophageal cancer: an international study on the impact of extent of surgical resection. *Ann Surg* 2008; 248: 549-556.
6. Rice TW, Zuccaro G Jr, Adelstein DJ, et al. Esophageal carcinoma: depth of tumor invasion is predictive of regional lymph node status. *Ann Thorac Surg* 1998; 65: 787-792.
7. Ajani JA, D'Amico TA, Almhanna K, et al. Esophageal and esophagogastric junction cancers, version 1.2015. *J Natl Compr Canc Netw* 2015; 13: 194-227.
8. Ajani JA, Bentrem DJ, Besh S, et al. Gastric cancer, version 2.2013. *J Natl Compr Canc Netw* 2013; 11: 531-546.
9. Strong VE, D'Amico TA, Kleinberg L, Ajani J. Impact of the 7th Edition AJCC staging classification on the NCCN clinical practice guidelines in oncology for gastric and esophageal cancers. *J Natl Compr Canc Netw* 2013; 11: 60-66.
10. Sano T, Aiko T. New Japanese classifications and treatment guidelines for gastric cancer: revision concepts and major revised points. *Gastric Cancer* 2011; 14: 97-100.
11. McColl KE, Going JJ. Aetiology and classification of adenocarcinoma of the gastro-oesophageal junction/cardia. *Gut* 2010; 59: 282-284.

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REVIEW

Indications and the role of neoadjuvant chemoradiotherapy in oesophageal cancer

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ABSTRACT

Esophageal cancer is the sixth most common cause of cancer death worldwide, with its incidence is continuously growing. Due to obesity and Barett's esophagous, adenocarcinoma consists of the majority of cases in western countries mainly to the lower third and the gastroesophageal junction. What concerns local and metastatic disease the data about the treatment plan are more clear, this is becoming more complicated to locally advanced disease T3, T4 or N+. Chemotherapy and radiotherapy alone either on neoadjuvant or adjuvant treatment have only limited contribution to local control of the disease, but not much to overall survival, due to distant metastases. The better and more encouraging results come from the neoadjuvant concomitant chemoradiotherapy.

KEY WORDS: esophageal cancer, neoadjuvant, locally advanced, chemotherapy, radiotherapy, combined therapy

INTRODUCTION

Esophageal cancer is the sixth most common cause of cancer deaths worldwide and its incidence is increasing over the last 20 years. The two predominant histologies are adenocarcinoma and squamous carcinoma. At the time of presentation nearly half 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 oesophageal 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 tumour board.

For example the wide use of PET/CT has revealed occult metastases to 20% of the cases and converted the locoregional disease to metastatic. Also the 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.[4,5]

EARLY STAGE (T1, T2)

For early T1 and T2 stages that is locoregional

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disease, surgery is the gold standard of therapy with 5-year survival rates ranging from 10%-40% and distant metastasis being the most common mode of treatment failure.[3] The value of the neoadjuvant chemoradiotherapy in stage I or II oesophageal cancer compared with surgery alone evaluated in a multicenter French study from 2000 to 2009 in 30 centres. 195 patients were randomized: 98 were assigned to surgery alone and 97 to neoadjuvant CRT. 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 the surgery group vs. 7.3% in the CRT group (p=0.054) respectively. After a median follow-up of 5.7 years, the median survivals were 43.8 in the surgery group vs. 31.8 months in the 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.[6]

LOCALLY ADVANCED TUMOURS (T3, T4, N+)

Resectable locally advanced oesophageal cancer refers to T3-T4 or documented LN involvement (N+ disease) which consists of 30% of all oesophageal cases.[3,7]

Surgery only

Surgery with radical lymphadenectomy in terms of achieving local control is a demanding technique with poor survival rates, high early and late postoperative morbidity rates and metastatic or locoregional recurrences. These poor outcomes after surgery alone and analyses of disease recurrence patterns have prompted the addition of adjuvant treatment and multimodal strategy has shifted to neoadjuvant treatment.[12]

Radiotherapy only

The value of radiation therapy is mainly to the control of locoregional disease. The efficacy of neoadjuvant radiation therapy has been studied without interesting results regarding the overall survival.[8,9] A meta-analysis has not shown a statistically significant survival benefit for preoperative radiation. At a median follow-up of 9 years, the survival benefit at 2 and 5 years was 3% and 4%, respectively (p= 0.062). Thus neoadjuvant radiation therapy alone cannot be advocated for the management of oesophageal cancer.[10]

Chemotherapy only

Chemotherapy for locally advanced oesophageal cancer has a response rate of 45% to 75%. In numerous studies but relapse rates are high and long-term survival rates are very low. Use of chemotherapy with or without radiation therapy before surgery has several theoretical benefits such as: a) improve baseline dysphagia, the most common symptom on presentation, b) can help downstage the tumour, which may increase resection rates, c) treat micro-metastatic disease that is not detected on imaging studies, and d) has the potential to indicate the biologic behaviour of the tumour by its response to treatment that may help guide further therapy. Unfortunately these theoretical advantages don't contribute a lot to significant overall survival of these patients.[11] There are many studies that have shown the efficacy of neoadjuvant chemotherapy but with mixed results.[13-15] The variability of these results can be explained partly because of different chemotherapy agents and protocols, different patient population and histologies. A meta-analysis of 12 randomized trials in which pre-operative chemotherapy was used, the 5-year overall survival benefit was only 4%. The benefit was somewhat smaller for squamous cell cancer compared to adenocarcinoma (4% vs. 7%). Thus, the available data do not suggest that the use of neoadjuvant chemotherapy significantly improves survival.[16]

Chemoradiotherapy

Neither preoperative radiation therapy nor chemotherapy alone in the neoadjuvant setting

has been proven beneficial based on the trials. This may be related to the low complete pathologic response rates, mostly between 2.5%-4%. The improvement in R0 resection and overall survival has been limited as well. Most patients who undergo surgical resection die from distant metastatic disease in spite of a R0 resection. Considering these results and for the reasons listed earlier using neoadjuvant therapy, combination therapy with all three modalities has been utilized to try to improve overall survival outcomes. The most promising results for neoadjuvant treatment have come from the combination of the two methods.

Neoadjuvant chemoradiation therapy vs. surgery alone has evaluated in several trials but the responses are mixed with a trend to increase the overall survival, but with good response rates and disease-free survival.[18-21] The most encouraging results come from a multi-institutional phase III study (CROSS trial)[18] which evaluated the benefit of induction therapy using carboplatin/taxol/41Gy radiation vs. surgery alone. The overall 5-year survival was much improved in the combined therapy arm (47% vs. 34%, p=0.03). Patients with squamous histology derived a larger benefit. An updated analysis of this group of patients showed a lower local recurrence rate (34% vs. 14%, p<0.001) and lower risk of peritoneal carcinomatosis (14% vs. 4%, p <0.001) following neoadjuvant chemoradiation and that squamous cell carcinoma was an independent prognostic variable in the surgery alone group.[17]

Regarding the administration of sequential or concomitant chemoradiotherapy the answer comes from a meta-analysis, where there was no survival benefit of sequential concomitant for patients with squamous cell carcinoma (HR for mortality 0.9 (0.72-1.03); p=0.18). The results of sequential CRT were similar to that for patients with squamous cell carcinoma assigned neoadjuvant chemotherapy. Concomitant CRT in patients with squamous cell carcinoma had a significant benefit (HR for mortality 0.76 (0.59-0.98); p=0.04). On this basis, the use of concomitant neoadjuvant chemoradiotherapy is strongly recommended compared to sequential.[16]

The value of neoadjuvant chemoradiation vs. neoadjuvant chemotherapy alone has studied in some trials in an effort to avoid radiation therapy and its early and late complications.[22]

In a recent meta-analysis of 10 randomized trials of trimodality therapy vs. surgery alone and 8 trials of preoperative chemotherapy vs. surgery alone, trimodality therapy was associated with a 13% benefit in survival at 2 years, both in squamous and adenocarcinoma. Preoperative chemotherapy alone translated to a 7% benefit in survival at 3 years, more in adenocarcinoma than in squamous cell cancer. Thus, these data suggest a synergistic benefit using neoadjuvant chemotherapy plus radiotherapy in the management of oesophageal cancer.[16]

CONCLUSIONS

The three mainstays of treatment for oesophageal cancer surgery, chemotherapy, and radiation therapy result in poor overall survival and high relapse rates when used alone. Preoperative combination therapy offers several theoretical advantages but for stage I and II oesophageal cancers, there is, as of now, no convincing evidence that neoadjuvant chemoradiation is of any benefit. Neoadjuvant concurrent chemoradiotherapy achieves the best complete pathologic response rates, R0 resection rates, and improves 3-5 years survival rates in patients with locally advanced oesophageal cancer T3, T4 or N+. The addition of neoadjuvant radiotherapy to preoperative chemotherapy may facilitate a better complete surgical resection via its effect on the periphery of the tumour. Squamous cell cancer and adenocarcinoma appear to have similar disease-free and overall rates following neoadjuvant chemoradiotherapy. Many unanswered questions remain regarding the accuracy and the value of PET/CT after neoadjuvant treatment, the efficacy of EUS due to fibrosis and adherence and the optimal chemoradiotherapy protocol. Further

randomized, prospective trials will be required to build on these early studies to try to improve the prognosis of patients with this terrible disease.

