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DISEASES OF THE ESOPHAGUS

Original article

Role of endoscopic ultrasound in superficial esophageal cancer

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SUMMARY. **The recent increase in the incidence of superficial esophageal cancer and promising developments in potentially curative endoscopic therapies have placed endoscopic ultrasound in a central position with regard to decision making. This is a review of the literature to determine the role of endoscopic ultrasound and high frequency probe ultrasonography in the assessment of superficial esophageal carcinomas.**

KEY WORDS: **cancer, endosonography, esophagus.**

INTRODUCTION

More than 90% of primary esophageal cancers are esophageal epithelial tumors (squamous cell carcinoma and adenocarcinoma). Marked epidemiologic changes have been observed over the last several decades. Until the 1970s, more than 90% of all esophageal cancers were squamous cell carcinoma. Over the last 40 years, esophageal adenocarcinoma has the fastest growing incidence rate of all cancers in the USA.[1–4] This increase is most dramatic among white males. Currently, the majority of esophageal cancers in the western hemisphere are adenocarcinoma.[2]

Although esophageal cancer is an important cause of cancer mortality worldwide, it is relatively uncommon in North America. In the USA, estimated new cases and deaths due to esophageal cancer in 2007 are expected to be 15 560 and 13 940, respectively.[5] The outcome depends on the depth of tumor invasion and presence of metastases. Given the extensive esophageal submucosal lymphatic network and absence of serosa,[6] the risk of early nodal metastasis and local spread to surrounding tissues is common. Longitudinal, rather than segmental esophageal submucosal lymphatic drainage is probably the reason for skip metastasis in lymph nodes.[7] A large portion of patients with esophageal cancer present with advanced stage, therefore, the prognosis is poor in the majority of cases.

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STAGING OF ESOPHAGEAL CANCER

The outcome and treatment options of esophageal cancer depend on the stage of tumor. The degree of tumor invasion (T), the presence or absence of nodal metastasis (N), and distant metastasis (M) are used in the TNM classification for staging (Table 1).[8] Accurate initial staging of esophageal cancer is critical, because initial triage of patients determines subsequent management. The initial evaluation of a patient diagnosed with esophageal cancer begins with the assessment of operative risk, investigation of the primary tumor region, and presence of metastatic disease. Computed tomography (CT) and/or positron emission tomography (PET) are used to evaluate for the presence of metastatic disease. Patients without evidence of distant metastasis should undergo locoregional staging. The precise differentiation of esophageal wall layers, direct imaging of the surrounding organs and tissues, and tissue sampling with fine needle aspiration (FNA) has allowed endoscopic ultrasound (EUS) to play a pivotal role in the staging of patients with esophageal cancer.

The transducer at the tip of an EUS scope emits ultrasound waves at several high frequencies. Higher frequency ultrasound improves resolution of the image but decreases the scanning depth. As in other locations within the gastrointestinal tract, the esophagus can be visualized as five layers with EUS scopes operating at frequencies from 5 MHz to 12 MHz.[9] The layers are as follows: first hyperechoic layer, superficial mucosa; second hypoechoic layer, deep mucosa; third hyperechoic layer, submucosa; fourth hypoechoic layer, muscularis propria; and fifth hyperechoic layer, adventia. The esophagus

Table 1 TNM classification system of esophageal cancer

T-staging	
Tx	Tumor not assessable
T0	No evidence of primary tumor
Tis	Tumor *in situ*
T1	Tumor invading lamina propria (T1m) or submucosa (T1sm)
T2	Tumor invading muscularis propria
T3	Tumor invading through the muscle layer into the adventitia
T4	Tumor invading local structures
N-staging	
Nx	Nodal involvement not assessable
N0	No evidence of nodal involvement
N1	Evidence of nodal involvement
M-staging	
Mx	Metastases not assessed
M0	No evidence of metastatic disease
M1a	Celiac nodes involved in lower esophageal cancer Cervical nodes involved in upper esophageal cancer
M1b	Beyond locoregional node involvement i.e. cervical nodes in lower esophageal cancer and celiac nodes in upper esophageal cancer Metastatic involvement of visceral organs, pleura, peritoneum

may be seen as nine layers with miniprobes operating at higher frequencies (20–30 MHz).

The detailed visualization of esophageal wall layers and surrounding tissues allows accurate tumor staging. Esophageal wall layers cannot be delineated with other imaging techniques such as CT and PET; therefore, the extent of tumor invasion cannot be determined as accurately as EUS with other imaging modalities. CT imaging relies only on the size and shape of a lymph node; however, EUS not only assesses the imaging characteristics such as size, shape, echotexture, and margins of a suspicious lymph node, but can also allow cytological evaluation of a suspicious lymph node by using FNA. With this method, a metastatic lymph node can be distinguished from reactive hyperplasia or inflammatory nodes. Celiac lymph nodes are the most important lymph node group to assess. In the setting of proximal and middle esophageal cancer, presence of celiac lymph node metastasis is a sign of distant metastasis and unresectability. These patients are staged as M1b. However, involvement of celiac lymph node with metastatic cells in distal esophageal or gastroesophageal tumors is considered as regional metastasis and staged as M1a. EUS accuracy in esophageal cancer staging has been evaluated in multiple studies; it was found to be the most accurate imaging modality in the assessment of tumor invasion and locoregional lymph node status.[10–19]

