CLINICAL PRACTICE UPDATE

AGA Clinical Practice Update on the Utility of Endoscopic Submucosal Dissection in T1b Esophageal Cancer: Expert Review

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Among esophageal neoplasms, the 2 most common cancers by cell type are squamous cell carcinoma (ESCC) and adenocarcinoma (EAC). Whereas ESCC is the most common type of cancer worldwide,[1] EAC is more prevalent than ESCC in the Western world, especially in North America.[2]

During the last 2 decades, EAC has shown an increasing trend in incidence of diagnosis. Yet overall survival for EAC remains disappointing with a poor 5-year survival rate. Early stage EACs (T1a and T1b) have a much better prognosis than late stage EACs. It is remarkable that these early staged cancers comprise approximately 20% of all cases of EAC diagnosed in the United States.[3]

Esophagectomy has been the mainstay for esophageal cancer (EC) but has high morbidity and mortality. Even a high volume center such as Mayo Clinic reported a surgical mortality of 4% for T1a esophageal cancer.[4] Moreover, 34% of patients developed postoperative complications such as anastomotic leaks, anastomotic strictures, cardiopulmonary complications, and feeding jejunostomy leaks.

The majority of patients who successfully undergo esophagectomy will experience gastroesophageal reflux symptoms[5] with the surgically absent lower esophageal sphincter, which brings a profound negative impact on their quality of life. Therefore, a less invasive alternative to esophagectomy would be extremely valuable in the management of early stage of EC if proven effective.

Endoscopic submucosal dissection (ESD) has been gaining momentum as an alternative to surgery in treating early gastrointestinal neoplasms. If ESD provides treatment as effective as surgical resection for T1b EC, the patients with T1b EC will benefit from a shorter hospital stay without diminished quality of life from new or increased reflux symptoms. On the other hand, if ESD for T1b EC is an inadequate treatment with a decreased survival rate when compared with esophagectomy, it should be discouraged as a primary form of therapy for these curable patients. The combination of ESD with adjuvant chemotherapy and radiation therapy may also prove to be better tolerated without the need for long recovery needed for surgical therapy.

Definition and Assessment of T1b Esophageal Tumor

Within early EC, tumors limited to mucosa are defined as T1a on the basis of TNM classification. T1b early EC is limited to the submucosa without any deeper invasion to the muscularis propria. T1b tumors can be subdivided into SM1, SM2, and SM3 tumors. SM1 tumors are limited to the superficial submucosa, with a limited depth of 200 μm or 500 μm for ESCC or EAC, respectively. SM2 and SM3 tumors are invading the submucosa, with a depth more than 200 μm for ESCC or more than 500 μm for EAC.[6,7]

The detection of early EC has improved because of the advances in optical imaging techniques such as narrow-band imaging (NBI), magnifying endoscopy, endomicroscopy, and chromoendoscopy. Lugol's iodine is a chromoendoscopy agent that is commonly used for the detection of ESCC. Lugol's iodine selectively stains normal squamous mucosa as dark brown, leaving precancerous and early cancerous lesions unstained, "void lesions". (Figure 1 illustrates early ESCC lesion seen by chromoendoscopy as Lugol's voiding lesion). Lugol's voiding lesions can be false positive for areas of neosquamous tissue and in certain well-differentiated squamous cell cancers, so careful observation and biopsy are still required. For better identification of margins within Barrett's esophagus, methylene blue or crystal violet is used. Both agents have affinity to intestinal epithelium within Barrett's esophagus, and they highlight dysplastic pit patterns within Barrett's epithelium.

Abbreviations used in this paper: AJCC, American Joint Committee on Cancer; CRT, chemoradiation; EAC, esophageal adenocarcinoma; EC, esophageal cancer; EMR, endoscopic mucosal resection; ESCC, esophageal squamous cell carcinoma; ESD, endoscopic submucosal dissection; EUS, endoscopic ultrasound; IPCL, intrapapillary capillary loop; LNM, lymph node metastasis; NBI, narrow-band imaging; RFA, radiofrequency ablation.