REFERENCES

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010; 127: 2893-2917.
2. Devesa SS, Blot WJ, Fraumeni JF. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. *Cancer* 1998; 83: 2049-2053.
3. Kelsen DP, Ginsberg R, Pajak TF, et al. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. *N Engl J Me*d 1998; 339: 1979-1984.
4. Low DE. Evolution in surgical management of esophageal cancer. *Dig Dis* 2013; 31: 21-29.
5. Hulscher JB, van Sandick JW, de Boer AG, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. *N Engl J Med* 2002; 347: 1662-1669.
6. Mariette C, Seitz JF, Maillard E, et al. Surgery alone versus chemoradiotherapy followed by surgery for localized esophageal cancer: Analysis of a randomized controlled phase III trial FFCD 9901. *J Clin Oncol* 2010; 28: abstr 4005.
7. Rice TW, Rusch VW, Ishwaran H, et al. Worldwide Esophageal Cancer Collaboration. Cancer of the esophagu and esophagogastric junction: data-driven staging for the seventh edition of the American Joint Committee on Cancer/International Union Against Cancer Cancer Staging Manuals. *Cancer* 2010; 116: 3763-3773.
8. Kelsen DP, Minsky B, Smith M, et al. Preoperative therapy for esophageal cancer: a randomized comparison of chemotherapy versus radiation therapy. *J Clin Oncol* 1990; 8: 1352-1361.
9. Nygaard K, Hagen S, Hansen HS, et al. Pre-operative radiotherapy prolongs survival in operable esophageal carcinoma: a randomized, multicenter study of pre-operative radiotherapy and chemotherapy. The second Scandinavian trial in esophageal cancer. *World J Surg* 1992; 16: 1104-1109.
10. Arnott SJ, Duncan W, Gignoux M, et al. Preoperative radiotherapy for esophageal carcinoma. *Cochrane Database Syst Rev* 2005: CD001799.
11. Shah RD, Cassano AD, Neifeld JP. Neoadjuvant therapy for esophageal cancer.*World J Gastrointest Oncol* 2014; 6: 403-406.
12. D'Journo XB, Thomas PA. Current management of esophageal cancer. *Thorac Dis* 2014; 6(Suppl 2): S253-S264.
13. Boonstra JJ, Kok TC, Wijnhoven BP, et al. Chemotherapy followed by surgery versus surgery alone in patients with resectable oesophageal squamous cell carcinoma: long-term results of a randomized controlled trial. *BMC Cancer* 2011; 11: 181.
14. Medical Research Council Oesophageal Cancer Working Group. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. *Lancet* 2002; 359: 1727-1733.
15. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006; 355: 11-20.
16. Gebski V, Burmeister B, Smithers BM, Foo K, Zalcberg J, Simes J. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a metaanalysis. *Lancet Oncol* 2007; 8: 226-234.
17. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012; 366: 2074-2084.
18. Bosset JF , Gignoux M, Triboulet JP, et al. Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. *N Engl J Med* 1997; 337: 161-167.
19. Burmeister BH, Smithers BM, Gebski V, et al. Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial. *Lancet Oncol* 2005; 6: 659-668.
20. Urba SG, Orringer MB, Turrisi A, Iannettoni M, Forastiere A, Strawderman M. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. *J Clin Oncol* 2001; 19: 305-313.
21. Walsh TN, Noonan N, Hollywood D, Kelly A, Keeling N, Hennessy TP. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. *N Engl J Med* 1996; 335: 462-467.
22. Stahl M, Walz MK, Stuschke M, et al. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. *J Clin Oncol* 2009; 27: 851-856.

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REVIEW

Esophagectomy or not for early esophageal cancer?

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The significant development in the field of diagnostic and therapeutic endoscopy offers not only the possibility of early detection of tumors of the esophagus, but also an alternative treatment consisting in endoscopic resection of selected tumors. The aim of endoscopic resection is to maintain the integrity of the esophagus and avoid the significant morbidity and mortality of esophagectomy. Whether this approach may present an «undertreatment» for patients with early tumors, thus compromising their long-term survival is still an object of debate between surgeons, endoscopists and oncologists.

DEFINITION OF EARLY ESOPHAGEAL CANCER

Early esophageal cancer is defined as a cancer infiltrating the mucosa (PT1a) or submucosal layer (pT1b) of the esophageal wall, without infiltration of the muscular layer. Submucosal lesions are further sub-classified as Sm1 tumors invading the more superficial layer of the submucosa (superficial one third of its thickness), Sm2 for tumors invading the middle third, and Sm3 for tumors invading the deeper third of the submucosal layer. In Japan superficial lesions are conventionally called the types 0 in reference to the classification of Borrmann advanced gastric tumors. There are three subtypes of superficial lesions: protruded (type-I 0), flat (type II-0) and excavated (type III-0). The lesions are subclassified into protruding pedunculated (0-Ip), subpedunculated (0-Isp) and sessile (0-Is).

There seems to be significant differences between the two types of early esophageal carcinoma namely squamous cell carcinoma and adenocarcinoma concerning the incidence of lymph node metastasis and the prognosis. According to available data from resected specimens of early esophageal carcinomas, squamous cell carcinomas tend to present with higher incidence of lymph node metastases, lymphatic infiltration, and have increased incidence of poor differentiation (G3.4) compared to adenocarcinomas. Furthermore, the incidence of pT1b tumors is significantly increased among squamous cell carcinomas compared to adenocarcinomas. These facts generally reflect a significantly worse prognosis for squamous cell carcinomas, even in the stage of early (PT1) disease.

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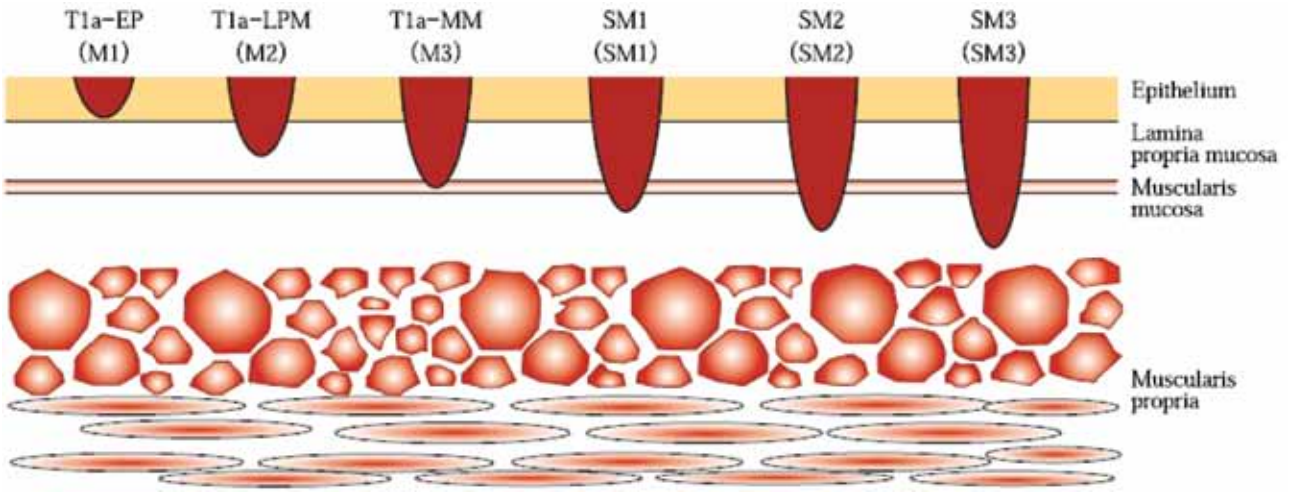

Figure 1. Types of early esophageal cancer.