SUPERFICIAL ESOPHAGEAL CANCER

Superficial esophageal cancer is a terminology used for tumors confined to the mucosa or submucosa. Early esophageal cancer is a localized lesion with low risk of lymph node metastasis and a high potential for cure following complete resection. Recently, as a result of frequent use of endoscopic screening for upper gastrointestinal cancers and advances in endoscopic techniques to detect high-grade dysplasia and early esophageal carcinoma, the incidence of superficial esophageal cancer defined as Tis and T1 lesions have been increased in some Asian countries as well as the western world.[20–22] Carcinoma *in situ* (Tis) is the earliest stage, in which malignant cells are confined within the epithelium and the lamina propria is intact.[8] This is a histopathologic description and cannot be imaged endosonographically. When malignant cells invade the lamina propria, the tumor is then defined as a T1 lesion.[8] T1 lesions can be subdivided into T1m (tumor invading lamina propria) and T1sm (tumor invading submucosa).[23–30] The prognostic importance of the depth of tumor invasion required a more comprehensive subclassification of T1 lesions based on the depth of invasion. Mucosal lesions are subdivided into three groups: m1, carcinoma limited to the epithelium; m2, carcinoma with invasion into the lamina propria; and m3, carcinoma with invasion into but not through the muscularis mucosa. Submucosal lesions are also subdivided into three groups: sm1, lesions with invasion into the superficial one-third of submucosa (<200 μm); sm3, lesions with invasion into the deepest one-third of submucosa; and sm2, lesions with penetration into the intermediate one-third of submucosa (Fig. 1).

This subclassification is important for appropriate prognostication of superficial esophageal cancers as well as consideration of potentially curative endoscopic therapeutic options such as endoscopic mucosal resection (EMR),[31–33] or endoscopic ablative therapies such as photodynamic therapy[34–36] or argon plasma coagulation.[37] The major advantage of EMR over endoscopic ablative therapies is the opportunity for histologic examination of the resected specimen. EMR can serve dual purposes – being both a staging tool and also having curative potential in early esophageal cancers. Recently published studies on both superficial esophageal adenocarcinomas and squamous cell carcinomas revealed virtually nonexistent lymph node metastasis with m1 and m2 lesions.[38–43]

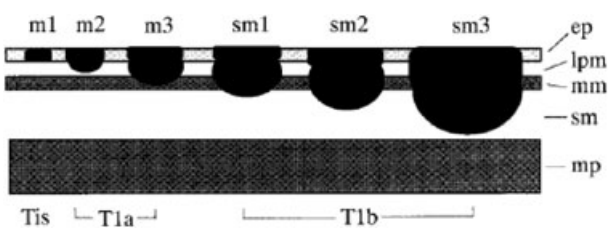

Fig. 1 Subclassification of esophageal T1 tumors (m1: limited to the epithelial layer; m2: invades lamina propria; m3: invades into but not through muscularis mucosa; sm1–sm3: invades different thirds of the submucosa) (published with the permission of Springer). ep, epithelium; lpm, lamina propria mucosae; mm, muscularis mucosa; sm, submucosa; mp, muscularis propria.

Endoscopic therapies are performed for curative intent in m1 and m2 lesions. The risk of lymph node metastasis when there is invasion of the muscularis mucosa (m3) is approximately 7%, ranging between 4 and 12% of cases.[38–43] When the tumor invades into the superficial submucosal layer, the average risk of lymph node metastasis is 15%, with a range of 0–32%.[38–43] This increase in the prevalence of lymph node metastasis in patients with submucosal invasion is probably related to the rich submucosal lymphatic network. The presence or absence of lymph node metastasis has direct impact on the outcome of esophageal tumors. This is best demonstrated by the study of Westerterp *et al.*, which showed a 5-year recurrence-free survival rate of 97% in patients with T1m1–3/sm1 lesions versus 57% in patients with T1sm2–3 lesions.[41] Although the risk of lymph node metastasis is small with m3 and sm1 lesions, endoscopic therapies carry a potential risk for inadequate treatment. Therefore, the optimal treatment for these patients remains controversial and should be individualized. Surgical resection is considered as standard treatment for tumors with submucosal invasion. EUS with FNA may potentially play an important role in the risk stratification of early esophageal cancer by detecting malignant lymphadenopathy. Further studies are needed to accurately determine which patients with m3 and sm1 lesions would benefit from endoscopic therapies with potential curative intent. The indications and contraindications of endoscopic resection of superficial esophageal tumors are beyond the scope of this paper; Pech *et al.* recently published a review on this topic.[44]

ROLE OF EUS IN SUPERFICIAL/EARLY ESOPHAGEAL CANCER

Given the considerable morbidity and mortality of esophagectomy, accurate EUS staging of early esophageal cancer is crucial to choose among endoscopic, surgical, or palliative therapies. The ability to visualize different esophageal wall layers is the major advantage of EUS over other imaging modalities. EUS imaging with higher frequencies produces more detailed visualization of esophageal wall layers in trade off with depth of penetration. EUS is currently considered to be the most accurate noninvasive method to determine the depth of esophageal tumor invasion.

Until recently, most of the studies comparing EUS and CT focused on the staging of advanced esophageal malignancies. Increasing number of patients with early esophageal tumors and encouraging results from curative endoscopic therapies elicited the need for accurate staging of early esophageal cancers.

A study by Pech *et al.* was the first prospective evaluation of the accuracy of EUS and CT on the TNM staging of early cancer in Barrett's esophagus.[45] T1 and >T1 could not be differentiated by CT. However, differentiation between T1 and >T1 using EUS was possible in all cases (with sensitivity, specificity, positive predictive value, and negative predictive value of 100%). On the other hand, even with the use of high-frequency probes, differentiation between T1m and T1sm was suboptimal; sensitivity of EUS for submucosal tumor invasion in the setting of Barrett's esophagus was found to be only 27%. The overall accuracy of EUS for T-staging was 76%. EUS was also found to be superior to CT scan for N-staging. Sensitivity of EUS and CT was found to be 75 and 38%, respectively. Because the CT scan did not provide any information on TNM staging in patients with early cancer in Barrett's esophagus beyond that of EUS, it was suggested to discontinue the use of CT in early cancer in Barrett's esophagus.

