Management of superficial esophageal cancer

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INTRODUCTION

The epidemiology of esophageal cancer has evolved over the last two decades. Although the most marked change is a reversal in the ratio of squamous cell cancers to adenocarcinomas [1], there has also been a shift in stage distribution. The incidence of superficial esophageal cancer (invading no deeper than the submucosa) is increasing, particularly in Asian countries where screening for upper digestive tract cancers is common [2-4]. A similar trend has been seen in the United States and attributed, at least in part, to routine endoscopic surveillance for malignancy and high-grade dysplasia (HGD) in patients with Barrett's esophagus, a complication of longstanding gastroesophageal reflux disease [5-7]. (See "Barrett's esophagus: Pathogenesis and malignant transformation" and "Barrett's esophagus: Surveillance and management" and "Epidemiology and pathobiology of esophageal cancer".)

For many years, the standard treatment for both HGD and superficial esophageal cancer has been esophagectomy. High cure rates were achieved but at the cost of treatment-related morbidity and mortality. Endoscopic approaches to definitive therapy (eg, endoscopic resection) have increasingly been used in this country following encouraging early reports from Japan and Europe. However, these techniques are only appropriate for patients who have a very low risk of lymph node metastases or who are poor candidates for esophageal surgery.

This topic review will focus on treatment strategies for superficial esophageal cancer. The epidemiology, clinical presentation, diagnosis, and staging of esophageal cancer; surgical techniques for esophagectomy; and combined modality approaches for the treatment of

muscle-invasive disease are discussed in detail elsewhere. (See "Epidemiology and pathobiology of esophageal cancer" and "Clinical manifestations, diagnosis, and staging of esophageal cancer" and "Endoscopic ultrasound for evaluating patients with esophageal cancer" and "Surgical management of resectable esophageal and esophagogastric junction cancers" and "Radiation therapy, chemoradiotherapy, neoadjuvant approaches, and postoperative adjuvant therapy for localized cancers of the esophagus".)

INITIAL ASSESSMENT

A critical component of choosing the appropriate management strategy for a superficial esophageal cancer is an accurate assessment of disease extent. Submucosal involvement is the most important prognostic determinant for early esophageal cancers because the presence of lymphatic vessels within the submucosa facilitates dissemination of cancer cells. Thus an accurate assessment of tumor extent is needed to direct therapy. For most patients, this entails endoscopic resection (ER), high-frequency endoscopic ultrasound, and in selected cases, integrated positron emission tomography (PET)/computed tomography (CT) using fluorodeoxyglucose (FDG).

Pathologic subclassification and the risk of nodal metastases — Early esophageal cancers are those that are classified as Tis (high-grade dysplasia [HGD], which includes all noninvasive neoplastic epithelial that was formerly called carcinoma in situ) or T1 tumors, which are split into T1a and T1b subcategories depending on the depth of invasion (table 1) [8]. The risk of nodal metastases is higher for T1b than for T1a tumors [9,10]. In one series, of 3963 patients derived from the National Cancer Database (NCDB) who were treated surgically for localized esophageal cancer, the risk of nodal metastases for T1a and T1b tumors was 5 versus 16.6 percent [9].

However, this classification by itself is inadequate to distinguish clinically meaningful differences in lymph node involvement among T1a versus T1b esophageal cancers [11]. There are two main strategies to further refine the assessment of nodal involvement: subclassification of tumor (T) status, and use of pathologic factors other than depth of invasion. (See "Clinical manifestations, diagnosis, and staging of esophageal cancer".)

More comprehensive T stage subclassification — A more comprehensive subclassification scheme has been proposed by Japanese investigators for early esophageal cancers and is useful for determining prognosis and selecting treatment (figure 1) [12,13]. According to this classification, mucosal tumors are divided into three types based on the depth of invasion:

- M1 – Limited to the epithelial layer
- M2 – Invades the lamina propria
- M3 – Invades into but not through the muscularis mucosa

M1 tumors correspond to the Tis stage in the American Joint Committee on Cancer (AJCC) stage definition, while M2 and M3 tumors would be considered T1a lesions.

Tumors invading the submucosa are subclassified as follows [13]:

- SM1 – Penetrates the shallowest one-third of the submucosa
- SM2 – Penetrates into the intermediate one-third of the submucosa
- SM3 – Penetrates the deepest one-third of the submucosa

All of these subcategories would be considered T1b disease according to the AJCC stage definitions, regardless of histology (table 2 and table 3).

The incidence of lymph node metastases in published series of patients with early esophageal cancer, stratified according to depth of invasion, is summarized in the table (table 4) [12-21]. The following conclusions can be drawn from these data:

- Although there are fewer data on superficial adenocarcinomas, rates of nodal metastases are no higher [18] than with squamous cell carcinomas (SCCs), which have been more extensively investigated.

- M1 and M2 tumors are not associated with lymph node metastases and hence are well suited to endoscopic treatment.

- The risk of nodal metastases with M3 tumors is zero in many studies, but as high as 12 percent in others (table 4) [22]. Patients with evidence of lymphovascular invasion are the most likely to harbor lymph node metastases:

    - In a report of 464 consecutive patients with superficial esophageal cancer who underwent radical esophagectomy with node dissection, only four of the 38 patients with M3 lesions and no lymphatic invasion had lymph node metastases, whereas five of the 12 patients with lymphatic invasion were found to have nodal metastases [23].

    - In a second report of 402 patients with superficial esophageal SCC, the cumulative five-year metastasis rate (both lymphatic and distant) in patients with M3 cancers was 8.7 percent; among patients with mucosal cancer (M1, 2, or 3), the five-year rate of metastases with and without lymphovascular invasion was 47 versus 0.7 percent, respectively [21].

Thus, for patients with M3 tumors without evidence of lymphovascular invasion, endoscopic therapy is also a reasonable strategy [24-26].

- All submucosal tumors have a risk of lymph node metastases. Endoscopic mucosal resection (EMR) should be avoided in these patients, as it exposes the patients to an unacceptably high risk of both local and distant recurrence [26,27]. As an example, one series reported on outcomes after esophagectomy for 23 patients who had undergone an EMR for adenocarcinoma with submucosal involvement and negative margins [27]. Twenty-six percent had nodal disease at the time of esophagectomy, and 48 percent had residual disease in the resected specimen.

  However, this has not been seen in all series, particularly when patients were carefully selected for shallow invasion into the submucosa and otherwise favorable histologic features [28]. In this study of 66 patients who underwent endoscopic submucosal dissection (ESD) for low-risk T1b esophageal cancer (macroscopically polypoid or flat, good to moderate differentiation, no lymphovascular invasion), there were eight patients with noncurative resections and of the 53 who achieved a complete ER, 10 (19 percent) had residual/recurrent disease, predominantly amenable to further ER. Long-term remission was achieved by 51 of the 53 patients (96 percent) and only one patient developed a nodal metastasis.

  Available guidelines are disparate. While one guideline from Japan suggests that selected superficial submucosal esophageal squamous cell cancers with shallow invasion (SM1, defined as ≤200 micrometers in depth) may be considered for ESD by expert endoscopists [29], other guidelines suggest that the presence of any submucosal invasion should prompt esophagectomy, regardless of histology [30]. NCCN guidelines do not include endoscopic management as an option for T1b tumors, regardless of histology. In our view, esophagectomy with therapeutic lymphadenectomy provides the greatest chance for potentially curative therapy in this setting. (See 'Esophagectomy' below.)

Notably, most centers in North America have not adopted the Japanese classification system and instead rely on the broad AJCC T1a versus T1b classification scheme (any invasion of submucosa, regardless of depth) for superficial esophageal cancer (table 2 and table 3).

Other features — In addition to depth of invasion, other tumor features that may impact on the risk of lymph node metastases are macroscopic appearance of the lesion (flat-type versus non-flat [elevated, depressed, or ulcerated]), tumor size, the presence of lymphovascular invasion, and possibly histologic grade of differentiation [10,13,14,21,31-33]:

- In the Shimada series described above, the risk of positive nodes was significantly higher for non-flat type lesions as compared with flat-type lesions (37 versus 17 percent, respectively), while it was no different among patients with histologically poorly differentiated versus differentiated lesions (31 and 29 percent, respectively) [13]. Tumors with lymphatic invasion also had a higher rate of nodal metastases.

