Communication from the ASGE Standards of Practice Committee

The role of endoscopy in the assessment and treatment of esophageal cancer

This is one of a series of statements discussing the use of GI endoscopy in common clinical situations. The Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy (ASGE) prepared this text. This guideline updates a previously issued guideline on this topic.[1] In preparing this guideline, a search of the medical literature was performed by using PubMed. Additional references were obtained from the bibliographies of the identified articles and from recommendations of expert consultants. When few or no data exist from well-designed prospective trials, emphasis is given to results from large series and reports from recognized experts. Guidelines for appropriate use of endoscopy are based on a critical review of the available data and expert consensus at the time that the guidelines are drafted. Further controlled clinical studies may be needed to clarify aspects of this guideline. This guideline may be revised as necessary to account for changes in technology, new data, or other aspects of clinical practice. The recommendations are based on reviewed studies and are graded on the strength of the supporting evidence (Table 1).[2] The strength of individual recommendations is based on both the aggregate evidence quality and an assessment of the anticipated benefits and harms. Weaker recommendations are indicated by phrases such as "We suggest . . ." whereas stronger recommendations are typically stated as "We recommend . . ."

This guideline is intended to be an educational device to provide information that may assist endoscopists in providing care to patients. This guideline is not a rule and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment. Clinical decisions in any particular case involve a complex analysis of the patient's condition and available courses of action. Therefore, clinical considerations may lead an endoscopist to take a course of action that varies from these guidelines.

INTRODUCTION

The management of esophageal cancer remains clinically challenging, not only in terms of identifying patients at high risk, but also because of the overall poor prognosis of the disease. While cancers diagnosed through a Barrett's esophagus (BE) surveillance program may be early stage, most esophageal cancers are diagnosed after symptoms develop and tumors are locally advanced. In 2008, there were 16,640 new cases and 14,500 deaths due to esophageal cancer reported in the United States,[3] and there were an estimated 400,000 deaths caused by esophageal cancer worldwide.[4] This document is an update of the 2003 ASGE guidelines describing the endoscopic aspects of managing esophageal cancer and will discuss diagnosis, staging, endoscopic treatments, and palliation.[1]

RISK FACTORS FOR ESOPHAGEAL CANCER

Adenocarcinoma

Population-based studies from 2003 to 2007 estimate the incidence of esophageal adenocarcinoma (EAC) to be 5.31/100,000.[5] Men are 8 times more likely than women, and people in the white population are 5 times more likely than those in the African American population to be diagnosed with EAC. Major risk factors for EAC include BE, GERD, smoking, and obesity. GERD is associated with both EAC and gastric cardia malignancies (odds ratios [OR] 7.7 and 2.2, respectively), and patients with long-standing or severe GERD have a much higher risk of developing EAC (OR 43.5, 95% confidence interval [CI], 18.3-103.5) than the general population.[6] In a recent meta-analysis that pooled 10 population-based and 2 cohort studies, cigarette smoking conveyed an increased, dose-related risk for developing EAC (OR 1.96, 95% CI, 1.64-2.34).[7] Obesity as a distinct risk factor for EAC has recently been established. A body mass index of 25 kg/m^2 is associated with an OR for developing EAC of 1.52 (95% CI, 1.15-2.01), and a body mass index >30 kg/m^2 increases the OR to 2.78 (95% CI, 1.85-4.16).[8] Although erosive esophagitis is associated with alcohol ingestion, no large studies have identified alcohol use as a distinct risk factor for EAC, nor has alcohol intake been linked to BE.[9]

Squamous cell carcinoma

Squamous cell carcinoma (SCC) of the esophagus is the predominant histologic type of esophageal cancer outside the United States. Incidence rates in China are estimated to be as high as 140 per 100,000 in some provinces,[10] with similar rates seen in Africa and Iran.[4] In the United States,

TABLE 1. GRADE system for rating the quality of evidence for guidelines

Quality of evidence	Definition	Symbol
High quality	Further research is very unlikely to change our confidence in the estimate of effect.	⊕⊕⊕⊕
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.	⊕⊕⊕◯
Low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.	⊕⊕◯◯
Very low quality	Any estimate of effect is very uncertain.	⊕◯◯◯

Adapted with permission from Guyatt et al.[2]

the incidence is estimated to be 3/100,000 and is declining.[11] Men and women are affected equally in high-incidence areas, but in the United States, those of the African American population have a higher risk of developing SCC than those in the white population.[12-14] Alcohol use is a known risk factor for SCC when ingestion exceeds 170 g/week and the risk increases in a linear fashion with increasing consumption.[15] Smokers have a 9-fold risk of developing SCC over nonsmokers (hazard ratio 9.3, 95% CI, 4.0-21.3).[16] Other risk factors for SCC include tylosis,[17] a history of aerodigestive cancers,[18] a history of caustic ingestion,[19] and achalasia.[20] In developing nations, risk factors other than alcohol and tobacco include diets high in n-nitrosamines,[21] pickled vegetables,[22] and frequent ingestion of hot beverages.[23,24]