Most current article

1542-3565/$36.00
https://doi.org/10.1016/j.cgh.2019.05.045

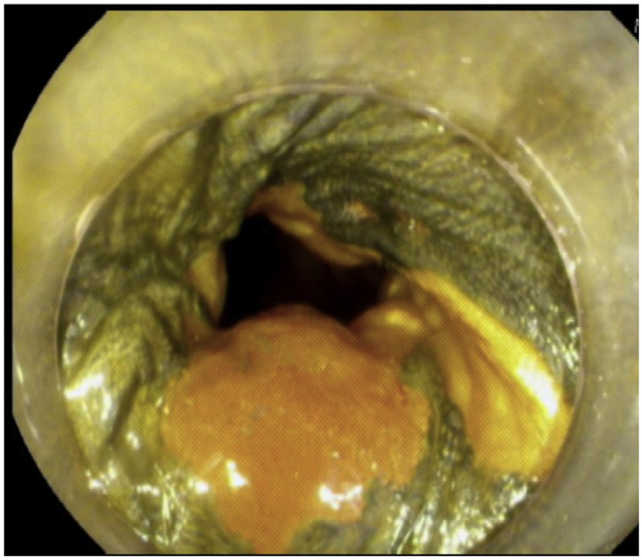

Figure 1. Early esophageal squamous cell carcinoma: Lugol's voiding lesion.

Recognizing features of deep invasion is important in assessing early EC and in differentiating T1b tumor from other stages of EC. Assessment of the depth of invasion by using endoscopy has been more rigorously investigated in ESCC as compared with EAC. In a retrospective analysis of 203 patients with ESCC, surface nodularity, granularity, deep depression, and thick notch (a very deep groove within a mass) were all associated with higher risk of deep invasion beyond the upper third of the submucosa (SM1).[8] Paris classification of lesion's morphology subdivided superficial tumors (Paris type 0) into 3 categories, type 0-I for protruding lesions, type 0-II for flat lesions, and type 0-III for excavated lesions. Paris type 0-II lesions can be subdivided into subtypes 0-II A, B, or C according to the degree of elevation/depression[7] (Figure 2). In ESCC, type 0-I protruding lesions and type 0-III excavated lesions carry the highest risk of deep submucosal invasion (79% and 84%, respectively).[9] This contrasts with the morphology of the lesions in the colon in which type 0-I protruding lesions are generally superficial. Japan Esophageal Society developed a NBI classification with magnified endoscopy to assist in prediction of depth of invasion for ESCC. The classification depends on the degree of microvascular irregularity in intrapapillary capillary loops (IPCLs). Generally speaking, IPCLs with irregularity, dilation, and loop-like formation are labeled as type B vessels (type A is normal IPCL pattern). When significant dilation, increase in caliber, or tortuosity is noted in type B vessels, the suspicion for tumor invasion into deep submucosa (SM2) increases. Type B vessels had 90.5% accuracy in estimating the depth of invasion in early ESCC.[10] It is worth mentioning that the unavailability of magnified endoscopy poses limitations for the application of NBI with magnified endoscopy classifications in many centers in the United States. Newer endoscopes are available with similar magnification systems as in Japan, which should improve the situation in the United States.

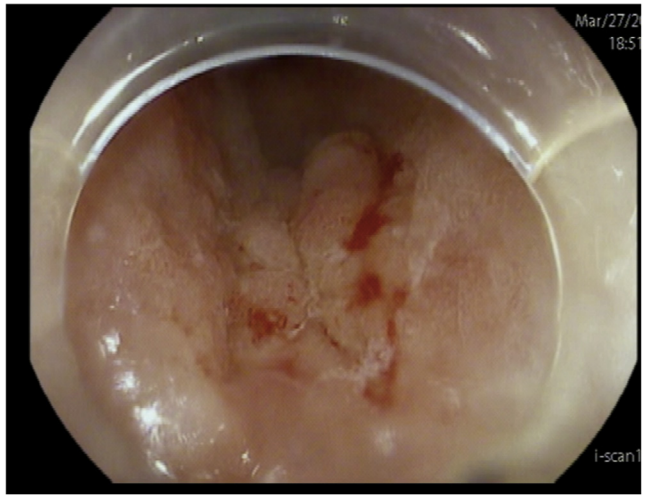

Figure 2. Paris type II A + C esophageal adenocarcinoma.

Endoscopic ultrasound (EUS) can overstage neoplasia in Barrett's esophagus, especially T1b tumors. In a meta-analysis of 11 studies that evaluated the diagnostic accuracy of EUS in staging patients with Barrett's esophagus, the pooled false-positive rate was 35.85% (95% confidence interval, 25.3%–47.8%). In other words, 36% of patients diagnosed as having T1b lesions on EUS were found to have low-grade dysplasia, high-grade dysplasia, or T1a tumor on histology.[11] Similar findings were also noted in ESCC. In a retrospective study of 174 patients with ESCC, NBI was shown to have higher accuracy than EUS in differentiating tumors limited to superficial mucosa compared with tumors with muscularis mucosa or SM1 invasion.[12] (Figure 3 illustrates a T1b lesion on EUS.)