DIAGNOSIS OF EARLY ESOPHAGEAL CANCER

The diagnosis of esophageal cancer in an early stage is not always easy. The use of screening endoscopy especially among patients with predisposing factors for esophageal cancer may detect early tumors, even in asymptomatic patients. Endoscopic findings in early esophageal cancer may include an epithelium discolouration, roughness of the mucosal surface or differentiation of the microvascular pattern. Chromoendoscopy using Lugol's solution may be used for diagnosis of squamous cell carcinoma. Iodine strongly stains the squamous cells of the mucosa, which are rich in glycogen and differentiates them from dysplastic or malignant cells, which are not stained. On the other hand, early adenocarcinoma of the esophagus is almost always associated with the presence of Barrett's esophagus (BE). Large observational studies show that the risk for adenocarcinoma development rises from 0,12-0,4% per year in patients with non-dysplastic BE to 1% for patients with low-grade dysplasia and >5% for patients with high-grade dysplasia. Patients with known Barrett esophagus should undergo screening endoscopies for early detection of adenocarcinoma. According to current guidelines, random endoscopic biopsies should be taken in all 4 quadrants and each 2 cm of columnar epithelium.

The use of endoscopic ultrasonography is very useful in determining the presence of suspicious peritumoural lymph nodes or even guide FNA biopsy of these lymph nodes. However, it is not so accurate in the differentiation between pT1a and pT1b tumors.

ENDOSCOPIC TECHNIQUES FOR RESECTION OF EARLY ESOPHAGEAL CANCER

There are two main techniques of endoscopic resection of early esophageal cancer, namely the endoscopic mucosal resection (EMR) and the endoscopic submucosal dissection (ESD). Both techniques begin with injection of a substance under the lesion, in order to lift the lesion and protect from deeper resection and possible perforation. With EMR, the lesion is then resected with the use a snare or suctioned into a cap and snared. With ESD, the submucosa is dissected under the tumor with a specialized knife. The disadvantage of EMR is the fact that the resection margins cannot always be evaluated accurately. ESD allows theoretically the removal of larger and deeper lesions with a curative intent than can

be accomplished with EMR. On the other hand EMR may be used as a tool for assessment of the infiltration of the tumor in order to definitely decide about treatment.

Indications for the application of either EMR or ESD, according to the Japanese Society of Gastrointestinal Endoscopy include lesions smaller than 2 cm including less than one third of the circumference of the esophagus.

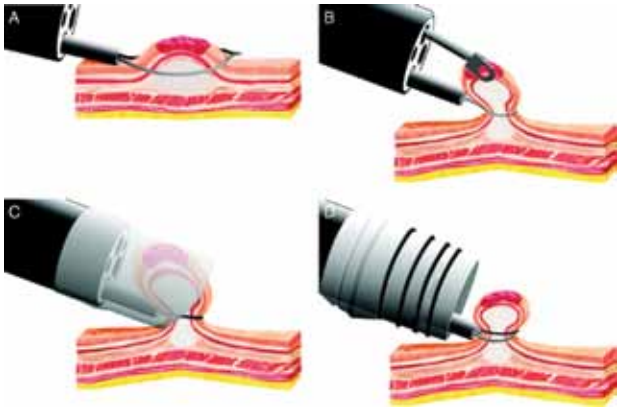

Figure 2. Endoscopic mucosal resection.

In a recent meta-analysis comparing available data from studies comparing EMR with ESD, the en-bloc resection rate after ESD seems to be significantly higher than EMR. Concerning the post-procedural complications, the perforation rate was significantly higher after ESD, whereas no significant difference was noted between the two methods concerning post-procedural bleeding or stricture formation. The overall recurrence rate seems to be significantly higher after EMR than after ESD. However, the subgroup analysis showed that the recurrence rate for ESD was not higher than that for EMR when lesions smaller than 20 mm were considered.

SURGICAL RESECTION OF EARLY ESOPHAGEAL CANCER

The principles of surgical resection of early esophageal cancer are the same as for advanced esophageal cancer, namely resection of the tumor baring part of the esophagus along with the respective lymphadenectomy. The type of surgical

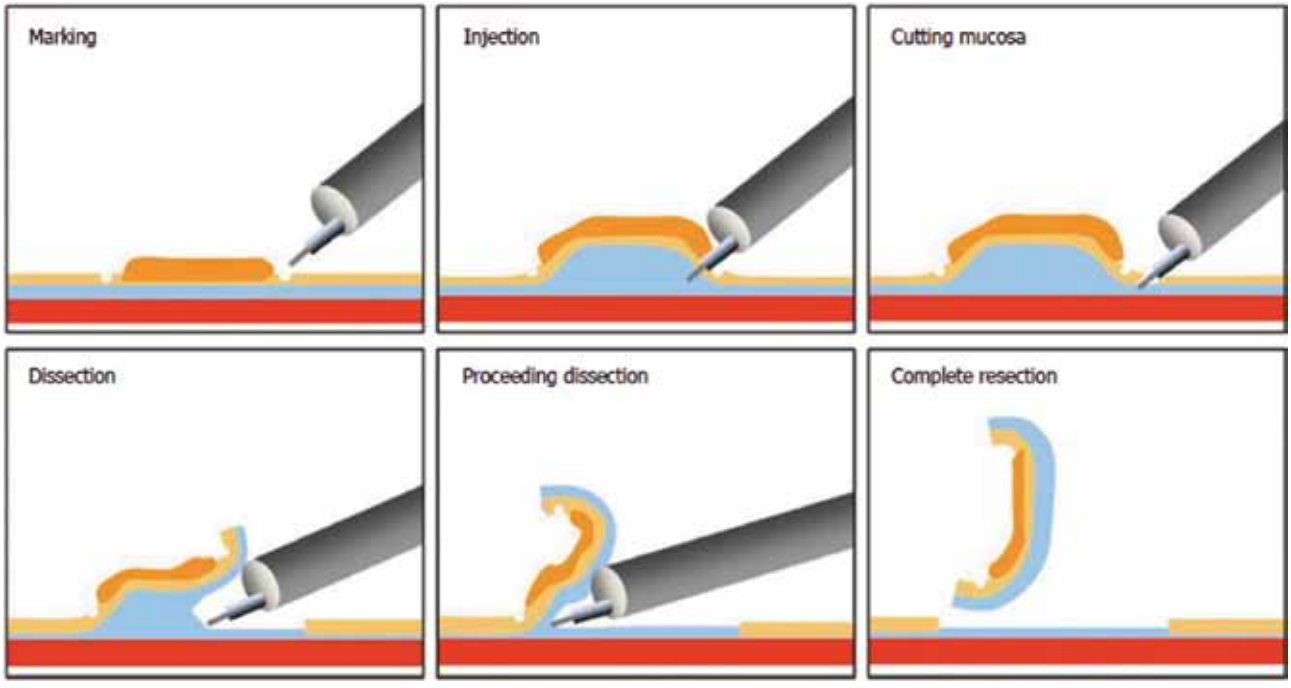

Figure 3. Endoscopic submucosal dissection.

resection depends on the location of the tumor. Tumors of the lower third of the esophagus are treated mainly with Ivor-Lewis esophagogastrectomy and intrathoracic anastomosis. Tumors of the middle and upper third of the esophagus necessitate total esophagectomy and cervical anastomosis. Stomach or colon is used as substitutes of the esophagus in order to restore the continuity of the gastrointestinal tract. Total esophagectomy may be perfomed with or without thoracotomy (transiatal esophagetomy).

As an alternative for early malignancies of the distal esophagus, Merendino described the limited resection of the peripheral esophagus and the interposition of pedicled jejunal graft between the esophagus and the stomach.

The 5-year survival rate of surgically resected early esophageal carcinomas are as high as 80% for pN0 tumors and falling to 40-45% for pN1 tumors. Especially for early pN0 adenocarcinomas the 5-year survival rate may be as high as 95%.

ENDOSCOPIC VS SURGICAL RESECTION OF EARLY ESOPHAGEAL CANCER

There is a significant lack of evidence concerning the comparison of endoscopic vs surgical resection for early esophageal cancer. There is no randomized control trial on this topic. The few comparative studies do not allow accurate comparison between the two methods, since there are not homogeneous in terms of comorbidities, stage, depth of invasion etc. Furthermore, long-term survival studies are available mostly for surgical resections. Concerning short-term (2 year) survival, no significant difference is noted between the two methods.

Arguments for surgical resection of early esophageal carcinoma include the following a) surgical resection enables R0 resection in all directions as well as resection of other premalignant lesions of the esophagus b) none of the currently available diagnostic tools can exclude the presence of malignant peritumoral lymph nodes, the incidence of which among pT1b is considerably high, leading these patients to oncological undertreatment and possible oncologic risk c) the postoperative complication rate and mortality in high volume centers are low and d) there are no available data on long-term survival and recurrence rates after endoscopic resections in order to evaluate their long term efficacy.