EUS has been evaluated for use in patients with Barrett's esophagus and high-grade dysplasia to detect occult malignancy. Falk *et al.* evaluated the role of EUS (7.5 and 12 MHz) to detect endoscopically non-visualized tumors in nine patients with Barrett's esophagus with high-grade dysplasia.[46] One out of three patients with cancer was identified, but this lesion was overstaged. EUS incorrectly identified invasive carcinoma in two out of six patients with high-grade dysplasia, and correctly identified absence of carcinoma in four patients. Overstaging was attributed to esophageal wall inflammation, overlapping folds pulled up by the balloon, or tangential esophageal wall imaging. The authors concluded that conventional EUS could not reliably differentiate benign and malignant wall thickening in Barrett's esophagus with high-grade dysplasia. However, in the study by Scotiniotis *et al.* on the accuracy of EUS (7.5 and 12 MHz) in Barrett's esophagus with high-grade dysplasia and intramucosal carcinoma, EUS detected all five cases of tumor with submucosal invasion based on disruption of the third sonographic wall layer and one case with lymph node involvement.[47] EUS was false positive for submucosal involvement in one patient and for lymph node malignancy in four patients. The sensitivity, specificity, and negative predictive values of preoperative EUS for submucosal invasion were 100, 94 and 100%, respectively, while the values for lymph node involvement was 100, 81 and 100%, respectively. Presence of a nodule or stricture was found to be associated with increased likelihood of submucosal invasion.

There are several challenges in performing EUS on small early carcinomas. Localization of early esophageal tumors with the side-viewing EUS scopes can sometimes be difficult. Overdistention of the water-filled balloon surrounding the EUS transducer may compress the esophageal wall layers and compromise accurate tumor staging. As an alternative to the echoendoscope, small-caliber high-frequency EUS probes (15–30 MHz) can be introduced through the

working channel of standard endoscopes and placed over the lesion under direct visualization. Because the esophagus is filled with water, EUS probes do not need a balloon to obtain acoustic coupling. High-frequency probes produce nine esophageal layers.[48] The mucosa consists of four layers; the first two (m1 and m2) represent the epithelium, the third layer (m3) is the lamina propria, and the fourth layer (m4) is the muscularis mucosa. The fifth layer is hyperechoic and represents submucosa. The muscularis propria is composed of three layers; the sixth layer is the circular muscle, the seventh is an interface connective tissue, and the eighth layer is the longitudinal muscle. The ninth layer represents adventia. High-frequency ultrasound probes limit the penetration depth of the ultrasound beam; therefore, the visualization of mediastinal lymph nodes is suboptimal.

Larghi *et al.* initially staged 48 patients with Barrett's esophagus with high-grade dysplasia and adenocarcinoma with EUS (5–20 MHz).[49] Patients with disease confined to the mucosa underwent EMR. Patients with T1sm or deeper lesion or regional lymph node metastases were referred to surgery. The staging accuracy of EUS was found to be 85% (41 out of 48 patients). Surgical or EMR pathologic staging revealed that one patient was overstaged and six patients were understaged by EUS. Surgical pathology confirmed endosonographic submucosal invasion in seven out of eight patients. One patient with endosonographic T1m disease was overstaged. Submucosal invasion was identified on EMR specimens of 6 out of 15 (40%) patients with intramucosal adenocarcinoma staged by EUS. EMR following EUS provided valuable information to accurately stage patients with high-grade dysplasia and early cancer confined to the mucosa in the setting of Barrett's esophagus.

Hasegawa *et al.* compared the accuracy of a high-frequency EUS probe (15 MHz) with a standard echoendoscope (12 MHz) in preoperative staging of superficial esophageal carcinoma.[50] The accuracy rates of the depth of invasion by the ultrasound probe were 86% (6 of 7 patients) for mucosal carcinoma and 94% (17 of 18 patients) for submucosal carcinoma, with an overall accuracy of 92% (23 of 25 patients); accuracy by EUS were 71% (5 of 7 patients) for mucosal carcinoma and 78% (14 of 18 patients) for submucosal carcinoma, with an overall accuracy of 76% (19 of 25 patients). The accuracy of lymph node metastasis was found to be 56% by ultrasound probes and 67% by EUS. The authors concluded that the ultrasound probe was more convenient to use and more accurate than EUS in the evaluation of the depth of invasion of superficial esophageal carcinoma. The study by Murata *et al.* accurately determined cancer limited to the lamina propria in 84% of cases with high-frequency ultrasound probes (15 and 20 MHz).[49] Correct differentiation between mucosal and submucosal cancers was reported in 94% (46 of 49 patients). Overall accuracy of high-frequency ultrasound probes in 54 patients studied was 75%.

A prospective evaluation of high-frequency probe ultrasonography revealed limited accuracy for identifying invasive cancer in patients with high-grade dysplasia or intramucosal carcinoma in the setting of Barrett's esophagus.[51] High-frequency probe ultrasonography correctly diagnosed the presence or absence of tumor in six of nine patients (67%): three without cancer and three with a T1 lesion. Cancer staging was correct in only one out of three cases detected by high-frequency probe ultrasonography. The results of high-frequency probe ultrasonography were false negative in two esophageal cases, both of which had T1 lesion in the resected specimen. In only four out of nine patients, preoperative high-frequency probe ultrasonography findings were in complete correlation with postoperative pathologic findings.

The largest study prospectively evaluating staging in early esophageal cancer using high-frequency ultrasound probes revealed an overall accuracy of 80%.[52] However, the sensitivity for submucosal invasion fell to 48%. The location of tumor with submucosal invasion was found to play an important role in staging. Submucosal tumors located in the tubular esophagus (10 of 11 patients) were significantly better staged than submucosal tumors close to gastroesophageal junction (2 of 14 patients). Tumors with deeper submucosal invasion were also found to be better staged than those with superficial submucosal invasion. In addition, this study also showed that high-resolution endoscopy was as good as high-frequency ultrasound probe in the assessment of early esophageal tumor penetration. Although the endoscopic characteristics of esophageal lesions have been classified according to the Japanese system for early carcinomas,[53] this system has been felt to be too complex and impractical for use in the west. The recent availability of high-resolution endoscopes – chromoendoscopy as well as endoscopic therapeutic modalities – have increased interest in the endoscopic classification of these lesions.[52,54–56] Further prospective studies on high-resolution endoscopy and macroscopic classification of superficial esophageal neoplasms in comparison with EUS are needed. High-resolution endoscopic classification of superficial esophageal neoplasms and EUS findings would potentially be complimentary to each other in therapeutic decision making.