Computed tomography scan with positron emission tomography for early stage cancer does not appear to be needed, although it is often recommended as part of EC staging and work-up. In particular, benign lesions that are found during initial staging often can be confounders, and the evaluation of these lesions can delay needed therapy.[13] At the current time, imaging of the submucosa is clinically best done with EUS, although there are suggestions that volume laser endomicroscopy using infrared light appears to be capable to discern the submucosal presence of disease and may be more accurate in determining submucosal invasion.[14]

Risk of Lymph Node Metastasis in T1b Tumor

The risk of lymph node metastasis (LNM) depends on the depth of invasion, histologic type, and molecular characterization of the tumor. Table 1 summarize predictors of higher risk for lymph node metastasis in esophageal cancer. For T1a EAC, lymph node involvement is rarely seen regardless of the depth of invasion in the mucosa. Early ESCC limited to the epithelium (M1) or to the lamina propria (M2) has a negligible risk for LNM. However, there is a slight increase in LNM in ESCC

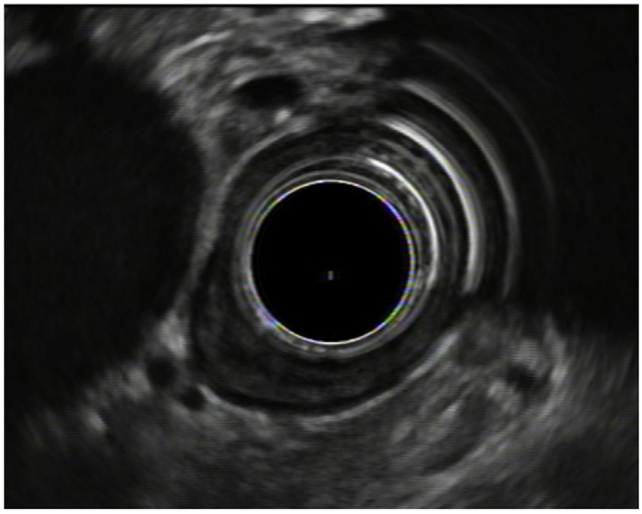

Figure 3. Radial endoscopic ultrasound showing esophageal lesion involving the submucosa (T1b).

invading into deep mucularis mucosa (M3 lesions), which is estimated to be ~10% in published literature.[15,16] Therefore, the majority of T1a tumors are considered curable by endoscopic resection, with a favorable 5-year survival rate as seen in multiple Japanese studies. In ESCC, T1b lesions with SM1 invasion have a relatively low risk of LNM (8%–26.5%), whereas T1b lesions with SM2 invasions have a significantly higher LNM risk, up to 60%.[10] Well-differentiated T1b EAC with tumor size smaller than 2 cm had a low risk of LNM (4.2%) in 782 patients who underwent esophagectomy in the United States. Tumors that were poorly differentiated and/or larger than 2 cm had a higher rate of LNM in the same cohort.[17] In a similar cohort of 90 patients who underwent esophagectomy for T1 EAC at M. D. Anderson, Houston, TX, LNM was noted in 8% of patients who had tumor invading into the superficial submucosa. When lesions were stratified by tumor size, 75% of T1b tumors larger than 1.2 cm had LNM.[18] In a meta-analysis of 7645 patients who had T1b early EC, the risk of LNM was dependent on the depth of invasion within the submucosa and the histology of the tumor. EAC patients with SM1 tumor had the lowest LNM (6%), whereas ESCC patients with SM3 had the highest LNM (55%). Overall, the rate of LNM was higher in SM1 and SM2 ESCC patients compared with that of EAC patients. In addition, micrometer-based assessment for depth of invasion can be more difficult to obtain in U.S. centers and should be discussed with pathologists when beginning endoscopic resections.[19] Emerging studies showed that several immunohistochemistry markers are associated with higher LNM such as E-cadherin and cyclin D1.[20]

It is worth noting that the muscularis mucosa could be duplicated or trifurcated in Barrett's esophagus. This may result in overstaging of tumor by EUS or when evaluating specimens removed by endoscopic mucosal resection (EMR). Early studies suggested that the space between the duplicated muscularis mucosa could be as rich in lymphatic channels as submucosal space.[21] However, more recent analysis of the duplicated area suggests that the lamina propria of this region is similar to the mucosa. In retrospective analysis of 99 patients who underwent esophagectomy for early EAC, 41 patients had duplicated muscularis mucosa. In this cohort, the risk of LNM was similar between tumor invading into the space between the duplicated muscularis mucosa and tumor limited to mucosa (T1a). This finding suggests that tumor invading into the duplicated muscularis mucosa space should be classified as T1a tumor rather than T1b tumor.[22] Overall, the data mentioned above suggest that well-differentiated, small (less than 2 cm) T1b early EC localized to SM1 and without lymphovascular invasion on the resected specimen is the ideal scenario for endoscopic treatment alone. Table 2 summarize risk of LNM in submucosal esophageal cancer based on cancer type.