- On the other hand, in the NCDB series described above, predictors of nodal metastases other than depth of invasion included tumor size >2 cm and intermediate/high-grade (versus low-grade) lesions [9]. As an example, 0.5 percent of low-grade T1a lesions <2 cm had nodal metastases. Among T1b tumors, 17 percent of all patients had at least one positive node, which decreased to 8.9 percent for low-grade lesions <2 cm.

Accuracy of EUS in the staging evaluation — As noted above, the depth of invasion is an important indicator of the risk for nodal metastases in patients with superficial esophageal cancer. At present, endoscopic ultrasound (EUS) is the most accurate noninvasive method to assess depth of invasion (image 1). (See "Endoscopic ultrasound: Examination of the upper gastrointestinal tract" and "Endoscopic ultrasound for evaluating patients with esophageal cancer".)

The accuracy of EUS for T staging of superficial tumors has been controversial. While an earlier meta-analysis suggested that EUS may not be as accurate for T staging in patients with early esophageal cancer compared with those with more advanced tumors [34], a subsequent larger meta-analysis found that EUS was accurate for staging T1a and T1b tumors, with an area under the receiver operating characteristic (ROC) curve of 0.93 to 0.96 [35]. However, the accuracy of EUS for T staging of superficial tumors is highly dependent on operator experience and technique.

If the EUS identifies esophageal cancer that invades the muscularis mucosa or if there is evidence of lymph node involvement, then surgical therapy is often recommended. On the other hand, if the EUS identifies only mucosal disease and the patient is potentially eligible for endoscopic treatment, an ER is then performed to precisely define the depth of invasion. The pathology result from the ER (particularly the presence or absence of lymphovascular invasion) can be used to guide the final decision as to whether endoscopic therapy alone is sufficient or if surgery should be recommended.

This approach has been questioned by some who suggest that EUS should not be used to determine which patients should go to surgery and that instead all patients with an apparently superficial esophageal cancer should undergo careful endoscopic examination with ER without EUS. This position is supported by at least two retrospective studies suggesting that the

addition of EUS in this setting does not improve diagnostic accuracy of cancer invasion depth [36,37]. This subject is discussed elsewhere. (See "Endoscopic ultrasound for evaluating patients with esophageal cancer", section on 'EUS for T staging of superficial tumors'.)

Given that ER provides more precise histologic staging, EUS appears to be of diminishing importance in the diagnostic workup of a superficial esophageal cancer, except to exclude that there is not deeper involvement (ie, T3 or T4 disease) or lymph nodes. Upfront EUS may not be necessary if endoscopic inspection suggests that ER is feasible. If a diagnostic ER confirms a low-risk neoplasm, the additional impact of EUS is questionable. (See "Overview of endoscopic resection of gastrointestinal tumors".)

Utility of FDG-PET — For patients whose esophagogastroduodenoscopy (EGD) findings are more advanced than just a small solitary focus ≤15 mm) with no suspicion for locally advanced disease, we obtain a PET/CT if the results might impact therapy. Importantly, the results may be confusing if the PET/CT is done after EMR, and ideally this test should precede ER. On the other hand, if the initial EGD is suggestive of superficial or nonadvanced disease, we proceed directly to EUS to locally stage the tumor, and resect if the lesion meets criteria (ie, no submucosal invasion or suspicion for nodal disease).

There is no consensus as to the role of integrated FDG-PET/CT scan in the evaluation of patients with superficial esophageal cancer. National Comprehensive Cancer Network (NCCN) guidelines suggest obtaining FDG-PET/CT for all patients with esophageal cancer, but they do not provide specific guidance for superficial cancers [38].

Clinically based assessment modalities, including PET/CT, have low diagnostic performance in superficial esophageal cancer, particularly for detecting N1 disease [39]. The low sensitivity of FDG-PET in this setting is likely due to the small size of involved lymph nodes at diagnosis (median 3 mm in one study [40]).

However, the documented relationship between the depth of the primary tumor and risk for nodal metastases in superficial esophageal cancer has prompted investigations of the role of FDG positivity of the primary tumor site in predicting the risk for clinically occult nodal metastases:

- In an early Japanese report of 41 patients with superficial thoracic esophageal SCCs, 51 percent were FDG avid, including 68 percent of SM2/SM3 tumors and 15 percent of M1, M2, M3, or SM1 tumors [41]. FDG uptake correlated with both depth of tumor invasion and lymph node metastasis. Although no nodal metastases were detected by the FDG-PET, among the 13 patients with pathologically involved lymph nodes, FDG uptake in the primary tumor was the only identifiable risk factor for nodal metastasis.

- Others suggest that the extent of FDG uptake (as measured by the maximum standardized uptake value [SUV]) by the primary tumor may serve to differentiate tumors that are more versus less likely to have clinically occult nodal metastases. In this Japanese series, 40 consecutive patients diagnosed with clinical T1N0 superficial esophageal SCC underwent FDG-PET prior to esophagectomy with lymphadenectomy [42]. Tumors invaded the middle submucosal layer or beyond (SM2 or higher) in 53 percent, and six (15 percent) had lymph node metastases. Analysis of the areas under the ROC curves for the maximum SUV of the primary tumor was used to predict factors involved in tumor infiltration to SM2 or beyond or clinically occult nodal metastases. The optimal SUV cutoff was 2.7. Patients with a maximum SUV ≥2.7 were 20-fold more likely to have invasion to SM2 or beyond and were eightfold more likely to have pathologically involved nodes.

- In another report, 80 consecutive patients with superficial esophageal cancer had a pretreatment FDG-PET; 57 then underwent esophagectomy, and 23 had ER [43]. FDG uptake in the primary tumor correlated with depth of tumor invasion, lymph node metastasis, and lymphatic as well as vascular invasion. All patients with a ≥4.4 maximum SUV in the primary tumor had deeper invasion of the submucosa (SM2 to SM3 disease). Among the 16 patients who had pathologically node-positive disease at the time of esophagectomy, only two had lymph node metastases detected by FDG-PET.

TREATMENT

An algorithmic approach to treatment is provided (algorithm 1) and options are discussed in detail in the following sections.

Endoscopic therapy — For most patients who have favorable intramucosal tumors (ie, M1, M2, M3 without lymphovascular invasion), who are interested in an esophagus-sparing approach or are older adults with multiple comorbidities or otherwise high surgical risk, and who are treated by endoscopists with expertise in this technique, we suggest endoscopic resection (ER) rather than surgical resection. For fit patients with M3 disease and lymphatic invasion, esophagectomy is preferred over endoscopic therapy. (See 'More comprehensive T stage subclassification' above.)

The use of endoscopic therapy for T1 esophageal cancers has increased significantly over the past 15 years [44]. The aims of endoscopic therapy are to preserve the integrity of the esophagus while providing a potentially curative option for superficial cancers. Several recent reviews have highlighted the preference for endoscopic resection rather than radical surgery for appropriately selected patients with superficial esophageal cancer [45-47].

The available options are ER and various ablation methods, including RFA and cryotherapy. The below sections will focus on ER and other endoscopic treatments as alternatives to esophagectomy. The utility of other ablative methods (RFA, cryotherapy), instead of or in addition to ER for Barrett's esophagus and intramucosal carcinoma, is covered elsewhere. (See "Barrett's esophagus: Surveillance and management", section on 'High-grade dysplasia or intramucosal carcinoma'.)

Initial endoscopic resection — ER is a commonly performed (although not universally accepted [48,49]) alternative to surgery for the treatment of superficial esophageal cancer. Although preservation of the esophagus and reduced posttreatment mortality are major benefits, there is a lack of randomized trials comparing ER with esophagectomy and a limited number of studies reporting long-term follow-up data after ER.

Nevertheless, ER is a reasonable option for selected patients with superficial cancers that are limited to the mucosa (T1a (table 1)), and who are willing to trade ease of treatment and esophageal preservation for some level of uncertainty as to long-term outcomes and the potential need for multiple repeat endoscopies, or for those who are poor candidates for surgical resection. It is important to balance the risk of nodal metastases and procedural risk when counseling patients regarding their treatment options. The ideal candidate has a solitary, small (ie, <1.5 cm diameter) mucosal lesion without evidence of lymphovascular invasion (figure 1) within a short segment of Barrett's esophagus. Patients in whom a diagnostic ER is not feasible because of poor lifting, a sign of possible submucosal growth, should be referred for multidisciplinary evaluation.