Indications for referral for surgical resection include: Complete EMR or ESD not feasible or not achieved (positive margins in histology), presence of T1b tumour (≥20% incidence of nodal metastasis), presence of unfavourable histological characteristics in the resected tumor such as poor differentiation or presence of lymphovascular invasion and, finally, the presence of multi-focal carcinoma or periesophageal lymphadenopathy at EUS.

CONCLUSION

pT1a tumors are best treated with endoscopic resection (either EMR or ESD). pT1b are best treated with surgical resection, respecting the rules of oncologic surgery (lymphadenectomy). In selected patients and after information of the patient concerning the possible oncologic risk, pT1b patients may also be treated with endoscopic methods. However, a very strict follow-up schedule must be applied for early detection and treatment of recurrence.

REFERENCES

1. Guo HM, Zhang XQ, Chen M, Huang SL, Zou XP. Endoscopic submucosal dissection vs endoscopic mucosal resection for superficial esophageal cancer. *World J Gastroenterol* 2014; 20: 5540-5547.
2. Stein HJ, Schweigert M, Dubecz A. Early esophageal cancer: pro surgical resection. *Chirurg* 2011; 82: 495-499
3. Theisen J, Feith M, Stein HJ, Siewert JR. Management of early esophageal cancer. *Adv Surg* 2007; 41: 229-239.
4. Kubota Y, Kojima T, Fukuda D, et al. Comparison of

endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) for large squamous cell carcinoma of the esophagus. *Gastrointest Endosc* 2010; 72.

5. Das A, Singh V, Fleischer DE, et al. A comparison of endoscopic treatment and surgery in early esophageal cancer: an analysis of surveillance epidemiology and end results data. Am J Gastroenterol 2008;103:1340-5.
6. Prasad GA, Wu TT, Wigle DA, et al. Endoscopic and surgical treatment of mucosal (T1a) esophageal adenocarcinoma in Barrett's esophagus. *Gastroenterology* 2009; 137: 815-823.
7. Pech O, Bollschweiler E, Manner H, et al. Comparison between endoscopic and surgical resection of mucosal esophageal adenocarcinoma in Barrett's esophagus at two high-volume centers. *Ann Surg* 2011; 254: 67-72.

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REVIEW

Stomach or colon for esophageal reconstruction

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ABSTRACT

Esophagectomy, followed by different reconstruction techniques, continues to be the treatment of choice for patients with resectable cancer of the esophagus. The decision of which conduit to use is based on multiple factors including the required length, the blood supply of the intended conduit, the local anatomy, and which conduits are available. When technically feasible the stomach is the organ of choice. Advantages of the stomach as an esophageal substitute include the relative ease of mobilization and the need for a single anastomosis. Disadvantages of the technique include gastric reflux disease and dumping syndrome in the 15 to 20% of all patients due to the absence of a gastroesophageal sphincter. Prolonged contact of the residual squamous esophageal epithelium to reflux of gastric contents has led to recurrent Barrett's and even adenocarcinoma in the esophageal remnant. Successful swallowing can be achieved for 83 to 98% of patients, and stricture rates vary in the literature from 0 to 29% with overall mortality from 5 to 10%. Advantages for colon interposition include long length, acid resistance, typically excellent blood supply, and the potential for a wide gastric resection margin in patients with cancers of the gastroesophageal junction. Disadvantages include the fact that use of the colon requires preoperative evaluation with colonoscopy or barium enema, and consideration of angiography. Even today debate exists concerning the more suitable substitute for the esophagus. The choice of organ that will replace esophagus depends mainly on the surgeon's experience and familiarization with the particular technique.

KEY WORDS: esophageal cancer, esophagectomy, stomach pull-up, colon interposition

INTRODUCTION

Esophageal carcinoma is an aggressive tumor with poor prognosis. Although various therapeutic options exist, esophagectomy, followed by different reconstruction techniques, continues to be the treatment of choice for patients with both resectable cancer of the esophagus and end-stage esophageal diseases with benign conditions. The purpose of this formidable operation is twofold: (1) eradication of the disease and (2) restoration of comfortable swallowing. In many patients with esophageal cancer, the latter is often achieved whereas the former is more elusive.[1] Esophagectomy is highly associated with pulmonary complications. The incidence of these complications is associated with age, operation, duration, proximal

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tumor location and surgical techniques.[2] The clinical procedure for the decision making about the treatment to be followed must outweigh the specific treatment dangers and the probable benefits for survival and quality of life. The choice for esophagus substitute may have a serious impact on both matters.

Various options are available for the gastrointestinal tract restoration after esophagectomy. The decision of which conduit to use is based on multiple factors including the required length, the blood supply of the intended conduit, the local anatomy, and which conduits are available.[3] The ideal conduit for esophagus substitution must an adequate length in order to reach the cervical esophagus, a reliable blood supply and a good swallowing function. The surgical procedure should have a low risk for complications. Important matters to be considered for esophagealreconstruction are: the choice of conduit that will replace the resected part of the esophagus (stomach, colon or jejunum), the technique for conduit (whole stomach or gastric tube, left or right colon), the site of anastomosis (thoracic or cervical), the need for additional drainage operation (pyloroplasty, pyloromyotomy or no drainage) and the route of reconstruction (orthotopic, left or right chest, retrosternal or subcutaneous). The stomach and the colon, as opposed to the jejunum, can be easily transposed to the neck. There are instances when the stomach cannot be used, such as the presence of previous gastric resection or if the tumor involves a substantial part of the stomach. In these situations use of the colon is preferred. When there is an intrinsic colon disease (polyps, diverticula, etc) or variations in the blood supply that prevent the use of the colon, stomach pull-up or jejunal transposition must be preferred. Although the method of reconstruction has no apparent impact on oncological resection, it may affect operative morbidity and long-term quality of life.[4]

Occurrence of early complications of conduit ischemia and anastomotic leakage had a major impact on the outcomes of esophagectomy. Risk factors for both complications are conditions known for their impact on tissue perfusion and oxygenation. As a result healing is affected. These are comorbid conditions that require therapy: namely diabetes, cardiovascular disorders such as hypertension, arrhythmia, and reduced cardiac contractility, and chronic obstructive pulmonary disease.[5]

CHOICE OF RECONSTRUCTION

Stomach

The choice of esophageal reconstruction even by stomach pull-up or by colon interposition is based in several factors. When technically feasible the stomach is the organ of choice. Esophageal reconstruction by gastric pull-up involves replacement of the esophagus by transposition of the stomach, based on the right gastric and gastroepiploic arteries through the posterior mediastinum. This procedure is generally indicated when total esophagectomy is required for complete cancer resection and is less applicable for high cervical esophageal or hypopharyngeal lesions.[6] Advantages of the stomach as an esophageal substitute include the relative ease of mobilization and the need for a single anastomosis. In most patients stomach has sufficient length to reach the neck for a cervical esophagogastric anastomosis and, typically, is quite hardy.

Disadvantages of the technique include gastric reflux disease and dumping syndrome in the 15 to 20% of all patients due to the absence of a gastroesophageal sphincter.[7] Patients who have an intrathoracic stomach often experience postprandial discomfort and early satiety, probably related to loss of normal gastric function such as receptive relaxation.[4] They have the increased potential compared with a colon graft for noxious aspiration, particularly at night in the supine position, given the presence of acid bile in the

stomach within the chest.[8] These manifestations can minimize by changing eating habits (including having multiple small meals), and avoiding lying in the supine position after meals and walking.[9] Further, prolonged contact of the residual squamous esophageal epithelium to reflux of gastric contents after esophagectomy and gastric pull-up has led to recurrent Barrett's and even adenocarcinoma in the esophageal remnant. In addition, large tumors near the gastroesophageal junction often force a compromise between a wide excision margin along the lesser curve and preserving enough stomach to enable it to serve as the esophageal replacement.[8]

The vascular supply of the stomach is sufficient, but somewhat less reliable than a good colon graft.[8] The greatest fear during gastric preparation for use as a conduit is damage to the right gastroepiploic vascular arcade. If this occurshigh on the greater curvature, it may not be an issue. However if this vessel is damaged close to its origin, delayed reconstruction or jejunal or colonic interposition may be necessary. In this case, if the colon is not prepared, intraoperative cleansing can be done but is less desirable and carries the risk of greater infectious complications.[1]