Staging for Early Staged Cancers

As noted by the American Joint Committee on Cancer (AJCC), current guidelines would suggest that the early stage cancers are T1a or T1b cancers, depending on their grade, which has become a new modifier in the AJCC. The grading system is categorized as GX for tumors in which differentiation cannot be assessed, G1 for well-differentiated tumors, G2 for moderately differentiated tumors, and G3 for poorly differentiated tumors.

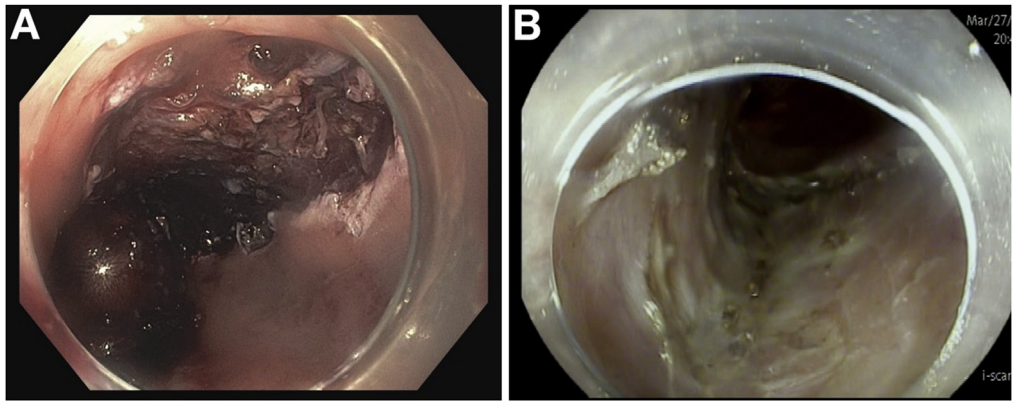

Figure 4. Post–endoscopic submucosal dissection resection of T1b lesion with central fibrosis and exposure of few muscularis propria fibers in (*A*) lesion A and (*B*) lesion B.

Table 1. Predictors of Higher Risk of Lymph Node Metastasis in Esophageal Cancer

Factors	
Tumor size	Tumors larger than 2 cm
Morphology	Paris type 0-I protruded lesions
	Paris type 0-III excavated lesions
Narrow-band imaging	Type B 3 IPCL pattern in ESCC
	Avascular area
Histology	Poorly differentiated tumors
	LVI on resected specimen
Depth of invasion	ESCC tumors with submucosal invasion >200 μm
	EAC tumors with submucosal invasion >500 μm
Biological markers	E-cadherin
	Cyclin D1

EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; IPCL, intrapapillary capillary loop; LVI, lymphovascular invasion.

Differentiation is assessed by the percentage of well-formed gland in the tumor (>95% in differentiated tumors and <50% in poorly differentiated tumors).[23] The grade of the cancer as determined by histopathology also now impacts overall staging. Higher-grade tumors including grade 2 to 3 cancers that are T1a would be staged as stage 1b cancer. Grade 1 cancers that are T1a would continue to be staged as stage 1a tumors. If they are T1b lesions that extend into the submucosa, they are all staged as stage 1b lesions. This is not location specific even in the setting of squamous cancers.

Survival Data for Patients With T1b Early Esophageal Cancer Who Underwent Endoscopic Resection Versus Esophagectomy

Endoscopic resection can be accomplished by either EMR or ESD. EMR has an inherent limitation of not being able to provide an accurate assessment of the lateral margins in piecemeal resection specimens, whereas ESD can provide en bloc specimens regardless of tumor size with lower residual and local recurrences. In addition to its therapeutic role, ESD is considered as a diagnostic tool. After obtaining a pathologic diagnosis with endoscopy and biopsy, ESD can accurately upstage or downstage the tumor pathology on the basis of careful examination of the entire resected tumor.[24] For T1b EC, however, esophagectomy remains the mainstay treatment because the prevalence of LNM in these patients is not negligible.