ER is technically demanding and should be performed by expert endoscopists only in specialized centers that have integrated expertise in gastrointestinal endoscopy, imaging, surgery, and histopathology. (See "Barrett's esophagus: Treatment of high-grade dysplasia or early cancer with endoscopic resection".)

Procedures and efficacy — ER has become the most common treatment for T1a esophageal cancer in the United States [9]. With ER, the neoplastic epithelium is excised rather than ablated, thus allowing for a definitive histologic diagnosis. A variety of techniques are available, which are discussed elsewhere. (See "Barrett's esophagus: Treatment of high-grade dysplasia or early cancer with endoscopic resection" and "Overview of endoscopic resection of gastrointestinal tumors".)

In general, there are two procedures available for ER. Endoscopic mucosal resection (EMR) involves snare resection of dysplastic lesion. By contrast, for endoscopic submucosal dissection (ESD), endoscopic tools are used to dissect lesions from the submucosa. Lesions larger than 1.5

cm are difficult to treat with EMR since piecemeal resection is often necessary, which requires a higher level of endoscopic expertise, increases the risk of complications, and often makes it impossible to be conclusive about the completeness of the resection at the lateral margins. While ESD can remove larger lesions intact, expertise in this technique for esophageal lesions is less widely available. Nevertheless, at least some data suggest that where available, ESD is preferred over EMR [50]. (See "Overview of endoscopic resection of gastrointestinal tumors".)

An understanding of the efficacy of ER for management of superficial esophageal cancer is evolving. Most observational series contain a small number of patients with both high-grade dysplasia (HGD) and superficial cancer (mainly treated at large centers), and the duration of follow-up in many reports is limited. The following represents the range of findings:

- One of the largest series included 349 patients with Barrett's esophagus and either HGD (n = 61) or intramucosal adenocarcinoma (n = 288) who underwent ER [51]. Most were treated with ER alone (n = 279), but others received PDT (n = 55), both ER and PDT (n = 13), or APC (n = 2). At a mean follow-up of 63.1 months, a complete response was found in 96.6 percent (n = 337) of treated patients. Surgery was needed in only 3.7 percent after endoscopic therapy failed. Recurrences were noted in 21.5 percent (n = 74), but no patient died from esophageal cancer.

- In a meta-analysis of 21 studies of ESD for early esophageal cancer, the pooled en bloc resection rate was 99 percent [52]. The pooled complete (R0) resection rate was 90 percent (95% CI 87-94 percent) while for large tumors (diameter more than 25 mm) it was 85 percent (95% CI 80-90 percent). The most common complications of ESD were esophageal stenosis (5 percent; 95% CI 3-8 percent) and perforation (1 percent, 95% CI 0-1 percent). Of note, the incidence of esophageal stenosis significantly decreased in studies reported after 2011 (2 percent, 95% CI 0-3 percent, $p < 0.001$).

- The importance of patient selection can be illustrated by a retrospective series of 53 consecutive patients with intramucosal adenocarcinoma of the esophagogastric junction who underwent ESD between 2001 and 2007 at a single Japanese institution; median follow-up was 6.4 years [53]. Complete (R0) resections were accomplished in 42 (79 percent), and of these, 36 (68 percent of the total) were described as having a "potentially curative resection" (defined as an R0 resection and no lymphovascular involvement, only minute submucosal penetration, if present, ≤3 cm if well-differentiated type, and ≤2 cm if undifferentiated type). Of the 36 patients who underwent potentially curative resection, five-year cause-specific survival was 100 percent, and there were no recurrences or metastases detected. By contrast, 3 of the 17 patients with a noncurative resection recurred (17 percent), and two of the three died of their disease.

- The superiority of ESD or EMR was suggested in a multicenter retrospective analysis of 148 tumors in 132 patients, 80 treated with EMR and 68 with ESD [50]. The recurrence rate was higher with EMR (23.7 versus 2.9 percent), and five-year recurrence-free survival rates were worse (73.4 versus 95.2 percent).

- Some data suggest a higher rate of recurrence with squamous cell carcinoma (SCC) as compared with adenocarcinoma. In a study from Japan the cumulative five-year rate of recurrence was significantly higher with SCC compared with adenocarcinoma (32 versus 4.2 percent, p = 0.023) [54]. The authors suggest that more rigorous follow-up may be needed in patients after ER of esophageal SCC as compared with patients with adenocarcinoma.

These and other data on the efficacy of ER, and a more in depth discussion of ESD for Barrett's related HGD and early cancer are described in more detail elsewhere. (See "Barrett's esophagus: Treatment of high-grade dysplasia or early cancer with endoscopic resection", section on 'Efficacy'.)

Versus surgery — Although randomized trials are not available, the available evidence suggests that, in appropriately selected patients with early stage esophageal cancer (disease limited to the mucosa), the long-term outcomes with ER are comparable with those with surgical treatment, with fewer complications but (at least in some series) a higher recurrence rate. (See 'Pathologic subclassification and the risk of nodal metastases' above.)

- **Retrospective reports** – Several retrospective comparisons suggest that outcomes are similar for individuals with superficial tumors limited to the mucosa [55-58]. As examples:

  - Outcomes of ER and esophagectomy were compared among 114 patients with superficial esophageal cancer limited to the mucosa, 38 of whom underwent resection and 76 ER with argon-plasma coagulation of the remaining nondysplastic Barrett's [55]. As expected, procedure-related morbidity and mortality rates were higher after esophagectomy. At a median follow-up of 4.6 years, there was one recurrence and four metachronous neoplasms after ER (overall recurrence rate 6.6 percent) versus none after surgery. However, repeat endoscopic treatment was possible in all patients, and the long-term complete response rates were similar after ER and esophagectomy (98.7 and 100 percent, respectively).

  - Another retrospective series examined long-term outcomes of 178 patients with mucosal (T1a) esophageal cancers, 132 treated by ER and 46 by surgery [56]. Of the patients treated endoscopically, 57 had photodynamic therapy in addition to ER (see below). The cumulative mortality was no higher in the endoscopically treated group (17

versus 20 percent with esophagectomy). At a median follow-up of 43 months, 12 percent of the endoscopically treated group recurred, and all were successfully treated (with ER, esophagectomy, or chemoradiotherapy) without an adverse impact on overall survival.

- In a propensity matched retrospective trial comparing the outcomes of 46 esophageal squamous cell cancer patients with T1aM3-T1b stage who underwent ER plus adjuvant therapy to 92 patients who underwent esophagectomy there was no significant difference in overall survival up to three years [58]. Relapse-free survival and local recurrence rates were also similar between the two groups.

- **Database analyses** – Another source of information on the comparative efficacy of ER and esophagectomy for early esophageal cancer comes from analyses of the population-based cancer registry series, which have come to different conclusions:

  - A National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) registry review included 742 patients diagnosed with Tis or T1 nonsquamous and squamous cell esophageal cancer between 1998 and 2003 and reported to the SEER registry [59]. Endoscopic treatment (ER alone in two-thirds) was given to 99 patients (13 percent), while the remainder (n = 643) were managed by surgical resection. In a Cox proportional hazards model, the relative hazard for esophageal cancer-specific mortality in the patients treated by endoscopic therapy was not significantly worse (relative hazard 0.89, 95% CI 0.51-1.56, p = 0.68).

  - On the other hand, a higher long-term mortality rate for endoscopic therapy was suggested in a report derived from the National Cancer Database (NCDB) that included 3595 patients who had a clinical T1 tumor that was diagnosed between 2004 and 2014 and had detailed data on tumor stage (T1a [68 percent] or T1b [32 percent]) [44]. In the T1a subgroup, 46 percent were treated endoscopically, 15 percent had chemoradiotherapy, and 18 percent underwent esophagectomy. In the T1b subgroup, 23 percent had endoscopic treatment, 17 percent had chemoradiotherapy, and 51 percent underwent esophagectomy. Among the T1a patients, Kaplan-Meier analysis demonstrated no significant survival difference between endoscopic and surgical treatment, whereas both treatments conferred better survival over chemoradiotherapy alone. For the T1b patients, there was a trend toward better survival with esophagectomy and toward poorer outcomes with chemoradiotherapy compared with either endoscopic or surgical therapy.