Large outcome series have shown that successful swallowing can be achieved for 83 to 98% of patients, and stricture rates vary in the literature from 0 to 29%. Fistula and leak rates vary throughout reported series from 3 to 48%. However gastric pull-up is a procedure with a higher morbidity. The most common morbidity is pulmonary and cardiac disease, which occurs between 15 and 60% in reported series. Mediastinitis may result after flap necrosis and has serious consequences. Additional problems are postoperative swallowing and vice rehabilitation.[7] Overall mortality ranges from 5 to10%.[10]

Colon interposition

The colon is typically used when gastric pull-up is impossible, such in patients with previous gastrectomy. It is also used when extended esophagogastrectomy is necessary for malignant disease. Intersposition of the colon involves dissecting and mobilizing the left colon and tunneling it to the proximal esophageal remnant, performing an esophagocolic anastomosis and an enterocolic anastomosis, and then rejoining the transverse colon to the remaining descending colon. Its main purpose is to bypass the entire thoracic esophagus, but it can also be used to replace just the cervical esophagus.[6]

The colon has a number of attributes that make it an excellent option for esophageal replacement. Advantages include long length, acid resistance, typically excellent blood supply, and the potential for a wide gastric resection margin in patients with cancers of the gastroesophageal junction. Disadvantages include the fact that use of the colon requires preoperative evaluation with colonoscopy or barium enema, and consideration of angiography to evaluate the arterial abnormalities that might preclude safe use of colon. Use of the colon requires preoperative cleaning, and additional time intraoperatively compared with gastric pull-up. The added time is in part related to the need to mobilize the colon, and the fact that rather than the one anastomosis needed with gastric pull-up there are three required when using the colon (esophago-colo, colo-gastric, and colo-colo).[8]

Caution should be used when the colon is planned to be used if there evidence by arteriography of atherosclerotic stenosis of the inferior mesenteric artery. Angiography to assess a potential colon graft is useful for the plan of the operation, as in a small percentage of patients there arterial anomalies that will influence the choice of the esophageal substitute or the vascular pedicle of the graft. A standard colon graft is unlikely to be feasible after repair of an abdominal aortic aneurysm as, in most cases, the inferior mesenteric artery has been ligated during this operation.

Other conditions that discourage use of the colon for esophageal replacement include inflam-

matory colonic disease such as ulcerative colitis, extensive diverticulosis, and prior colonic resection. The final decision regarding use of the colon as a graft is always made in the operating room after inspecting the colon and dissecting out the vessels. Fine vascular clamps should be placed on the arteries to be ligated, and the flow to the graft assessed with a Doppler prior to division of any vessels.[8]

The use of the right or left colon depends on surgeon's choice. The colon colon is favored by many surgeons in part because its blood supply has been shown to be more reliable in anatomic studies. The right colon is used successfully by others with a low incidence of conduit ischemia comparable well with that of 3% to 9% reported for the left colon.[11] The left colon is also preferred by some because of its smaller diameter compared with the right. But when in the part of the colon the terminal ileum is incorporated to be brought up to the neck for anastomosis with the esophagus, the size of the ileum matches well with that of the esophagus.

Unique to the colonic conduit is the risk for redundancy that has been reported for 15 to 30% of patients.This problem can manifest years later and can cause obstructive symptoms such as dysphagia and regurgitation. Its correction can be a complex undertaking. There is no reliable method that can prevent such complications from taking place.

A colon conduit has been suggested to be more durable, and the supposed long-term functional benefits of colon interposition make it the preferred esophageal substitute in those with benign disease and in patients whose cancer stage predicts long-term survival. A colonic conduit provides good long-term swallowing function, and normal oral intake is restored in 65 to 88% in patients with cancer of the esophagus. Colonic conduits arereported to have active peristalsis and this is presented as an explanation for their superior function as an esophageal substitute compared with a passive gastric conduit. Although peristalsis can be demonstrated immediately after surgery, long-term emptying likely relies on gravity.[4]

CONCLUSION

Even today debate exists concerning the more suitable substitute for the esophagus after an esophagectomy for cancer. As the target is survival of the patient with an acceptable quality of life studies are required to properly assess the long-term function of the gastric or colonic conduits. For most patients with advanced esophageal cancer, however, performing a safe esophagectomy is of paramount importance, and given the ease of preparation and reliability of gastric conduit, it will remain the preferred organ for esophageal substitution for most surgeons. On the other hand colonic interposition is an essential technique of esophageal reconstruction when the stomach is not available, and is used to salvage those patients with gastric necrosis. Finally, the choice of organ that will replace esophagus depends mainly on the surgeon's experience and familiarization with the particular technique.

REFERENCES

1. Parekh K, Iannettoni M. Complications of esophageal resection and reconstruction. *Semin Thorac Cardiovasc Surg* 2007; 19: 79-88.
2. Buise M, Kantering, van Bommel J. Complications following oesephagectomy, a review with future perspectives. *Neth J Crit Care* 2014; 18: 16-21.
3. Boukerrouche A. Left colonic graft in esophageal reconstruction for caustic stricture: mortality and morbidity. *Dis Esoph* 2013; 26: 788-793.
4. Davis P, Law S, Wong J. Colonic interposition after esophagectomy for cancer. *Arch Surg* 2003; 138: 303-308.
5. Briel J, Tambankar A, Hagen J et al. Prevalence and risk factors for ischemia, leak, and stricture of esophageal anastomosis: gastric pull-up versus colon interposition. *J Am Coll Surg* 2004; 198: 536-541.
6. Kim Evans KF, Mardini S, Salgado C, Chen HC. Esophagus and hypopharyngeal reconstruction. *Semin*

Plast Surg 2010; 24: 219-226.
7. Chu PY, Chang SY. Reconstruction of the hypopharynx after surgical treatment of squamous cell carcinoma. *J Chin Med Assoc* 2009; 72: 351-355.
8. De Meester SR. Colon interposition after esophagectomy. *Dis Esophagus* 2001; 14: 169-172.
9. Chen KN. Managing complications I: leaks, strictures, emptying, reflux, chylothorax. *J Thorac Dis* 2014; 6(S3): S355-S363.
10. Pesko P, Sabljak P, BjelovicM, et al. Surgical treatment and clinical course of patients with hypopharyngeal carcinoma. *Dis Esophagus* 2006; 19: 248-253.
11. Hagen JA, De Meester SR, Peters JH, et al. Curative resection for esophageal adenocarcinoma: analysis of 100 en bloc esophagectomies. *Ann Surg* 2001; 234: 520-530.

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REVIEW

Minimally invasive laparoscopic and thoracoscopic esophagectomy for esophageal carcinoma

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ABSTRACT

Esophagectomy remains the cornerstone of the treatment for esophageal cancer. Open resection, either transhiatal or transthoracic, carries significant morbidity and mortality. In an attempt to reduce the complication rate following esophagectomy, several types of minimally invasive approaches have been introduced. This article, reviews the recent literature of minimally invasive esophagectomy in an attempt to clarify its contemporary role in the treatment of esophageal cancer.

KEY WORDS: esophageal carcinoma, minimally invasive surgery, esophagectomy

INTRODUCTION:

Esophageal cancer is the eighth most common cancer and the sixth most common cause of cancer related mortality, reflecting the high malignant potential and the poor prognosis of the tumor. In fact, the global incidence of esophageal cancer has increased more than any other organ's during the past decades.[1] It often presents at an advanced stage, rendering a radical treatment unfeasible. In patients with localized disease, surgical resection remains the cornerstone of their treatment. However, despite advances in surgical procedures and perioperative management, esophagectomy with radical lymphadenectomy for invasive esophageal cancer carries a high incidence of morbidity and mortality even in experienced centers. Regardless of the approach, open esophagectomy is associated with 4-7% mortality and 70-80% major or minor complication rate.[2] Among the various complications, pulmonary complications have been proved to correlate with prolonged hospital stay and in-hospital mortality and they are more common following transthoracic rather than transhiatal approach.[3,4]

With the evolution of laparoscopic surgery in the late 80s, and the advancement in technical equipment, the potential of a thoracoscopic and laparoscopic approach for esophageal resection has attracted the interest of many surgical teams, in an attempt to blunt the insult of open surgery,

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especially to the lungs, and to minimize the post-operative complication rate. The first report of minimally invasive esophagectomy (MIE) was by Cuschieri and colleagues in 1992.[5] Since that time, many groups have described various methods for MIE with two or three field lymphadenectomy and intrathoracic or cervical anastomosis.[6-10] Although laparoscopic surgery for benign esophageal diseases has been widely accepted, the minimally invasive approach for the treatment of esophageal cancer is still far from being established as superior to the open technique. In this paper we review the English literature on MIE regarding indications, technique and short and long terms outcomes of MIE in comparison to the open esophagectomy (OE).