A retrospective study evaluating 106 lesions (52 adenocarcinoma in Barrett's mucosa and 54 squamous cell carcinoma) with high-frequency probe ultrasonography (20 or 30 MHz) had an accuracy, sensitivity and specificity to differentiate T1sm from T1m tumors of 73.5, 62 and 76.5%, respectively.[57] No significant difference between the two frequencies was found. Among lesions with incorrect tumor invasion

assessed by high-frequency probe ultrasonography, 70% were erroneously overstaged as submucosal lesions, while histopathologic examination of these lesions (endoscopically or surgically resected specimens) revealed only mucosal cancer. Given the risk of overstaging, the authors suggested considering EMR for T1sm lesions in surgically high-risk patients. A risk factor for misinterpretation was the location of the tumor; almost 90% of tumors located in mid- to upper esophagus were correctly staged; however, less than half of the lesions in distal esophagus were correctly staged. The diagnostic accuracy that decreases progressively from the upper esophagus toward the gastroesophageal junction has also been described by others.[52,58] This has been attributed to the difficulty in creating an acoustic interface by water filling at the gastroesophageal junction. Unfortunately, balloon-sheathed catheters did not overcome this problem. To the contrary, staging with water-filled lumen was found to be superior to the balloon-sheathed catheters,[57] likely secondary to the pressure applied by the balloon to the mucosa. The histological type of esophageal cancer (adenocarcinoma and squamous cell carcinoma) did not significantly affect the accuracy of endosonographic staging of early esophageal cancers.[57,58] Statistically nonsignificant greater accuracy for squamous cell carcinoma[57,58] is likely due to the more proximal location of squamous cell carcinomas relative to adenocarcinomas within the esophagus, rather than histopathological architectural differences of these tumors. This assumption is supported by the study of Chemaly *et al.* which showed incorrect staging of all of the squamous cell carcinomas located in the distal esophagus.[57] Only 19% of the squamous cell carcimomas were incorrectly staged in other locations of the esophagus. Presence of a nodule or protruding lesion is another factor that negatively affected the diagnostic accuracy of EUS.[58] This is probably secondary to the changed pattern of the sonographic layer from inflammatory changes.[46]

A recent evaluation of 55 patients with high-frequency probe ultrasonography (12 and 20 MHz) in superficial esophageal carcinomas (33 adenocarcinoma, 21 squamous cell carcinoma, 1 lymphoepithelial-like carcinoma) pathologically confirmed the absence of submucosal invasion in 86% of patients staged with T1m on EUS and confirmed the presence of submucosal invasion in 66% of patients staged with T1sm on EUS.[58] The positive predictive value of EUS for submucosal invasion was 67%, negative predictive value was 86%, sensitivity and specificity were 88% and 62%, respectively, and diagnostic accuracy was 75%. The accuracy of EUS to determine lymph node metastases was 71%, with a negative predictive value of 84%. This imperfect nodal staging accuracy is likely due to the use of only endosonographic criteria, rather than EUS-FNA to identify malignant lymph nodes. Similar to other studies,[52,57] the diagnostic accuracy of EUS was worse in the distal esophagus than in proximal to mid-esophagus. Presence of a nodule or protruding lesion is one of the factors that negatively affected the diagnostic accuracy of EUS. In the literature, the diagnostic accuracy of high-frequency probe ultrasonography for superficial esophageal cancer ranges between 65 and 93% (Table 2).

Table 2 Accuracy of high frequency probe ultrasonography (HFPUS) in the assessment of the depth of invasion of superficial esophageal carcinoma

Author	Number of lesions	Frequency of HFPUS (MHz)	Histopathology	Accuracy (%)
Larghi[49]	48	20	ACa	85
Hasegawa[50]	25	15	SCC	92
Murata[48]	54	15 and 20	SCC	75
May[52]	100	20	81 ACa, 19 SCC	80
Chemaly[57]	106	20 or 30	52 ACa, 54 SCC	74
Rampado[58]	55	12 and 20	33 ACa, 21 SCC	75
Kawano[59]	96	20	N/S	93
Yanai[60]	17	20	SCC	67

ACa: Adenocarcinoma; N/S: not specified; SCC: squamous cell carcinoma.

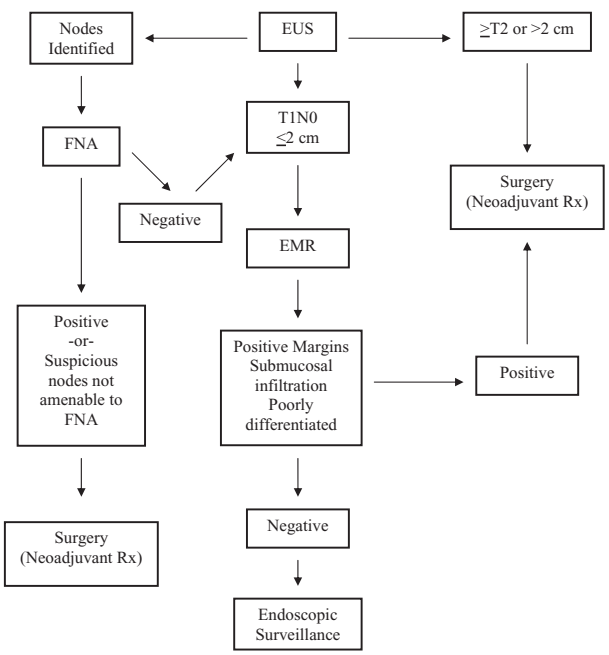

Fig. 2 Algorithm for Suspected Early Esophageal Cancer. EUS is performed for T- and N-staging. Tumors that are T1N0 and less than or equal to 2 cm in size are amenable to endoscopic mucosal resection (EMR) with curative intent. If final pathology shows positive margins, submucosal infiltration or poorly differentiated histology, surgery should be performed. Otherwise, patients may be followed with endoscopic and endosonographic surveillance. Patients with nodes identified should undergo endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA), if possible. FNA-negative patients may be candidates for EMR if the other criteria are fulfilled.