- **Meta-analysis** – Additional information is available from a year 2021 meta-analysis, which included 15 reports (12 retrospective analyses, 3 database studies) totaling 2467 and 2264 patients who underwent ER or surgery for superficial esophageal cancer, respectively [60]. Patients undergoing ER had significantly fewer major adverse events (RR 0.46, 95% CI 0.33-0.64), lower procedure-related mortality rate, and a similar number of postprocedure stricture events (RR 0.89, 95% CI 0.53-1.49). However, those undergoing ER also had higher recurrence rates (RR 1.69, 95% CI 0.99-2.89), lower complete (R0) resection rates (RR 0.92, 95% CI 0.86-0.98) and modestly but significantly worse long-term survival rates (HR 1.21, 95% CI 1.02-1.43). A major flaw of this analysis was the absence of data on depth of invasion in both groups.

Plus RFA — The addition of radiofrequency ablation (RFA) to ER may allow for treatment of larger lesions with a lower recurrence rate; furthermore, for patients with extensive areas of Barrett's mucosa, it permits treatment of the whole Barrett's segment in one session. RFA for patients with Barrett's esophagus and dysplasia or intramucosal carcinoma is discussed in more detail elsewhere. (See "Barrett's esophagus: Treatment with radiofrequency ablation".)

Complications — Complications of ER include acute perforations and bleeding, and delayed esophageal strictures. Post-ER bleeding (typically managed by endoscopic methods) is reported in 3 to 33 percent of cases and may be more frequent if fluid is not used to lift the lesion before removal [61]. Strictures are more common after resection of circumferential resections and this complication must be considered when deciding upon ER, especially in longer lesions. (See "Barrett's esophagus: Treatment of high-grade dysplasia or early cancer with endoscopic resection", section on 'Complications'.)

Management of recurrent disease after endoscopic resection — A drawback of ER monotherapy for HGD or early esophageal cancer in Barrett's esophagus has been the high rate of recurrent/metachronous lesions during follow-up in some series (as high as 22 percent in the series described above [51]). Some argue that the majority of patients who recur can be salvaged with repeat ER, and they do not die of their disease [25,55,56,62,63]. As an example, Saeki and colleagues reported on the outcomes of esophagectomy in 40 patients after noncurative ER of deep T1a and superficial T1b lesions. There were no recurrences identified during follow-up, and five-year overall survival was 90 percent [62].

If endoscopic surveillance after ER demonstrates a local recurrence usually either esophagectomy or definitive radiotherapy (RT) or chemoradiotherapy is chosen as an appropriate treatment. Most patients should be re-staged with a PET/CT in that circumstance. Several reports indicate the majority of these patients can be salvaged. One Japanese study reported on 37 patients who had salvage RT (and 25 also had chemotherapy) after previous ER.

The five-year survival was 78 percent [64]. Another Japanese study reported on 160 patients after noncurative ER, 123 receiving chemoradiotherapy and 37 who underwent esophagectomy. The five-year disease specific survival was 100 percent with esophagectomy and 93 percent in the chemoradiotherapy group [65].

Esophagectomy — Esophagectomy is the treatment of choice for fit patients with superficial esophageal cancers invading the submucosa (T1b) (figure 1). Although the preferred treatment for intramucosal superficial cancers has previously been surgery, endoscopic resection (ER) is our preferred approach for patients with M1 and M2 tumors, as well as those with well-differentiated M3 disease without lymphovascular invasion (figure 1). Esophagectomy is still preferred for patients with intramucosal M3 carcinomas with lymphovascular invasion. In addition, we still recommend esophagectomy for persistent positive margins after endoscopic therapy, recurrences that cannot be endoscopically treated, long-segment lesions not amenable to endoscopic therapy, and rarely, patient preference. Because outcomes are directly related to surgeon as well as institutional experience, patients needing esophagectomy should be referred to a high-volume center that specializes in esophageal cancer care.

Prior to the emergence of endoscopic techniques, esophagectomy was the treatment of choice for superficial esophageal cancers. The potential advantages of esophagectomy include precise pathologic staging information, the permanent removal of all Barrett's mucosa at risk to develop a malignant focus, and treatment is definitive, without the need for posttreatment surveillance or salvage therapy in the event of a local recurrence. Among the disadvantages are an average 10-day hospital stay, a substantial risk of major complications, a small but real risk of perioperative death (approximately 2 percent in high-volume centers, see below), a recovery period that can take several months, and the potential for long-term problems with swallowing.

The volume-performance relationship — In the past, esophagectomy was associated with perioperative morbidity and mortality rates that were among the highest of all standard cancer operations as well as other major procedures such as cardiac or vascular surgery. As such, it earned a reputation as high-risk surgery, prompting reluctance on the part of clinicians to refer patients for resection, particularly if they had early-stage disease.

However, patients who undergo esophagectomy by experienced surgeons at hospitals that perform large numbers of procedures have lower perioperative mortality rates and better early clinical outcomes than those who undergo resection at lower-volume institutions [66-74]. In the most often-quoted study on the volume-performance relationship for esophagectomy, the Medicare claims database for 1998 and 1999 was analyzed to determine the relationship between surgeon and hospital volume and operative mortality [66]. In general, these were older

adult patients with significant comorbidity and usually advanced disease. Perioperative mortality rates were significantly related to surgeon volume: They were 19, 13, and 9 percent for surgeons performing fewer than two, between two and six, and more than six esophagectomies per year, respectively ($p < 0.001$). This effect held true even among low-volume surgeons working in high-volume hospitals.

There was also a significant correlation between hospital volume and perioperative mortality. When compared with the lowest volume hospitals (fewer than two procedures annually), the adjusted odds ratio for mortality for patients treated at the highest volume hospitals (more than 19 procedures annually) was 0.36 (95% CI 0.26-0.50). A second series found that high-volume hospitals were able to reduce their esophagectomy-related mortality over time (from 11 to 7.5 percent, $p = 0.003$), presumably from increasing experience with the procedure, while low-volume hospitals could not (procedure-related mortality rates were 15.3 versus 14.5 percent, respectively) [67]. Other reports document lower complication rates in high-volume hospitals and more successful management of complications compared with low-volume hospitals [68].

A meta-analysis sought to define the number of esophagectomies needed for a center to achieve an acceptably low mortality rate [69]. Hospitals that performed more than 20 resections per year had a perioperative mortality rate of only 4.9 percent, and the odds ratio of death for hospitals performing more than 20 resections per year compared with a lesser number was 0.43 (95% CI 0.31-0.58). Thus, a minimum of 20 esophagectomies per year has become a benchmark, with most large high-volume centers now reporting perioperative mortality rates in the range of 1 to 4 percent.

In summary, the weight of evidence supports the view that "practice makes perfect" in this high-risk, demanding operation. As such, the optimal management strategy is to refer patients needing esophagectomy to a high-volume center that specializes in esophageal cancer care. Nevertheless, a large proportion of esophagectomies in the United States are still performed in low-volume centers.

Outcomes — Several published reports detail outcomes from esophagectomy for superficial esophageal cancer (table 5) [2,9,11,12,75,76]. However, interpretation of these data is limited by high perioperative morbidity and mortality rates in many series, attributable both to the long time period over which cases were collected and to the volume-performance issues discussed above. Nonetheless, these reports provide an approximation of expected outcomes after esophagectomy in patients with superficial cancers. The following conclusions can be drawn:

- Results are much better than standard surgical series of esophagectomy for muscle-invasive cancers, where three to five-year survival rates are 25 to 30 percent. Likewise,

recurrence rates are relatively low, with most patients dying of other causes, again unlike standard surgical series. (See "Surgical management of resectable esophageal and esophagogastric junction cancers".)

- There is a clear difference in outcomes when mucosal and submucosal cancers are compared [16,77]. This is best illustrated by the series by Westerterp and colleagues which analyzed recurrence-free survival according to depth of invasion [16]. There was only one local recurrence among 79 patients with M1, M2, M3, or SM1 tumors (figure 1) (five-year recurrence-free survival 97 percent). Recurrence rates were higher among those with SM2 and SM3 tumors (8 of 41 patients, five-year recurrence-free survival 57 percent). In this series, 19 patients already had nodal metastases at the time the superficial cancer was diagnosed; their outcomes were significantly worse after resection than those for patients without nodal metastases (five-year recurrence-free survival 33 versus 94 percent).