INDICATIONS

MIE is a technically demanding procedure and therefore it was initially used only for T1 or T2 tumors in patients who did not receive neoadjuvant therapy, because of the extensive adhesions in the mediastinum and the increased risk of bleeding.[9] However, the indications of MIE have evolved over time along with the increasing surgical experience to include more advanced cancers as well as patients submitted to neoadjuvant treatment. Nowadays, most authors agree that the indications of MIE are almost the same as with OE with the only exception of preoperative radiation to the mediastinum and one lung ventilation failure, which are considered as contraindications for thoracoscopy.[11]

SURGICAL PROCEDURES

As with open procedures, several different approaches to MIE have been described depending on the tumor size, the stage of the disease and the patient's general condition. In 1992, Cuschieri et al[5] first reported on 5 patients who underwent esophagectomy with cervical anastomosis under right video assisted thoracoscopy (VATS), while Liu et al.[12] reported the first thoracoscopic esophagectomy with intrathoracic anastomosis. De Paula et al.[13] published their experience with laparoscopic transhiatal esophagectomy in 1995. In order to simplify the various techniques of esophagectomy we can divide them into those including cervicotomy and a cervical anastomosis with or without thoracoscopy (transhiatal or three-field) and those with an intra-thoracic anastomosis (Ivor Lewis). In a narrow sense, only a total thoracoscopic and laparoscopic approach would be considered as MIE. However, in a wider sense, video assisted thoracoscopy with a mini thoracotomy and laparoscopy is also included in minimally invasive techniques.[14] For the purpose of this article, any combination of laparoscopy instead of laparotomy and thoracoscopy or mediastinoscopy instead of thoracotomy is considered as MIE.

Laparoscopic – Thoracoscopic esophagectomy

The laparoscopic stage includes the dissection of the hiatus, the abdominal and the lower mediastinal esophagus, the abdominal lymphadenectomy, the pyloroplasty (or pyloromyotomy or botox or nothing), the preparation of the gastric conduit and the positioning of the feeding jejunostomy. At the end of the abdominal stage, the gastric conduit is sutured on the esophageal specimen in order to be retrieved from the thorax or the neck. The thoracospopic part of the procedure includes the dissection of the thoracic esophagus and thoracic lymphadenectomy. The esophagus is mobilized from the hiatus up to the thoracic inlet after division of the azygos vein. The esophageal anastomosis is performed above the level of the azygos vein, or the operation continues with a cervicotomy and the gastric conduit is joined with the esophagus in the neck. In 2003, Luketich et al[15] one of the pioneers of MIE, published his promising results of combined thoracoscopic and laparoscopic approach with anastomosis performed in the neck. In his series, the operative mortality was 1.4% and the anastomotic leak

rate was 11.7%. The advantage of the cervical approach is that an anastomotic leak or fistula is easier to deal with and rarely leads to mortality, return to ICU or reoperation. In addition, with the three field approach, a longer segment of esophagus is removed and the lymphadenectomy performed is more extensive. Despite their excellent results with three fields MIE, the Pittsburg group switched to Ivor Lewis esophagectomy with high intrathoracic anastomosis either with a hybrid approach (laparoscopy and planned mini thoracotomy) or with totally laparoscopic thoracoscopic approach.[16] The advantages of this approach are the significantly lower (but clinically more significant) anastomotic leak rate, the lower risk of recurrent laryngeal nerve injury and the elimination of a neck scar.[17]

Laparoscopic transhiatal esophagectomy

The laparoscopic transhiatal esophagectomy (LTE), is performed using laparoscopy alone and, depending on the site of the tumor, either retrograde (distal to proximal) or antegrade (proximal to distal) inversion of the esophagus with a vein stripper. The upper esophageal dissection is performed under direct vision through a cervicotomy and the lower esophageal dissection is transhiatal under laparoscopic view. In fact only the middle part of the esophagus is stripped out of its bed. A transcervical mediastinoscopy can also be used to facilitate the mediastinal dissection.[18] The main advantage of this approach is that it does not require one lung ventilation and repositioning of the patient during the operation. Although there is a concern regarding the extend of the periesophageal dissection that can be performed transhiatally most authors report comparable results to thoracoscopy in terms of the significant postoperative and survival outcomes.[19,20] However, the risk of severe injury to structures like the inferior pulmonary vein or the left mainstem bronchus is higher during LTE, especially in advanced bulky tumors.[17]

TECHNICAL CONSIDERATIONS

Positioning

Until now, two types of patient positioning have been used for thoracoscopic esophagectomy. The initial reports included right thoracoscopic esophagectomy with the patient in left lateral decubitus position, similar to open transthoracic esophagectomy.[5] However, since Cuschieri et al[21] first described thoracoscopic dissection of the esophagus in the prone position, this approach is becoming increasingly popular. The main advantage of the prone positioning is that the right lung falls away from the operating field with gravity and pneumothorax. Therefore, retraction of the lung is not necessary and the assistant skill is less important. The blood pools at the anterior mediastinum, away from the operating field and the surgeon's position is more ergonomic than with left lateral decubitus positioning. In addition, the operation can be performed without the need of single lung ventilation. Palanivelu et al[22] published a series of 130 patients who underwent MIE with thoracoscopic mobilization of the esophagus in the prone position. He reported very low incidence of pulmonary complications, reduced operative time, low mortality rate and short hospital stay. The authors advocate the prone position arguing that it prevents postoperative atelectasis due to allowing of partial intermitted right lung ventilation. The functional residual capacity and the ventilation – perfusion matching are better in the prone even compared to the supine position. Noshiro et al[23] also published their experience in MIE with prone position. They noted significantly less blood loss and shorter operative time with prone position with no compromise in left recurrent laryngeal nerve exposure and injury even when accompanied by extensive lymphadenectomy. However, no randomized controlled trials have ever compared the two approaches. Most studies are small in size, have significant limitations and do not uniformly superiority of the prone approach.

The main disadvantages of the prone posi-

tioning are that the airway management by the anesthesiologist and the emergency conversion to open are difficult.[14] In addition, the dissection in the upper mediastinum, especially around the left recurrent laryngeal nerve is more difficult in the prone position. In attempt to combine the advantages of both positions, Kawakubo et al[24] introduced a hybrid position which can be changed from prone to left semi-prone and left lateral decubitus position by just rotating the operating table.

Prevention of anastomotic leak

An anastomotic leak following esophagectomy is a potentially life threatening complication. The impaired arterial inflow to the tip of the gastric conduit is a key factor in the development of anastomotic leakage. The importance of the width of the gastric conduit was addressed by Luketich et al.[15] He reported increased gastric tip necrosis and subsequent anastomotic leakage when a narrow (3-4cm in diameter) gastric tube was created. Thus, he emphasized that a 5-6cm in diameter gastric tube should created. In a meta-analysis of technical factors affecting the integrity of the anastomosis, Markar et al. found that ischemic preconditioning, location of the anastomosis (neck vs thorax) and exposure (open vs minimally invasive) had no impact on leak rates.[25] On the other hand, Bhat et al[26] in a prospective randomized study demonstrated that the pedicled omental transposition for reinforcing the anastomotic suture line significantly reduces the incidence of leakage after esophagogastrectomy for carcinoma of the esophagus, thus decreasing the morbidity and mortality of the procedure. Regarding the type of esophagogastric anastomosis, several variations have been described. The anastomotic leak rate ranges from 0 to 10% and the stricture rate from 0 to 28.6%.[27] Although no comparative studies are available, most minimally invasive surgeons favor stapled anastomoses rather than hand sutured ones basically because of their efficiency and consistency.