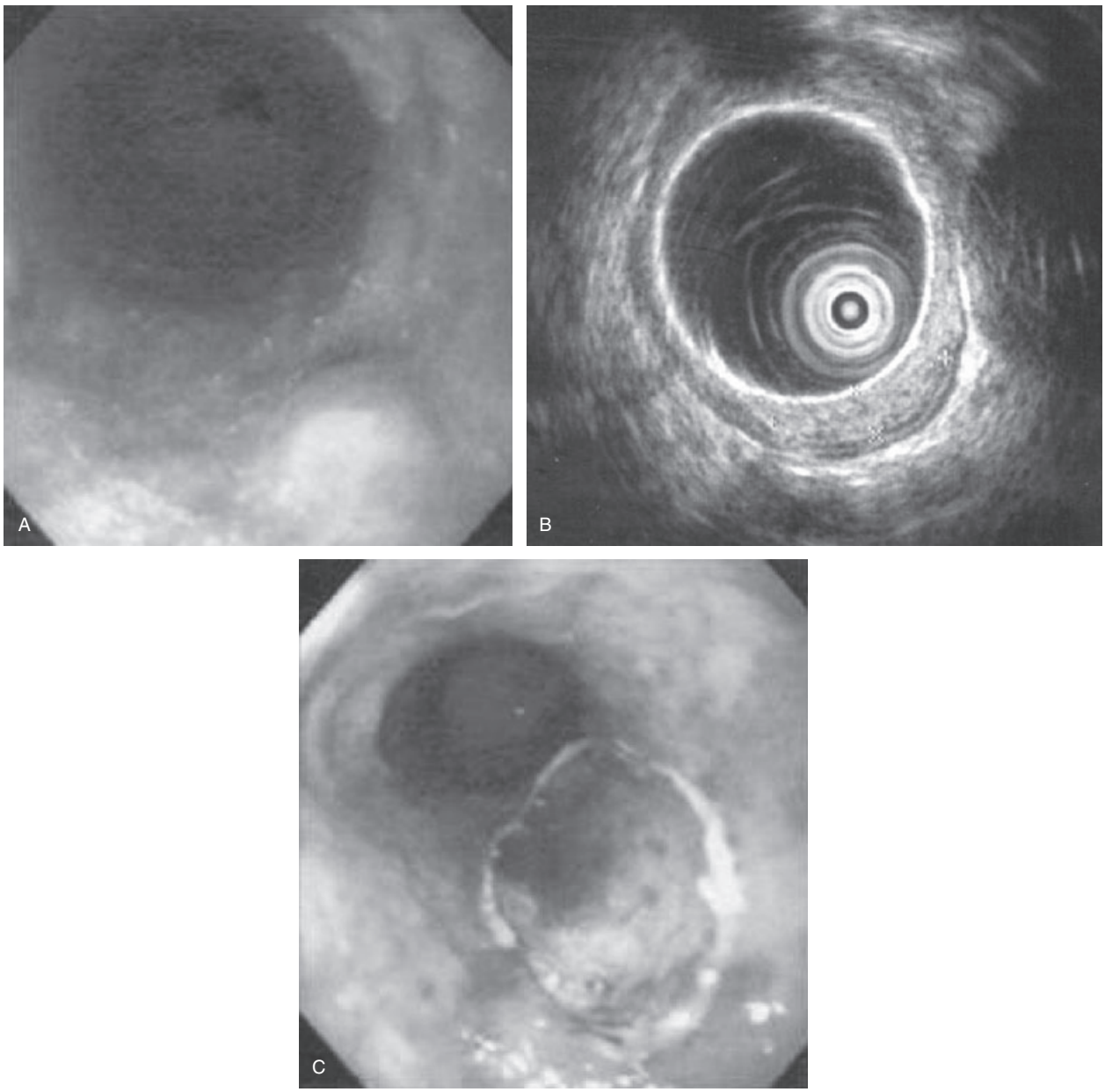

Fig. 3 (A) Endoscopic picture showing esophageal nodule in the setting of Barrett's esophagus. (B) Endoscopic ultrasound image showing a mucosal hypoechoic lesion consistent with superficial esophageal tumor without invasion of submucosal layer. (C) Endoscopic image showing esophagus following endoscopic mucosal resection.

The risk of missing a lymph node metastasis in a patient undergoing an EMR for an early esophageal malignancy has important implications. Originally, lymph node echo features such as size greater than 1 cm, echo-poor appearance, distinct margins and round shape were used to predict malignant involvement of a lymph node.[61] The accuracy of predicting malignant involvement of a lymph node is 80% when all four endosonographic criteria are present in a lymph node; however, only 25% of malignant lymph nodes had all four criteria.[62] Conventional EUS was found to be superior to high-frequency probe ultrasonography for N-staging in early esophageal cancers.[50,63] Although there are a number of endosonographic criteria, EUS-FNA has been found to be superior to lymph node echo features alone.[64] The important role of EUS in early esophageal cancer is not only limited to T-staging, but may also significantly change the management course in 20% of patients by detecting unsuspected malignant lymphadenopathy by EUS-guided FNA in patients with Barrett's esophagus with high-grade dysplasia and intramucosal carcinoma.[65] In this study, because of the presence of malignant lymphadenopathy, five out of 25 patients were excluded from EMR. To emphasize the importance of EUS-FNA over the use of only endosonographic criteria to exclude malignant lymph node involvement, two of the

positive lymph nodes were less than 10 mm in size in this study.