Additional information can be derived from series of patients undergoing esophagectomy for a biopsy diagnosis of high-grade dysplasia (HGD; sometimes called high-grade esophageal intraepithelial neoplasia [HGIN]) in the setting of Barrett's esophagus. Typically, these patients (largely in the past) have not had endoscopic ultrasound (EUS) or ER, so they are often understaged. The high incidence of finding invasive cancer in the resected specimen (approximately 40 percent) in the past led many surgeons to recommend esophagectomy for fit patients with a diagnosis of HGD, although others suggest endoscopic surveillance every three months until invasive cancer is detected [78-86]. A modern approach is that a biopsy diagnosis of HGD typically leads to endoscopic staging with endoscopic mucosal resection (EMR) with or without EUS, and a consideration of endoscopic therapy alone if HGD or a T1a lesion is confirmed and complete eradication is thought to be possible. (See "Barrett's esophagus: Treatment of high-grade dysplasia or early cancer with endoscopic resection".)

Outcomes from esophagectomy can be illustrated in a series of 96 patients treated for HGD at a single institution, 49 treated by esophagectomy, and 47 by endoscopic techniques (photodynamic therapy [n = 42] or EMR [n = 5]) [82]. Invasive adenocarcinoma was present in 37 percent of the specimens. The mortality of esophagectomy was 2 percent, and there were three recurrences (6 percent), compared with seven in the endoscopically treated group (15 percent). Among surgically treated patients, the five-year survival rate was 83 percent, and the disease-specific survival was 94 percent. When the analysis was limited to patients found to have either HGD alone or invasive cancer limited to the mucosa or submucosa and uninvolved lymph nodes (n = 41), the disease-specific five-year survival rate was 100 percent.

Impact on health-related quality of life — Esophagectomy can result in long-term symptoms such as dysphagia, cough, and reflux, all of which may impair health-related quality of life (HR-

QOL) [87-89]. However, much of the data are in patients who have undergone esophagectomy for invasive esophageal cancer, many of whom have a low performance status at the time of surgery due to progressive dysphagia and weight loss.

HR-QOL in patients undergoing esophagectomy for HGD (noninvasive neoplastic epithelia) was explored in a cohort study of 36 patients treated at a single institution over a 12-year period who were found to harbor invasive cancer [87]. Patients were contacted by mail postoperatively, and 28 completed self-administered surveys to assess current gastrointestinal symptoms and HR-QOL parameters.

The minor and major (cervical anastomotic or thoracic duct leak) perioperative complication rates were 44 and 11 percent, respectively, and no patient died within 30 days of surgery. On the gastrointestinal symptom questionnaire, 22 patients (79 percent) reported their perception of eating as "normal" or "insignificantly impaired." However, 93 percent needed to eat more slowly postoperatively, 18 percent had heartburn, and dysphagia or regurgitation were reported by 54 and 54 percent, respectively. Despite this, when the results of the Medical Outcomes Study 36-item Short Form Health Survey were compared with norm-based values for age- and sex-matched controls from the 1998 United States general population, the post-esophagectomy population equaled or exceeded HR-QOL scores in seven of eight domains.

Minimally invasive esophagectomy — Minimally invasive esophagectomy (MIE), which is performed through laparoscopic and thoracoscopic techniques, is increasingly utilized for esophageal cancer resection in high volume institutions. The potential advantages of this approach relative to open esophagectomy include smaller incisions, less intraoperative blood loss, a reduction in some postoperative complications, decrease in intensive care and overall hospital stay, and better preservation of postoperative pulmonary function. MIE can be performed by conventional laparoscopy and thoracoscopy or can be performed with robot assistance. It is not clear currently which is better and there are strong proponents of each approach. The available literature on MIE is limited by the lack of robust prospective trials comparing minimally invasive with open esophagectomy, and there are few reports that address long-term oncologic outcomes. This subject is discussed in detail separately. (See "Surgical management of resectable esophageal and esophagogastric junction cancers", section on 'Minimally invasive approaches'.)

Radiation with or without chemotherapy — External beam radiation therapy (EBRT), with or without concurrent chemotherapy, and/or intraluminal brachytherapy are potentially useful alternatives for patients with superficial invasive cancer. However, the available data on long-term outcomes are limited, and the place of EBRT and chemoradiotherapy in the treatment of superficial esophageal cancer remains uncertain. In our view, patients who are best suited for

this approach are those who are candidates for ER but for whom this approach is contraindicated (eg, liver disease with extensive varices, previous perforation, severe cervical spine disease), and those who are candidates for esophagectomy, but deemed poor surgical candidates. An important point is that the severity of the liver disease may preclude even chemotherapy and RT [90-96].

Concurrent definitive chemoradiotherapy is considered a standard approach for patients with muscle-invasive squamous cell cancer who have a good response to therapy, but the adequacy of nonsurgical approaches for invasive adenocarcinomas remains controversial. (See "Radiation therapy, chemoradiotherapy, neoadjuvant approaches, and postoperative adjuvant therapy for localized cancers of the esophagus", section on 'Necessity for surgery'.)

Unfortunately, as with endoscopic ablation, this approach does not eliminate the risk of a local recurrence, which is higher for patients with submucosal (T1b) as compared with mucosal tumors (T1a) (table 1). The following represents the range of findings:

- In the largest series, 104 patients with superficial esophageal cancer underwent EBRT alone or with concurrent chemotherapy [90]. The one-, two-, and three-year survival rates for patients with disease limited to the mucosa were 95, 90, and 90 percent, respectively; the corresponding rates for those with submucosal involvement were 90, 81, and 70 percent, respectively. Patients who received chemotherapy had a better survival than did those treated with RT alone, although the difference was not statistically significant.

- The utility of chemoradiotherapy was further explored in a retrospective Japanese series of 173 endoscopic ultrasound (EUS)-staged patients with T1b squamous cell esophageal cancer, of whom 102 were treated with radical esophagectomy and 71 had definitive chemoradiotherapy [96]. Chemoradiotherapy consisted of EBRT (at least 50 Gy) with concurrent fluorouracil (FU) plus cisplatin. At a median follow-up of 65 months for surgically treated patients and 42 months for those who received definitive chemoradiotherapy, the difference in overall survival was potentially clinically meaningful but not statistically significant (three-year survival 87 versus 78 percent for surgically and nonsurgically treated patients, respectively). The frequency of positive nodes was high (20 percent) in the group of surgically staged patients with T1b SCC. Recurrences were more frequent following chemoradiotherapy (20 of 71 versus 12 of 102 patients [28 versus 12 percent]). Furthermore, although post-chemoradiotherapy local recurrences could be controlled by salvage esophagectomy, only 4 of 12 patients with lymph node recurrence were cured of their disease.

Whether brachytherapy adds benefit to EBRT alone is unclear [93,94,97]. The benefit of intraluminal brachytherapy was evaluated in series of 59 consecutive patients with submucosal esophageal cancer who were treated with EBRT without chemotherapy, 36 of whom also received brachytherapy [93]. Eight of the 23 patients treated with EBRT alone recurred locoregionally, compared with 6 of 36 in the combined treatment group (35 versus 17 percent). Overall, deaths were more frequently observed in the EBRT alone group, but the difference in disease-specific death rates between the EBRT and intraluminal brachytherapy groups was not statistically significant (39 versus 14 percent). Since this is not a randomized trial, the true contribution of brachytherapy to outcomes is uncertain.

A disadvantage of RT as a form of nonsurgical therapy is the need for prolonged treatment (typically approximately five weeks of daily treatment) as opposed to a single treatment for ER.

POSTTREATMENT SURVEILLANCE

The importance of prolonged follow-up, especially for patients treated with an endoscopic approach, cannot be overemphasized, as late recurrences may develop. These recurrences can usually be effectively treated if detected at an early stage.

There is no consensus as to the appropriate surveillance intervals. The following represents our approach, which is consistent with NCCN guidelines:

- **Tis or T1a with or without Barrett's esophagus s/p endoscopic resection or ablation** – Upper GI endoscopy (esophagogastroduodenoscopy [EGD]) every three months for the first year then every six months for the second year, then annually. If there is sustained eradication of invasive malignancy, surveillance can be stopped or intervals prolonged to every three to five years. Surveillance imaging studies are not recommended.