Robotic esophagectomy

Root-assisted thoracoscopic esophagectomy is increasingly utilized for the treatment of esophageal cancer. Robotic surgery has the theoretical advantage of increasing freedom of instruments, improved ergonomics, 3D stereoscopic vision and minimization of instrument tremor. De la Fuente et al. published their initial results on robotic esophagectomy, with a 2% anastomotic leak and 10% pulmonary complication rate.[28] In a review of robotic assisted MIE, Watson suggested that robotic MIE is feasible, safe with equivalent outcomes to both open a laparoscopic MIE. However, the existing data could not improved outcomes by the use of the robot in terms of operative time, postoperative pain, postoperative complication rate, length of hospital stay while it increases total cost.[29]

Learning curve

Esophagectomy with radical lymphadenectomy is one of the most demanding surgical procedures, and in ordered to be performed in the minimally invasive setting, extensive experience is required. Luketich et al. noticed that MIE was not beneficial for their first 8 patients and of uncertain value for the next 77 patients.[30] In a prospective study, Osugi et al. compared the first 34 cased with the next 46 performed by the same team. The duration of the thoracoscopic procedure and blood loss were less ($p<0.0001$), the incidence of postoperative pulmonary infection was less ($p=0.0127$), and the number of mediastinal nodes retrieved was greater ($p=0.0076$) in the second group. He noted that the basic skills seem to be acquired after the first 17 cases.[31] Therefore, the primary education of the surgical team at a high volume centre is essential in order to safely perform MIE.

OUTCOMES

Short term outcomes

As with most novel procedures, the initial re-

ports on MIE were single institution case series. Those studies have demonstrated comparable results but no clear advantage to open surgery in terms of postoperative complications, mortality, blood loss, operative time and hospital stay. Mamidana et al,[32] in the first population based study, compared the outcomes following 6347 open versus 1155 MIE performed for cancer in England. There was no difference in the 30-day mortality and the overall medical morbidity between the two groups. However, MIE was associated with higher reintervention rate. Their conclusion was that although MIE performed in England is safe, it has no significant benefits over the conventional esophagectomy.[32] Biere et al,[33] in a multi-center randomized controlled trial, compared open esophagectomy to MIE in the prone position. The primary outcome of the trial was that pulmonary complications during the first two postoperative weeks were significantly lower in the MIE group (9% vs. 34%). In a meta-analysis, Nagpal et al[34] reviewed 12 studies comparing open to minimally invasive esophagectomy. He found no difference in 30-day mortality rate. In addition, a trend towards lower anastomotic leak rate in the MIE group was noted. The MIE group had also lower blood loss, shorter hospital stay and reduced pulmonary morbidity. In another meta-analysis, Sgourakis et al[35] included eight studies with a total of 1008 participants, comparing video assisted thoracoscopic/laparoscopic esophagectomy to open esophagectomy. He found that the MIE group had less postoperative complications, but it demonstrated higher incidence of anastomotic stricture. Similarly, Butler et al,[36] in a review of the literature, found that all types of MIE were at least comparable to open esophagectomy in the setting of benign and non locally advanced cancer and was associated with less blood loss but prolonged operative time. It is of note that Luketich et al,[37] who published one of the largest series of MIE, including more than 1000 cases, reported perioperative morbidity and mortality rate that is not only comparable but superior to most open series, reflecting the importance of the relatively long learning curve of MIE. Li et al,[38] in a recent retrospective study explored whether MIE is beneficial in elderly patients. They compared 89 elderly (age >70 years) who underwent MIE to 318 submitted to open surgery. The overall incidence of postoperative complications was significantly lower in the MIE group but no difference in mortality rate was noted. In summary, most meta-analyses and systematic reviews confirm the feasibility and safety of MIE pointing toward the potential for improved short term outcomes with the improvement and refinement of the MIE technique. However, randomized controlled trials are needed to provide more solid evidence for the superiority of the minimally invasive approach.

Oncologic outcomes

Theoretically, the minimally invasive techniques have the advantage of magnified view of the operative field, thus allowing the more thorough radical lymphadenectomy. On the other hand, the risk of bleeding and the difficulty to control it without the use of their hands may prohibit surgeons from dissecting close to major vascular structures. Few reports on the oncologic outcomes of MIE are available most of which refer to insufficient number of patients or short follow up period. In the largest published series of MIE, Luketich et al[37] reported 1 year survival rate of 89% for stage I, 76-80% for stage IIa/b, 63% for stage II and 44% for stage IV, results comparable to those of conventional open esophagectomy. The R0 resection was achieved in 98% of the cases which improved over time. The median number of lymph nodes harvested was 21 (15). Similarly, in a systematic review,[39] Decker found that for stage I disease, 3 and 5 year survival rate were comparable to open esophagectomy. In a more recent systematic review, Dantoc et al[40] reviewed case controlled studies comparing open esophagectomy to MIE or hybrid MIE (HMIE). A total of 1586 esophagectomies (718 open 494 MIE and 386 HMIE) were included. No statistical significant difference was found between the three

groups regarding the stage of the disease. Overall, the median number of lymph nodes harvested was higher in the MIE (16) and HMIE (17) group than in the open group (10). Regarding the 5-year survival rate, they found that although the range was narrower in the open esophagectomy studies, no significant difference was found between the open and MIE groups. Their result was that although MIE does not offer a survival benefit it does not compromise the oncological outcome.[40] In another systematic review, Watanabe et al also addressed the controversy as to whether MIE achieves equivalent oncologic outcomes to open surgery. In nine case controlled series comparing the oncologic results, four had reported significantly more lymph nodes harvested while the remaining demonstrated similar lymph nodes between the two groups. No significant difference in the long term survival was found.[41] Similarly, Sgourakis et al[35] in his meta analysis found no difference in 1,- 2-, 3- and 5-year survival rates between open esophagectomy and MIE. Regarding time to recurrence, Smithers et al[42] compared patients who underwent three different types of esophagectomy (open, thoracoscopic assisted and thoracoscopic/laparoscopic). The number of patients included was 114, 309 and 23 respectively. He found no difference in the disease free survival, as well as in the total number of lymph nodes retrieved and the overall survival rate.

Another issue that was raised with the adoption of MIE is whether it can be used in locally advanced cancers following neoadjuvant chemoradiotherapy, since neoadjuvant treatment is expected to increase the adhesions and thus the complexity of the procedure and the potential intra-operative complications. In a retrospective study Warner et al compared 62 patients who underwent MIE following neoadjuvant therapy with 34 patients treated with surgery alone. No statistically significant difference was found in terms of blood loss, postoperative complications rate or overall survival rate.[43]

Quality of life

Quality of life is increasingly becoming an important outcome in the assessment of treatment in patients with esophageal cancer. Parameswaran et al., in two consecutive studies,[44,45] investigated health related quality of life (HRQL) following MIE. He found that six weeks after MIE, patients reported deterioration in functional aspects of HRQL and more symptoms than at baseline. However, most of them improved by 3 months and had returned to baseline levels by 6 months. He concluded that MIE leads to rapid restoration of HRQL.[44] However, after prospectively comparing the HRQL of patients following MIE with those submitted to open surgery, he found that only small benefits came from the minimally invasive approach.[45] As expected, the most significant decline in physical activity and social functioning occur in the early postoperative period. During this period, pain related symptoms seem to be less significant after MIE, but after six months any potential difference tends to fade away.

CONCLUSIONS

Minimally invasive esophagectomy is becoming increasingly popular for the treatment of not only benign diseases but esophageal cancer as well and is a viable alternative to open surgery in the hands of experienced surgeons. To date, the data available suggest that MIE is safe, with an operative morbidity and mortality similar to or even better than open esophagectomy, without any compromise in the oncologic outcome of the procedure. However, most data come from retrospective studies or small case controlled studies. Recently, the preliminary results of a phase II multi-institutional study (Eastern Cooperative Oncology Group ECOG 2202) were reported. A total of 106 patients were enrolled. The perioperative morbidity was acceptable and the mortality was 2%.[46] The long term results are still awaited. Another multicentre prospective randomized trial

is also in progress in the Netherlands. The aim of the TIME trial is to define the role of minimally invasive esophageal resection in patients with resectable intrathoracic and junction esophageal cancer.[47] The results of these studies will through light on the existing controversies over the role of MIE and consolidate the existing evidence regarding its safety and oncologic effectiveness.