A recent study by Esaki *et al.* compared two different media for acoustic coupling.[66] Overall accuracy of high-frequency EUS probes (20 MHz) for the diagnosis of invasion depth in superficial esophageal cancer was 78% by a jelly-filled method and 59% by a water-filled method.

Endosonographic evaluation of superficial esophageal tumors also has limitations. The accuracy of EUS is operator-dependent. Catalano *et al.* demonstrated that operator's experience and machine-dependent factors play an important role in the accurate staging of esophageal carcinoma.[67] Improvement in technology will probably decrease instrument-dependent factors causing artifacts. Fockens *et al.* showed a definite learning curve for endosonographic T-staging of esophageal tumors and concluded that 100 procedures are needed to achieve acceptable accuracy rates.[68]

Taken together, these studies indicate that EUS is superior to CT for locoregional staging of esophageal cancer. In patients with macroscopically evident tumors, EUS has good accuracy to determine T-stage and for detecting and sampling nodal metastases. However, EUS – even with high-frequency probes – has limited accuracy in differentiating early tumors that are confined to the mucosa from those that invade the submucosa. In these cases, EMR is useful for staging and may be curative in superficial lesions.

CONCLUSION

The recent increase in the incidence of superficial esophageal cancer and promising developments in potentially curative endoscopic therapies have placed EUS to a central position in decision making (Figs 2,3). EUS should be performed to identify potential candidates for EMR. These include patients with T1 disease confined to the mucosa, well-differentiated histopathology, with a tumor size less than 2 cm and no suspicious adenopathy. Suspicious nodes should be sampled via EUS-guided FNA, if possible. Patients who do not meet these criteria should be treated surgically or referred for neoadjuvant therapy protocols. EUS cannot reliably differentiate between T1m and T1sm disease, and may not supplant the importance of histopathology on the EMR specimen. Patients with T1sm lesion on histology should be offered surgery as this stage is associated with a higher risk of residual cancer and also of lymph node metastasis.[61] Because of its inability to exclude T1sm, EUS may not be accurate enough to select cancer patients for ablative therapies such as photodynamic therapy and Argon plasma coagulation, if EMR is not also performed. In patients with Barrett's esophagus with high-grade dysplasia, EUS is primarily useful for the evaluation of discrete lesions prior to EMR.[62] The role of EUS in patients with flat dysplastic Barrett's is controversial.

References

1 Devesa S S, Blot W J, Fraumeni J F Jr. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. Cancer 1998; 83 (10): 2049–53.
2 Shaheen N J. Advances in Barrett's esophagus and esophageal adenocarcinoma. Gastroenterology 2005; 128 (6): 1554–66.
3 Devesa S S, Blot W J, Fraumeni J F Jr. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. Cancer 1998; 83 (10): 2049–53.
4 Pera M, Manterola C, Vidal O, Grande L. Epidemiology of esophageal adenocarcinoma. J Surg Oncol 2005; 92 (3): 151–9.
5 Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun M J. Cancer statistics. 2007. CA Cancer J Clin 2007; 57 (1): 43–66.
6 Skandalakis J E, Ellis H. Embryologic and anatomic basis of esophageal surgery. Surg Clin North Am 2000; 80 (1): 85–155.
7 Hosch S B, Stoecklein N H, Pichlmeier U *et al.* Esophageal cancer: the mode of lymphatic tumor cell spread and its prognostic significance. J Clin Oncol 2001; 19 (7): 1970–5.
8 American Joint Committee on Cancer. Esophagus. In: AJCC, (ed.) AJCC Cancer Staging Manual, 6th edn. New York: Springer, 2002; 91.
9 Kimmey M B, Martin R W, Haggitt R C, Wang K Y, Franklin D W, Silverstein F E. Histologic correlates of gastrointestinal ultrasound images. Gastroenterology 1989; 96 (2 Pt 1): 433–41.
10 Mariette C, Balon J M, Maunoury V, Taillier G, Van Seuningen I, Triboulet J P. Value of endoscopic ultrasonography as a predictor of long-term survival in oesophageal carcinoma. Br J Surg 2003; 90 (11): 1367–72.
11 Rosch T. Endosonographic staging of esophageal cancer: a review of literature results. Gastrointest Endosc Clin North Am 1995; 5 (3): 537–47.
12 Murata Y, Suzuki S, Hashimoto H. Endoscopic ultrasonography of the upper gastrointestinal tract. Surg Endosc 1988; 2 (3): 180–3.
13 Ziegler K, Sanft C, Zeitz M *et al.* Evaluation of endosonography in TN staging of oesophageal cancer. Gut 1991; 32 (1): 16–20.
14 Tio T L, Coene P P, Schouwink M H, Tytgat G N. Esophagogastric carcinoma: preoperative TNM classification with endosonography. Radiology 1989; 173 (2): 411–7.
15 Heintz A, Hohne U, Schweden F, Junginger T. Preoperative detection of intrathoracic tumor spread of esophageal cancer: endosonography versus computed tomography. Surg Endosc 1991; 5 (2): 75–8.
16 Vilgrain V, Mompoint D, Palazzo L *et al.* Staging of esophageal carcinoma: comparison of results with endoscopic sonography and CT. AJR Am J Roentgenol 1990; 155 (2): 277–81.
17 Botet J F, Lightdale C J, Zauber A G, Gerdes H, Urmacher C, Brennan M F. Preoperative staging of esophageal cancer: comparison of endoscopic US and dynamic CT. Radiology 1991; 181 (2): 419–25.
18 Botet J F, Lightdale C. Endoscopic ultrasonography of the upper gastrointestinal tract. Radiol Clin North Am 1992; 30 (5): 1067–83.
19 Grimm H, Binmoeller K F, Hamper K, Koch J, Henne-Bruns D, Soehendra N. Endosonography for preoperative locoregional staging of esophageal and gastric cancer. Endoscopy 1993; 25 (3): 224–30.
20 Wang G Q, Jiao G G, Chang F B *et al.* Long-term results of operation for 420 patients with early squamous cell esophageal carcinoma discovered by screening. Ann Thoracic Surg 2004; 77 (5): 1740–4.
21 Kanamoto A, Yamaguchi H, Nakanishi Y, Tachimori Y, Kato H, Watanabe H. Clinicopathological study of multiple superficial oesophageal carcinoma. Br J Surg 2000; 87 (12): 1712–5.
22 van Sandick J W, van Lanschot J J, Kuiken B W, Tytgat G N, Offerhaus G J, Obertop H. Impact of endoscopic biopsy surveillance of Barrett's oesophagus on pathological stage and clinical outcome of Barrett's carcinoma. Gut 1998; 43 (2): 216–22.