- **Tis or T1a s/p esophagectomy** – Patients with incompletely resected Barrett's esophagus should undergo ablation, and then endoscopic surveillance as described above. Otherwise, perform EGD as needed based on symptoms. Surveillance imaging studies are not recommended.

- **Pathologic (p) T1b disease (N0 by EUS) s/p endoscopic resection or ablation** – EGD every three months for the first year then every four to six months for the second year, then annually, indefinitely. Imaging (CT of the chest and abdomen with contrast, unless contraindicated) may be considered every 12 months for up to three years, and then as clinically indicated.

- **pT1b, any N** – For patients treated with esophagectomy, imaging (contrast-enhanced CT of the chest and abdomen) may be considered every 12 months for up to three years, if the patient is likely to tolerate additional curative-intent therapy for recurrence. Individuals with incompletely resected Barrett's esophagus should undergo ablation, and then EGD every three months for the first year then every four to six months for the second year, then annually for three more years. Otherwise, perform EGD as needed based on symptoms and radiographic findings.

  For individuals treated with chemoradiotherapy, EGD every three to six months for the first two years, then annually for three more years. Imaging (contrast-enhanced CT of the chest and abdomen, unless contraindicated) every six to nine months for the first two years, then annually up to five years. Patients who are candidates for salvage esophagectomy may also undergo periodic EUS as indicated based on imaging studies.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Esophageal cancer".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Esophageal cancer (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Definition** – Early (superficial) esophageal cancers are classified as Tis (high-grade dysplasia [HGD], which includes all noninvasive neoplastic epithelial neoplasia that was formerly called carcinoma in situ) or T1 tumors, which are split into T1a and T1b subcategories depending on the depth of invasion (table 1). The risk of nodal metastases is higher for tumors with submucosal invasion, especially those with deep submucosal invasion. (See 'Pathologic subclassification and the risk of nodal metastases' above.)

- **Initial assessment**

  - The two major treatment options for early esophageal cancer are esophagectomy and endoscopic resection (ER). An accurate assessment of tumor extent (particularly the depth of invasion into the wall of the esophagus) is needed to direct therapy. It is important to balance the risk of nodal metastases and procedural risk when counseling patients regarding their treatment options. An algorithmic approach to initial assessment and treatment selection is provided (algorithm 1), and summarized in the following bullets:

  - The depth of invasion is an important indicator of the risk for nodal metastases in patients with superficial esophageal cancer. At present, endoscopic ultrasound (EUS) is the most accurate noninvasive method to assess depth of invasion. (See 'Accuracy of EUS in the staging evaluation' above.)

    If the patient is a candidate for ER (small solitary focus ≤15 mm, no suspicion for submucosal invasion or nodal involvement), we suggest a diagnostic (and potentially therapeutic) ER to more accurately define the depth of invasion. The presence of submucosal invasion or muscularis mucosa invasion (ie, an M3 tumor) with lymphovascular invasion (figure 1) increases the risk for lymph node metastases, and these patients are not good candidates for endoscopic therapy alone. (See 'More comprehensive T stage subclassification' above.)

    For patients with larger tumors or suspicion for locally advanced disease, or if a diagnostic ER is not feasible because of poor lifting, a sign of possible submucosal invasion, EUS is indicated. (See 'Accuracy of EUS in the staging evaluation' above.)

    There is no consensus as to the role of integrated FDG-PET/CT in the evaluation of patients with superficial esophageal cancer. NCCN guidelines suggest obtaining FDG-PET/CT for all patients with esophageal cancer, but provide no specific guidance for superficial cancers. We obtain a PET/CT prior to EUS and endoscopic resection in all patients with tumors >15 mm or any suspicion for locally advanced disease, if the

results might impact therapy. If the PET/CT suggests disease that is limited to the mucosa, we then proceed to EUS to formally assess tumor stage. (See 'Utility of FDG-PET' above.)

- Other factors to consider in the selection of ER versus surgical treatment are lesion size, the presence of lymphovascular invasion, histologic grade of differentiation, the presence and extent of Barrett's mucosa, other esophageal pathology (particularly varices), comorbid medical conditions, patient age, local expertise, and patient preference. Regardless of the approach chosen, patients with superficial esophageal cancer are best treated in high-volume centers that specialize in treatment of esophageal cancer. (See 'Other features' above.)

- **Definitive treatment** – The following represents our general approach to treating superficial esophageal cancer (algorithm 1):

  - For fit patients with submucosal (T1b) (table 1) invasion, we recommend esophagectomy over ER, which will maximize the chance for cure (**Grade 1B**). (See 'Esophagectomy' above.)

  - For patients with M1 and M2 tumors, as well as those with well-differentiated M3 disease without lymphovascular invasion (LVI) (figure 1), who are interested in an esophagus-sparing approach or are older adults with multiple comorbidities or otherwise high surgical risk, and who are treated at institutions with expertise in this technique, we suggest ER rather than surgical resection (**Grade 2C**). (See 'More comprehensive T stage subclassification' above and 'Endoscopic therapy' above.)

    For fit patients with M3 disease and LVI, we suggest esophagectomy rather than ER. For poorer risk patients with M3 disease and LVI, ER may be used along with endoscopic ablation. This subject is discussed elsewhere. (See "Barrett's esophagus: Surveillance and management", section on 'High-grade dysplasia or intramucosal carcinoma'.)

  - Other indications for esophagectomy include persistent positive margins after ER, recurrences that cannot be endoscopically treated, long-segment intramucosal lesions not amenable to ER, and rarely, patient preference.

  - We reserve radiation therapy (RT) and/or chemoradiotherapy for patients with superficial esophageal cancer who are candidates for but ineligible for ER alone (eg, varices, previous perforation, severe cervical spine disease), for those unwilling/unable to travel to centers of excellence for treatment who can undergo RT closer to home,

and those who are poor surgical candidates. (See 'Radiation with or without chemotherapy' above.)

- **Posttreatment surveillance** – The importance of prolonged follow-up, especially for patients treated ER, cannot be overemphasized, as late recurrences may develop. These recurrences can usually be effectively treated if detected at an early stage. (See 'Posttreatment surveillance' above.)

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Topic 2494 Version 43.0

GRAPHICS

Esophagus and esophagogastric junction cancers TNM staging AJCC UICC 8th edition

Primary tumor (T), squamous cell carcinoma and adenocarcinoma	
T category	**T criteria**
TX	Tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia, defined as malignant cells confined to the epithelium by the basement membrane
T1	Tumor invades the lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades the lamina propria or muscularis mucosae
T1b	Tumor invades the submucosa
T2	Tumor invades the muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Tumor invades the pleura, pericardium, azygos vein, diaphragm, or peritoneum
T4b	Tumor invades other adjacent structures, such as the aorta, vertebral body, or airway
Regional lymph nodes (N), squamous cell carcinoma and adenocarcinoma	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastases in 1 or 2 regional lymph nodes
N2	Metastases in 3 to 6 regional lymph nodes
N3	Metastases in 7 or more regional lymph nodes
Distant metastasis (M), squamous cell carcinoma and adenocarcinoma	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastasis
Histologic grade (G), squamous cell carcinoma and adenocarcinoma	

G	G definition
GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated, undifferentiated

Location, squamous cell carcinoma

Location plays a role in the stage grouping of esophageal squamous cancers.

Location category	Location criteria
X	Location unknown
Upper	Cervical esophagus to lower border of azygos vein
Middle	Lower border of azygos vein to lower border of inferior pulmonary vein
Lower	Lower border of inferior pulmonary vein to stomach, including gastroesophageal junction

NOTE: Location is defined by the position of the epicenter of the tumor in the esophagus.