Table 2. Risk of Lymph Node Metastasis in Submucosal Esophageal Cancer Based on Cancer Type[19]

Depth of invasion	ESCC (%)	EAC (%)
SM1	27	6
SM2	36	23
SM3	55	58

EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; SM, submucosa.

A study specifically reported outcomes on clinical T1bN0M0 ESCC in 173 patients where 102 of 173 were treated with radical esophagectomy and the rest with definitive chemoradiation (CRT). The 3- and 5-year survival rates were 87.0% and 77.7% for the surgery group and 77.8% and 68.6% for the CRT group, respectively. The surgery group had disease recurrence in 12 patients (11.8%) and the CRT group in 20 patients (28.2%).[25]

ESD data on adenocarcinoma of the esophagus is sparse. A comparative retrospective study involving 79 patients with Siewert type II adenocarcinoma showed a 5-year overall survival rate of 93.9% for ESD group (40) and 97.3% for the surgery group (39) ($P = .376$). The treatment-related adverse events were similar in the 2 groups (10.0% vs 17.9%, $P = .308$), with no mortality in either group. Of all the tumors, 46 (58.2%) were well-differentiated, and 33 (41.8%) were moderately differentiated adenocarcinomas, with 64 (81.0%) T1a and 15 (19.0%) T1b. Synchronous or metachronous lesions developed in 4 patients in ESD group.[26] (Figure 4 highlights post-ESD resection of T1 b lesions with central fibrosis and exposure of few muscularis propria fibers.)

Combination of Endoscopic Submucosal Dissection With Other Treatment Modalities for Patients With T1b Early Esophageal Cancer

Endoscopic treatment of T1b EC followed by CRT in patients who decline or are unfit for surgery has been reported. In a retrospective study of 66 patients with ESCC (T1b lesions, 65%) who underwent endoscopic resection followed by CRT, the 3- and 5-year survival rates were 87% and 75%, respectively, which is similar to survival rates after esophagectomy. Six of 36 patients with LNM had metastatic recurrence, whereas none of the 30 patients without LNM had metastatic recurrence.[27] Another retrospective study compared ESD with CRT with CRT only in 47 patients with early ESCC. The 3-year overall survival rate in ESD with CRT group was 90% compared with 63.2% in the CRT only group. Recurrence was seen in 6.3% of patients in ESD CRT group compared with 29.0% for CRT group alone.[28] The aforementioned data are promising, and more data are expected to emerge regarding the role of ESD with CRT in EAC.

Combination of ESD with radiofrequency ablation (RFA) to achieve complete clearance of dysplasia in EAC has been reported in the literature. Subramaniam et al[29] evaluated the efficacy of ESD followed by RFA for eradication of dysplasia in a retrospective trial of 27 patients with Barrett's esophagus and high-grade dysplasia or

EAC (2 of them had T1b tumor). Clearance of dysplasia was achieved in 26 patients (96%), and clearance of intestinal metaplasia was achieved in 23 patients (85%). Similar results were seen in a prospective single center trial in which eradication of intestinal metaplasia was achieved in 8 of 10 patients with EAC who underwent ESD followed by RFA. Generally, 1–2 sessions of RFA were sufficient for eradication of intestinal metaplasia.[30]

Recommendations

At this time on the basis of a systematic review of the literature, we believe that ESD or EMR can be successfully applied to submucosal invasive cancers that have a low risk of metastatic potential. Overall, the risk of metastasis is higher in submucosal SCC in comparison with that of submucosal adenocarcinoma. Staging of these tumors should be conducted with EUS, although the accuracy of EUS in discerning the depth of invasion is limited. Additional treatment should be determined by factors such as tumor grade, status of lymphovascular invasion, and depth of tumor, which have a direct influence on metastatic potential. In those patients with submucosal invasion and risk factors, adjuvant chemotherapy and radiation may mitigate metastatic potential. Future research should focus on novel biological and immunohistochemistry markers that can aid in the prediction of tumor behavior and LNM in T1b esophageal cancer.

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Acknowledgment
This expert review was commissioned and approved by the AGA Institute Clinical Practice Updates Committee (CPUC) and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership, and underwent internal peer review by the CPUC and external peer review through standard procedures of Clinical Gastroenterology and Hepatology.

Conflicts of interest
These authors disclose the following: Mohamed Othman has been a consultant for Olympus, Boston Scientific, Lumendi, and Aries Pharmaceutical. Kenneth Wang has received research funding from Fujinon and has been a consultant for Olympus. The remaining author discloses no conflicts.