23 Kato H, Momma K, Yoshida M. Early esophageal cancer: radiologic estimation of invasion into the muscularis mucosae. Abdom Imaging 2003; 28 (4): 464–9.
24 Fujita H, Sueyoshi S, Yamana H *et al.* Optimum treatment strategy for superficial esophageal cancer: endoscopic mucosal resection versus radical esophagectomy. World J Surg 2001; 25 (4): 424–31.
25 Shimada H, Nabeya Y, Matsubara H *et al.* Prediction of lymph node status in patients with superficial esophageal carcinoma: analysis of 160 surgically resected cancers. Am J Surg 2006; 191 (2): 250–4.
26 Endo M, Yoshino K, Kawano T, Nagai K, Inoue H. Clinicopathologic analysis of lymph node metastasis in surgically resected superficial cancer of the thoracic esophagus. Dis Esophagus 2000; 13 (2): 125–9.
27 Liu L, Hofstetter W L, Rashid A *et al.* Significance of the depth of tumor invasion and lymph node metastasis in superficially invasive (T1) esophageal adenocarcinoma. Am J Surg Pathol 2005; 29 (8): 1079–85.
28 Westerterp M, Koppert L B, Buskens C J *et al.* Outcome of surgical treatment for early adenocarcinoma of the esophagus or gastro-esophageal junction. Virchows Arch 2005; 446 (5): 497–504.
29 Rice T W, Blackstone E H, Goldblum J R *et al.* Superficial adenocarcinoma of the esophagus. J Thorac Cardiovasc Surg 2001; 122 (6): 1077–90.
30 Araki K, Ohno S, Egashira A, Saeki H, Kawaguchi H, Sugimachi K. Pathologic features of superficial esophageal squamous cell carcinoma with lymph node and distal metastasis. Cancer 2002; 94 (2): 570–5.
31 Soetikno R M, Gotoda T, Nakanishi Y, Soehendra N. Endoscopic mucosal resection. Gastrointest Endosc 2003; 57 (4): 567–79.
32 Seewald S, Ang T L, Soehendra N. Endoscopic mucosal resection of Barrett's oesophagus containing dysplasia or intramucosal cancer. Postgrad Med J 2007; 83 (980): 367–72.
33 Tokar J L, Haluszka O, Weinberg D S. Endoscopic therapy of dysplasia and early-stage cancers of the esophagus. Semin Radiat Oncol 2007; 17 (1): 10–21.
34 Overholt B F, Lightdale C J, Wang K K *et al.* Group for High-Grade Dysplasia in Barrett's Esophagus. Photodynamic therapy with porfimer sodium for ablation of high-grade dysplasia in Barrett's esophagus: international, partially blinded, randomized phase III trial. Gastrointest Endosc 2005; 62 (4): 488–98.
35 Foroulis C N, Thorpe J A. Photodynamic therapy (PDT) in Barrett's esophagus with dysplasia or early cancer. Eur J Cardiothorac Surg 2006; 29 (1): 30–4.
36 Pech O, Gossner L, May A *et al.* Long-term results of photodynamic therapy with 5-aminolevulinic acid for superficial Barrett's cancer and high-grade intraepithelial neoplasia. Gastrointest Endosc 2005; 62 (1): 24–30.
37 Van Laethem J L, Jagodzinski R, Peny M O, Cremer M, Deviere J. Argon plasma coagulation in the treatment of Barrett's high-grade dysplasia and in situ adenocarcinoma. Endoscopy 2001; 33 (3): 257–61.
38 Endo M, Yoshino K, Kawano T, Nagai K, Inoue H. Clinicopathologic analysis of lymph node metastasis in surgically resected superficial cancer of the thoracic esophagus. Dis Esophagus 2000; 13 (2): 125–9.
39 Fujita H, Sueyoshi S, Yamana H *et al.* Optimum treatment strategy for superficial esophageal cancer: endoscopic mucosal resection versus radical esophagectomy. World J Surg 2001; 25 (4): 424–31.
40 Liu L, Hofstetter W L, Rashid A *et al.* Significance of the depth of tumor invasion and lymph node metastasis in superficially invasive (T1) esophageal adenocarcinoma. Am J Surg Pathol 2005; 29 (8): 1079–85.
41 Westerterp M, Koppert L B, Buskens C J *et al.* Outcome of surgical treatment for early adenocarcinoma of the esophagus or gastro-esophageal junction. Virchows Arch 2005; 446 (5): 497–504.
42 Shimada H, Nabeya Y, Matsubara H *et al.* Prediction of lymph node status in patients with superficial esophageal carcinoma: analysis of 160 surgically resected cancers. Am J Surg 2006; 191 (2): 250–4.
43 Kodama M, Kakegawa T. Treatment of superficial cancer of the esophagus: a summary of responses to a questionnaire on superficial cancer of the esophagus in Japan. Surgery 1998; 123 (4): 432–9.
44 Pech O, May A, Rabenstein T, Ell C. Endoscopic resection of early oesophageal cancer. Gut 2007; 56 (11): 1625–34.
45 Pech O, May A, Gunter E, Gossner L, Ell C. The impact of endoscopic ultrasound and computed tomography on the TNM staging of early cancer in Barrett's esophagus. Am J Gastroenterol 2006; 101 (10): 2223–9.
46 Falk G W, Catalano M F, Sivak M V Jr., Rice T W, Van Dam J. Endosonography in the evaluation of patients with Barrett's esophagus and high-grade dysplasia. Gastrointest Endosc 1994; 40 (2 Pt 1): 207–12.
47 Scotiniotis I A, Kochman M L, Lewis J D, Furth E E, Rosato E F, Ginsberg G G. Accuracy of EUS in the evaluation of Barrett's esophagus and high-grade dysplasia or intramucosal carcinoma. Gastrointest Endosc 2001; 54 (6): 689–96.
48 Murata Y, Suzuki S, Ohta M *et al.* Small ultrasonic probes for determination of the depth of superficial esophageal cancer. Gastrointest Endosc 1996; 44 (1): 23–8.
49 Larghi A, Lightdale C J, Memeo L, Bhagat G, Okpara N, Rotterdam H. EUS followed by EMR for staging of high-grade dysplasia and early cancer in Barrett's esophagus. Gastrointest Endosc 2005; 62 (1): 16–23.
50 Hasegawa N, Niwa Y, Arisawa T, Hase S, Goto H, Hayakawa T. Preoperative staging of superficial esophageal carcinoma: comparison of an ultrasound probe and standard endoscopic ultrasonography. Gastrointest Endosc 1996; 44 (4): 388–93.
51 Waxman I, Raju G S, Critchlow J, Antonioli D A, Spechler S J. High-frequency probe ultrasonography has limited accuracy for detecting invasive adenocarcinoma in patients with Barrett's esophagus and high-grade dysplasia or intramucosal carcinoma: a case series. Am J Gastroenterol 2006; 101 (8): 1773–9.
52 May A, Gunter E, Roth F *et al.* Accuracy of staging in early oesophageal cancer using high resolution endoscopy and high resolution endosonography: a comparative, prospective, and blinded trial. Gut 2004; 53 (5): 634–40.
53 Nishi M, Omori Y, Miwa K. Japanese Research Society for Gastric Cancer. Japanese Classification of Gastric Carcimoma, 1st English edn. Tokyo: Kanehara, 1995.
54 The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. Gastrointest Endosc 2003; 58 (Suppl 6): S3–43.
55 Schlemper R J, Hirata I, Dixon M F. The macroscopic classification of early neoplasia of the digestive tract. Endoscopy 2002; 34 (2): 163–8.
56 Pech O, Gossner L, Manner H *et al.* Prospective evaluation of the macroscopic types and location of early Barrett's neoplasia in 380 lesions. Endoscopy 2007; 39 (7): 588–93.
57 Chemaly M, Scalone O, Durivage G *et al.* Miniprobe EUS in the pretherapeutic assessment of early esophageal neoplasia. Endoscopy 2008; 40 (1): 2–6.
58 Rampado S, Bocus P, Battaglia G, Ruol A, Portale G, Ancona E. Endoscopic ultrasound: accuracy in staging superficial carcinomas of the esophagus. Ann Thorac Surg 2008; 85 (1): 251–6.
59 Kawano T, Ohshima M, Iwai T. Early esophageal carcinoma: endoscopic ultrasonography using the Sonoprobe. Abdom Imaging 2003; 28 (4): 477–85.
60 Yanai H, Yoshida T, Harada T *et al.* Endoscopic ultrasonography of superficial esophageal cancers using a thin ultrasound probe system equipped with switchable radial and linear scanning modes. Gastrointest Endosc 1999; 44 (5): 578–82.
61 Catalano M F, Sivak M V Jr., Rice, T, Gragg L A, Van Dam J. Endosonographic features predictive of lymph node metastasis. Gastrointest Endosc 1994; 40 (4): 442–6.
62 Bhutani M S, Hawes R H, Hoffman B J. 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 (6): 474–9.
63 Nesje L B, Svanes K, Viste A, Laerum O D, Odegaard S. Comparison of a linear miniature ultrasound probe and a