Prognostic stage groups, squamous cell carcinoma

Clinical (cTNM)

When cT is...	And cN is...	And M is...	Then the stage group is...
Tis	N0	M0	0
T1	N0-1	M0	I
T2	N0-1	M0	II
T3	N0	M0	II
T3	N1	M0	III
T1-3	N2	M0	III
T4	N0-2	M0	IVA
Any T	N3	M0	IVA
Any T	Any N	M1	IVB

Pathological (pTNM)

When pT is...	And pN is...	And M is...	And G is...	And location is...	Then the stage group is...
Tis	N0	M0	N/A	Any	0

T1a	N0	M0	G1	Any	IA
T1a	N0	M0	G2-3	Any	IB
T1a	N0	M0	GX	Any	IA
T1b	N0	M0	G1-3	Any	IB
T1b	N0	M0	GX	Any	IB
T2	N0	M0	G1	Any	IB
T2	N0	M0	G2-3	Any	IIA
T2	N0	M0	GX	Any	IIA
T3	N0	M0	Any	Lower	IIA
T3	N0	M0	G1	Upper/middle	IIA
T3	N0	M0	G2-3	Upper/middle	IIB
T3	N0	M0	GX	Any	IIB
T3	N0	M0	Any	Location X	IIB
T1	N1	M0	Any	Any	IIB
T1	N2	M0	Any	Any	IIIA
T2	N1	M0	Any	Any	IIIA
T2	N2	M0	Any	Any	IIIB
T3	N1-2	M0	Any	Any	IIIB
T4a	N0-1	M0	Any	Any	IIIB
T4a	N2	M0	Any	Any	IVA
T4b	N0-2	M0	Any	Any	IVA
Any T	N3	M0	Any	Any	IVA
Any T	Any N	M1	Any	Any	IVB

Post-neoadjuvant therapy (ypTNM)

When ypT is...	And ypN is...	And M is...	Then the stage group is...
T0-2	N0	M0	I
T3	N0	M0	II
T0-2	N1	M0	IIIA
T3	N1	M0	IIIB
T0-3	N2	M0	IIIB
T4a	N0	M0	IIIB

T4a	N1-2	M0	IVA
T4a	NX	M0	IVA
T4b	N0-2	M0	IVA
Any T	N3	M0	IVA
Any T	Any N	M1	IVB

Prognostic stage groups, adenocarcinoma

Clinical (cTNM)

When cT is...	And cN is...	And M is...	Then the stage group is...
Tis	N0	M0	0
T1	N0	M0	I
T1	N1	M0	IIA
T2	N0	M0	IIB
T2	N1	M0	III
T3	N0-1	M0	III
T4a	N0-1	M0	III
T1-4a	N2	M0	IVA
T4b	N0-2	M0	IVA
Any T	N3	M0	IVA
Any T	Any N	M1	IVB

Pathological (pTNM)

When pT is...	And pN is...	And M is...	And G is...	Then the stage group is...
Tis	N0	M0	N/A	0
T1a	N0	M0	G1	IA
T1a	N0	M0	GX	IA
T1a	N0	M0	G2	IB
T1b	N0	M0	G1-2	IB
T1b	N0	M0	GX	IB
T1	N0	M0	G3	IC
T2	N0	M0	G1-2	IC
T2	N0	M0	G3	IIA

T2	N0	M0	GX	IIA
T1	N1	M0	Any	IIB
T3	N0	M0	Any	IIB
T1	N2	M0	Any	IIIA
T2	N1	M0	Any	IIIA
T2	N2	M0	Any	IIIB
T3	N1-2	M0	Any	IIIB
T4a	N0-1	M0	Any	IIIB
T4a	N2	M0	Any	IVA
T4b	N0-2	M0	Any	IVA
Any T	N3	M0	Any	IVA
Any T	Any N	M1	Any	IVB
Post-neoadjuvant therapy (ypTNM)				
When ypT is…	**And ypN is…**	**And M is…**		**Then the stage group is…**
T0-2	N0	M0		I
T3	N0	M0		II
T0-2	N1	M0		IIIA
T3	N1	M0		IIIB
T0-3	N2	M0		IIIB
T4a	N0	M0		IIIB
T4a	N1-2	M0		IVA
T4a	NX	M0		IVA
T4b	N0-2	M0		IVA
Any T	N3	M0		IVA
Any T	Any N	M1		IVB

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control; N/A: not applicable.

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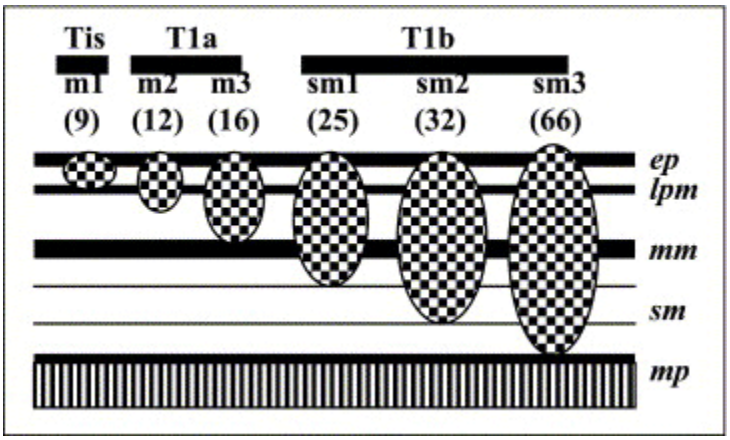
Graphic 111221 Version 9.0

Subclassification of the depth of superficial esophageal cancer (number of patients)



Subclassification of the depth of superficial esophageal cancer (number of patients) in a series of 160 patients with superficial esophageal cancer.

Ep: epithelial layer; lpm: lamina propria; mm: muscularis mucosa; sm: submucosa; mp: muscularis propria.

Graphic 64349 Version 5.0

TNM staging of esophageal and esophagogastric junction (EGJ) adenocarcinoma

Primary tumor (T)*	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia¶
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)Δ	
NX	Regional lymph node(s) 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
Anatomic stage/prognostic groups	

Adenocarcinoma carcinoma				
Stage	**T**	**N**	**M**	**Grade**
0	Tis (HGD)	N0	M0	1, X
IA	T1	N0	M0	1-2, X
IB	T1	N0	M0	3
	T2	N0	M0	1-2, X
IIA	T2	N0	M0	3
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

Note: cTNM is the clinical classification, pTNM is the pathologic classification.

---

* At least maximal dimension of the tumor must be recorded and multiple tumors require the T(m) suffix.

¶ High-grade dysplasia (HGD) includes all noninvasive neoplastic epithelia that was formerly called carcinoma in situ, a diagnosis that is no longer used for columnar mucosae anywhere in the gastrointestinal tract.

Δ Number must be recorded for total number of regional nodes sampled and total number of reported nodes with metastasis.

Graphic 52078 Version 7.0

TNM staging of esophageal squamous cell cancer (SCC)

Primary tumor (T)*	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia¶
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)Δ	
NX	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1 to 2 regional lymph nodes
N2	Metastasis in 3 to 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
Anatomic stage/prognostic groups	

Squamous cell carcinoma◇					
Stage	**T**	**N**	**M**	**Grade**	**Tumor location§**
0	Tis (HGD)	N0	M0	1, X	Any
IA	T1	N0	M0	1, X	Any
IB	T1	N0	M0	2 to 3	Any
	T2-3	N0	M0	1, X	Lower, X
IIA	T2-3	N0	M0	1, X	Upper, middle
	T2-3	N0	M0	2 to 3	Lower, X
IIB	T2-3	N0	M0	2 to 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

Note: cTNM is the clinical classification, pTNM is the pathologic classification.

---

* At least maximal dimension of the tumor must be recorded and multiple tumors require the T(m) suffix.

¶ High-grade dysplasia (HGD) includes all noninvasive neoplastic epithelia that were formerly called carcinoma in situ, a diagnosis that is no longer used for columnar mucosae anywhere in the gastrointestinal tract.

Δ Number must be recorded for total number of regional nodes sampled and total number of reported nodes with metastasis.

◇ Or mixed histology including a squamous component or not otherwise specified (NOS).

§ Location of the primary cancer site is defined by the position of the upper (proximal) edge of the tumor in the esophagus.