REFERENCES

1. Jemal A, Bray F, Center M, et al. Global cancer statistics. *CA Cancer J Clin* 2011; 61: 69-90.
2. Pierre AF, Luketich JD. Technique and role of minimally invasive esophagectomy for premalignant and malignant diseases of the esophagus. *Surg Oncol Clin N Am* 2002; 11: 337-350.
3. Atkins BZ, Shah AS, Hutcheson KA, et al. Reducing hospital morbidity and mortality following esphagectomy. *Ann Thorac Surg* 2004; 78: 1170-1176.
4. Hulscher JB, van Sandick JW, de Boer AG, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. *N Engl J Med* 2002; 347: 1662-1669.
5. Cuschieri A, Shimi S, Banting S. Endoscopic oesophagectomy through a right thoracoscopic approach. *J R Coll Surg Edinb* 1992; 37: 7-11.
6. Kawahara K, Maekawa T, Okabayashi K, et al. Video assisted thoracoscopic esophagectomy for esophageal cancer. *Surg Endosc* 1999; 13: 218-223.
7. Luketitch JD, Schauer PR, Christie NA, et al. Minimally invasive esophagectomy. *Ann Thorac Surg* 2000; 70: 906-911
8. Nguyen NT, Follete DM, Lemoine PH, et al. Minimally invasive Ivor Lewis esophagectomy. *Ann Thorac Surg* 2001; 72: 593-596.
9. Akaishi T, Kaneda I, Higushi N, et al. Thoracoscopic en block total esophagectomy with radical mediastinal lymphadenectomy. *J Thorac Cardiovasc Surg* 1996; 112: 1533-1140.
10. Shichinose T, Hirano S, Kondo S. Video assisted esophagectomy for esophageal cancer. *Surg Today* 2008; 38: 206-213.
11. Kawakubo H, Takeuchi H, Kitagawa Y. Current status and future perspectives on minimally invasive esophagectomy. *Korean J Thorac Cardiovasc Surg* 2013; 46: 241-248.
12. Liu HP, Chang CH, Lin PJ, et al. Video-assisted endoscopic esophagectomy with stapled intrathoracic esophagogastric anastomosis. *World J Surg* 1995; 36: 1608-1616.
13. DePaula AL, Hashiba K, Ferreira EA, et al. Laparoscopic transhiatal esopphagectomy with esophagogastroplasty. *Surg Laparosc Endosc* 1995; 5: 1-5.
14. Takeuchi H, Kawakubo H, Kitagawa Y. Current status of minimally invasive esophagectomy for patients with esophageal cancer. *Gen Thorac Cardiovasc Surg* 2013; 61: 513-521.
15. Luketich JD, Alvelo-Rivera M, Buenaventura PO, et al. Minimally invasive esophagectomy: outcomes in 222 patients. *Ann Surg* 2003; 238: 486-494.
16. Bizekis C, Kent MS, Luketich JD, et al. Initial experience with minimally invasive Ivor Lewis esophagectomy. *Ann Thorac Surg* 2006; 82: 402-406.
17. Hoppo T, Jobe BA, Hunter JG. Minimally invasive esophagectomy: the evolution and technique of minimally invasive surgery for esophageal cancer. *World J Surg* 2011; 35: 1454-1463.
18. Koide N, Takeuchi D, Suzuki A, Miyagawa S. Mediastinoscopy-assisted esophagectomy for esophageal cancer in patients with serious comorbidities. *Surg Today* 2012; 42: 127-134.
19. Cash JC, Zehetner J, Hedayati B. Outcomes following laparoscopic transhiatal esophagectomy for esophageal cancer. *Surg Endosc* 2014; 28: 492-499.
20. Dapri G, Himpens J, Cadière GB. Minimally invasive esophagectomy for cancer: laparoscopic transhiatal procedure or thoracoscopy in prone position followed by laparoscopy? *Surg Endosc* 2008; 22: 1060-1069.
21. Cuschieri A. Thoracoscopic subtotal esophagectomy. *Endosc Surg Allied technol* 1994; 2: 21-25.
22. Palanivelu C, Prakash A, Senthilkumar R, et al. Minimally invasive esophagectomy: thoracoscopic mobilization of the esophagus and mediastinal lymphadenectomy in prone position--experience of 130 patients. *J Am Coll Surg* 2006; 203: 7-16.
23. Noshiro H, Iwasaki H, Kobayashi K, et al. Lymphadenectomy along the left recurrent laryngeal nerve by a minimally invasive esophagectomy in the prone position for thoracic esophageal cancer. *Surg Endosc* 2010; 24: 2965-2973
24. Kawakubo H, Takeuchi H, Kitagawa Y. Current status and future perspectives on minimally invasive esophagectomy. *Korean J Thorac Cardiovasc Surg* 2013; 46: 241-248.
25. Markar SR, Arya S, Karthikesalingam A, Hanna GB.

Technical factors that affect anastomotic integrity following esophagectomy: systematic review and meta-analysis. *Ann Surg Oncol* 2013; 20: 4274-4281.
26. Bhat MA, Dar MA, Lone GN, et al. Use of pedicled omentum in esophagogastric anastomosis for prevention of anastomotic leak. *Ann Thorac Surg* 2006; 82: 1857-1862.
27. Maas KW, Biere SS, Scheepers JJ, Gisbertz SS, et al. Minimally invasive intrathoracic anastomosis after Ivor Lewis esophagectomy for cancer: a review of transoral or transthoracic use of staplers. *Surg Endosc* 2012; 26: 1795-1802.
28. de la Fuente SG, Weber J, Hoffe SE, et al. Initial experience from a large referral center with robotic-assisted Ivor Lewis esophagogastrectomy for oncologic purposes. *Surg Endosc* 2013; 27: 3339-3347
29. Watson TJ. Robotic esophagectomy: is it an advance and what is the future? *Ann Thorac Surg* 2008; 85: S757-S759.
30. Luketich JD, Nguyen NT, Weigel T, et al. Minimally invasive approach to esophagectomy. *JSLS* 1998; 2: 243-247.
31. Osugi H, Takemura M, Higashino M, et al. Learning curve of video-assisted thoracoscopic esophagectomy and extensive lymphadenectomy for squamous cell cancer of the thoracic esophagus and results. *Surg Endosc* 2003; 17: 515-519.
32. Mamidanna R, Bottle A, Aylin P, et al. Short-term outcomes following open versus minimally invasive esophagectomy for cancer inEngland: a population-based national study. *Ann Surg* 2012; 255: 197-203.
33. Biere SS, van Berge Henegouwen MI, Maas KW, et al. Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicentre, open-label, randomised controlled trial. *Lancet* 2012; 379: 1887-1892.
34. Nagpal K, Ahmed K, Vats A, et al. Is minimally invasive surgery beneficial in the management of esophageal cancer? A meta-analysis. *Surg Endosc* 2010; 24: 1621-1629.
35. Sgourakis G, Gockel I, Radtke A, et al. Minimally invasive versus open esophagectomy: meta-analysis of outcomes. *Dig Dis Sci* 2010; 55: 3031-3040.
36. Butler N, Collins S, Memon B, Memon MA. Minimally invasive oesophagectomy: current status and future direction. *Surg Endosc* 2011; 25: 2071-2083.
37. Luketich JD, Pennathur A, Awais O, et al. Outcomes after minimally invasive esophagectomy: review of over 1000 patients. *Ann Surg* 2012; 256: 95-103.
38. Li J, Shen Y, Tan L, et al. Is minimally invasive esophagectomy beneficial to elderly patients with esophageal cancer? *Surg Endosc* 2015; 29: 925-930.
39. Decker G, Coosemans W, De Leyn P, et al. Minimally invasive esophagectomy for cancer. *Eur J Cardiothorac Surg* 2009; 35: 13-20.
40. Dantoc MM, Cox MR, Eslick GD. Does minimally invasive esophagectomy (MIE) provide for comparable oncologic outcomes to open techniques? A systematic review. *J Gastrointest Surg* 2012; 16: 486-494.
41. Watanabe M, Baba Y, Nagai Y, Baba H. Minimally invasive esophagectomy for esophageal cancer: an updated review. *Surg Today* 2013; 43: 237-244.
42. Smithers BM, Gotley DC, Martin I, et al. Comparison of the outcomes between open and minimally invasive esophagectomy. *Ann Surg* 2007; 245: 232-240.
43. Warner S, Chang YH, Paripati H, et al. Outcomes of minimally invasive esophagectomy in esophageal cancer after neoadjuvant chemoradiotherapy. *Ann Thorac Surg* 2014; 97: 439-445.
44. Parameswaran R, Blazeby JM, Hughes R, et al. Health-related quality of life after minimally invasive oesophagectomy. *Br J Surg* 2010; 97: 525-531.
45. Parameswaran R, Titcomb DR, Blencowe NS, et al. Assessment and comparison of recovery after open and minimally invasive esophagectomy for cancer: an exploratory study in two centers. *Ann Surg Oncol* 2013; 20: 1970-1977.
46. Luketich JD, Pennathur A, Catalano PJ, et al. Results of a phase II multicenter study of MIE (Eastern Cooperative Oncology Group ECOG 2202). *J Clin Oncol* 2009; 27(suppl): 15s (Abstract 4516).
47. Biere SS, Maas KW, Bonavina L. Traditional invasive vs. minimally invasive esophagectomy: a multi-center, randomized trial (TIME-trial). *BMC Surg* 2011; 11: 2.

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