radial-scanning echoendoscope in TN staging of esophageal cancer. Scand J Gastroenterol 2000; 35 (9): 997–1002.
64 Chen V K, Eloubeidi M A. Endoscopic ultrasound-guided fine needle aspiration is superior to lymph node echofeatures: a prospective evaluation of mediastinal and peri-intestinal lymphadenopathy. Am J Gastroenterol 2004; 99 (4): 628–33.
65 Shami V M, Villaverde A, Stearns L *et al.* Clinical impact of conventional endosonography and endoscopic ultrasound-guided fine-needle aspiration in the assessment of patients with Barrett's esophagus and high-grade dysplasia or intramucosal carcinoma who have been referred for endoscopic ablation therapy. Endoscopy 2006; 38 (2): 157–61.
66 Esaki M, Matsumoto T, Moriyama T *et al.* Probe EUS for the diagnosis of invasion depth in superficial esophageal cancer: a comparison between a jelly-filled method and a water-filled balloon method. Gastrointest Endosc 2006; 63 (3): 389–95.
67 Catalano M F, Sivak M V Jr., Bedford, R A *et al.* Observer variation and reproducibility of endoscopic ultrasonography. Gastrointest Endosc 1995; 41 (2): 115–20.
68 Fockens P, Van den Brande J H, van Dullemen H M, van Lanschot J J, Tytgat G N. Endosonographic T-staging of esophageal carcinoma: a learning curve. Gastrointest Endosc 1996; 44 (1): 58–62.