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Graphic 62895 Version 13.0

Incidence of lymph node metastases in superficial esophageal cancers according to depth of invasion

Author, year	Histology	n	Percent LN Mets, mucosal lesion			Percent LN Mets, submucosal lesion		
			M1	M2	M3	SM1	SM2	SM3
Endo M; 2000	Squam	236	0	0	8	11	30	61
Fujita H; 2001	Squam	150	0	0	4	25	22	40
Westerterp M; 2005	Adeno	120	0	0	4	0	26	67
Eguchi T; 2006	Squam	464	0	6	18	53	54*	54*
Shimada H; 2006	Squam	160	0	0	6	32	31	42
Ancona E; 2008	Adeno Squam	31 67	0	0	0	8	29	54
Hölscher A; 2011	Adeno Squam	121 50	0	0	0	13	19	56
Yamashina T; 2013	Squam	402	0.4¶	0.4¶	9	8	36	NR
Akutsu Y; 2013	Squam	295	0Δ	0Δ	9Δ	16Δ	35Δ	62Δ

LN: lymph node; Squam: squamous cell cancer; Adeno: adenocarcinoma; NR: not reported.

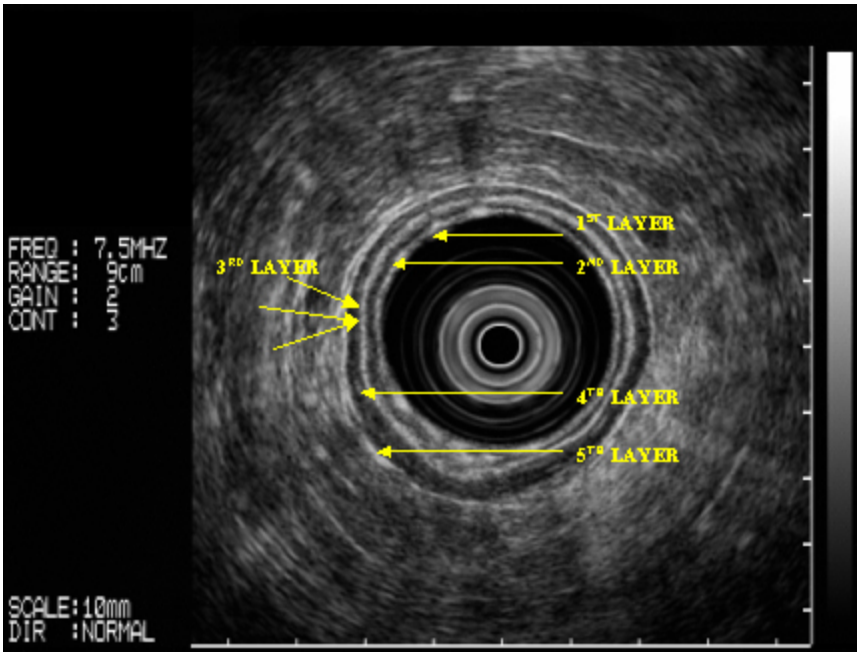
* SM2/SM3 combined.

¶ M1 and M2 combined; metastasis rate combined for nodal and distant spread.

Δ Risks for lymph node metastases (surgically treated patients) or lymph node recurrences (non-surgically treated patients).

Graphic 64478 Version 8.0

Endoscopic ultrasound (EUS) of normal esophagus

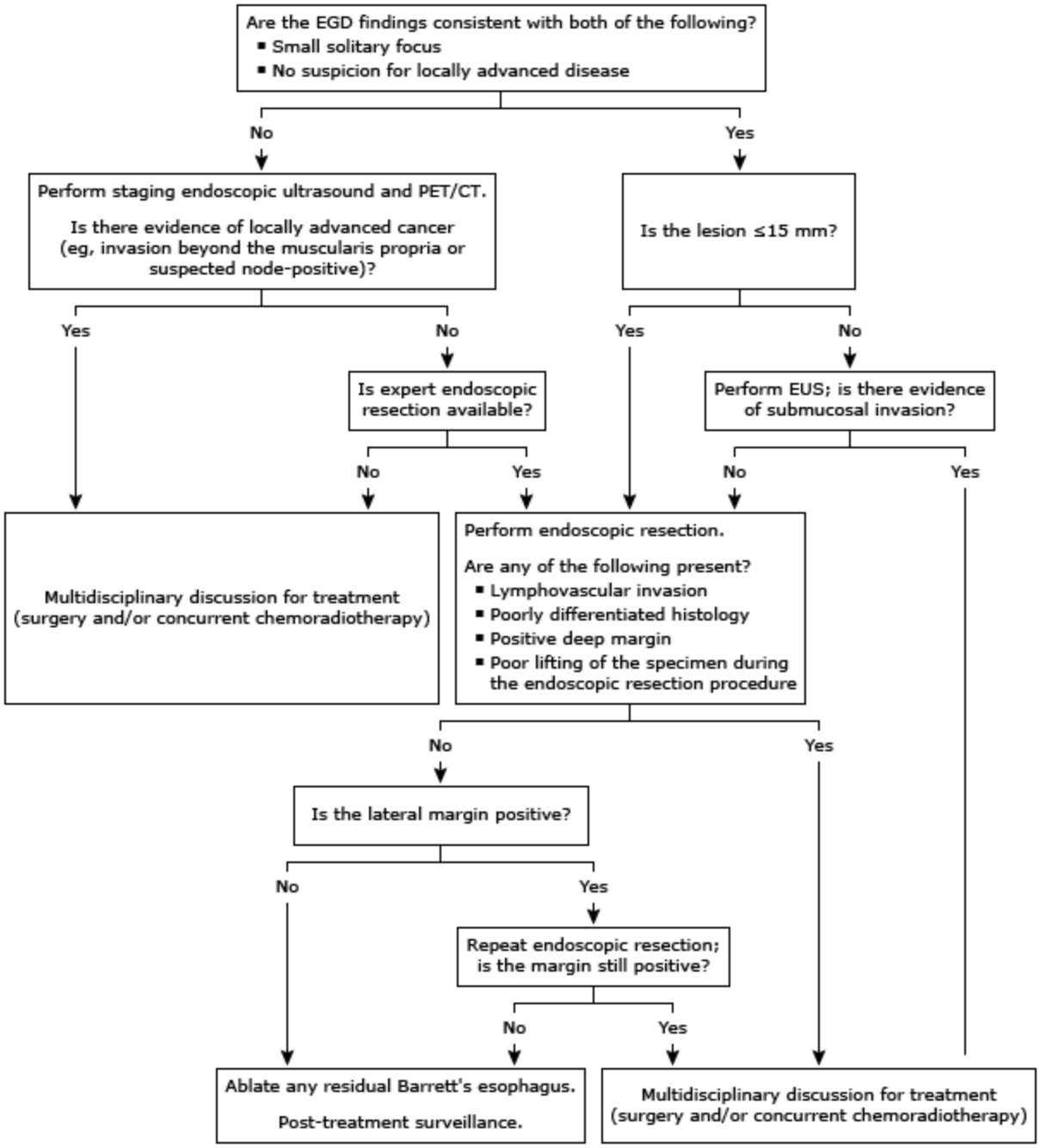


EUS examination of the normal esophagus showing the typical five-layer pattern: first hyperechoic layer (interface between lumen and mucosa), second hypoechoic layer (deep mucosa including muscularis mucosa), third hyperechoic layer (submucosa), fourth hypoechoic layer (muscularis propria), and fifth hyperechoic layer (adventitia interface).

Courtesy of Enrique Vazquez-Sequeiros, MD and Maurits J Wiersema, MD.

Graphic 73301 Version 4.0

Algorithmic approach to treatment of superficial esophageal cancer



EGD: esophagogastroduodenoscopy; PET/CT: positron emission tomography/computed tomography; EUS: endoscopic ultrasound.

Graphic 140122 Version 1.0

Esophagectomy outcomes in superficial esophageal cancer

Author, year (accrual time)	Patients	Histology	Mortality rate, percent	Survival (5-yr), percent	Recurrence rate, percent
Pennathur A; 2009 (1995 to 2004)	100	Squam (9) Adeno (91)	0	73 (T1a) 60 (T1b)	20
Barbour A; 2010 (1991 to 2008)	85	Adeno	0	97 (T1a) 70 SM1 60 SM2 71 SM3	11
Tanaka T; 2012 (1990 to 2008)	105	Squam (98) Adeno (7)	2	74	21

Squam: squamous carcinoma; Adeno: adenocarcinoma; NR: not reported; M: mucosal; SM: submucosal; Rad: radical en-bloc esophagectomy; Std: standard esophagectomy.

* Disease specific survival.

Graphic 59698 Version 6.0

Contributor Disclosures

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