Diagnosis of esophageal malignancies

Malignancies of the esophagus are diagnosed via upper endoscopy with mucosal biopsies. The sensitivity for mucosal biopsies to detect esophageal carcinoma reaches 96% when multiple samples are obtained.[25-27] The use of large-capacity biopsy forceps does not improve the sensitivity.[28] Strictures may prevent complete visualization and sampling of the obstructing malignancy. In these instances, brush cytology can improve the diagnostic accuracy by 20%.[29] Transoral or transnasal ultrathin endoscopes also may be used for obstructing malignancies to visualize the extent and length of the tumor. The sensitivity of detecting early stage carcinoma may be improved by adjunct techniques such as chromoendoscopy, narrow-band imaging, confocal microscopy, spectroscopy, magnification endoscopy, and other advanced endoscopic imaging techniques. Some of these techniques are discussed in detail elsewhere.[30,32]

Staging of esophageal malignancies

Accurate staging information is crucial to establishing appropriate treatment choices for esophageal cancer, whether it is determining the depth of tumor to determine the feasibility of endoscopic management or to establish tumor margins and/or lymph node involvement before possible surgical resection or chemoradiation. Complete

staging of esophageal cancer has traditionally involved EUS and FNA in conjunction with cross-sectional imaging. Numerous studies have demonstrated the superiority of EUS in both local tumor (T) and nodal (N) staging over CT.[31] Accuracy for T staging approaches 90% in superficial and partially obstructing esophageal cancers,[33,34] but accuracy declines in cases of completely obstructing tumors that prevent the echoendoscope from traversing the tumor.[33] Early studies of dilation of malignant strictures to facilitate echoendoscope passage for EUS staging reported high complication rates,[35] but more recent data have established the safety of this technique.[36] Ultrathin US probes or wire-guided instruments may be passed through the working channel of an upper endoscope for endosonography, but these have high frequency ranges that prevent deep sonographic penetration of the malignancies, limiting the ability to visualize lymph node regions.[37] Endosonographic characteristics of malignant lymph nodes include size >10 mm, round and smooth features, proximity to the primary tumor, and hypoechogenicity. The accuracy of EUS for nodal staging based solely on these acoustic criteria approaches 80%.[38,39] FNA of lymph nodes increases nodal staging accuracy to 92% to 98% by using pathologic staging as the criterion standard.[40,41] Tissue sampling contamination may occur when the endoscope traverses the tumor and it must be appreciated that false positive FNA is possible when detached malignant cells that are present within the GI lumen are picked up by the needle.[42]

Restaging of esophageal cancer with EUS after neoadjuvant chemoradiation is being used to determine the effectiveness of therapy before operative intervention. Results of prospective and retrospective studies have been mixed. Some studies demonstrate disappointing accuracy rates ranging from 29% to 60% for tumor staging and 38% to 71% for nodal staging.[43-46] Other studies suggest that a change in the maximum tumor thickness before and after treatment can predict recurrence or response.[47-51] FNA of abnormal lymph nodes improves the accuracy to 78%, but overall, fluorodeoxyglucose positron emission tomography/CT appears to have better accuracy than EUS or CT to detect response to

neoadjuvant chemoradiation.[50] The accuracy of EUS in this clinical situation may be weakened because radiation-induced mucosal inflammation of the esophageal wall may not always be distinguishable from residual disease.

Endoscopic therapy for esophageal cancer

Endoscopic therapy for esophageal cancer can be categorized broadly as therapy with curative intent or therapy to palliate symptoms. Endoscopic curative therapy is used for mucosal cancers, whereas palliation is used for patients unwilling or unable to undergo surgery, chemotherapy, or radiation. Distinguishing mucosal from submucosal invasion is an important factor that contributes to the success of endoscopic curative therapies. Stage T1a malignancies include lesions confined to the mucosa: M1 (intraepithelial), M2 (lamina propria invasion), or M3 (muscularis mucosa invasion). Submucosal or T1b malignancies are classified into Sm1 (superficial submucosa invasion), Sm2 (invasion to center of submucosa), or Sm3 (invasion to deep submucosa). Mucosal (T1a) malignancies have extremely low risk of local lymph node progression while submucosal invasion (T1b) markedly increases the risk of lymph node metastases. Metastatic disease is present in up to 21% of Sm1 and 56% of Sm3 cancers.[51,52] In addition, early cancers with features of lymphovascular invasion on histology or poorly differentiated cancers are generally considered to represent a higher risk for metastatic disease. These factors emphasize the need for accurate staging via EUS or en bloc tissue sampling.

Endoscopic therapy with curative intent

Endoscopic therapy of early stage esophageal cancer can be divided broadly into resection and ablation techniques. A distinct advantage of resection over ablation therapy is the availability of large tissue specimens for pathologic diagnosis and accurate cancer staging.[53] EMR and endoscopic submucosal dissection (ESD) are endoscopic techniques that permit targeted removal of superficial tissue of the GI tract.[54] EMR is indicated for nodular BE and T1a lesions and may be used for flat BE with high-grade dysplasia. ESD can be used in similar situations but is preferred to EMR for large areas of dysplasia (>2 cm) or T1b malignancies (ie, confined to the submucosa). There are a variety of methods used in removing the target mucosa via EMR/ESD. These techniques are reviewed elsewhere.[53] EMR successfully eradicates 91% to 98% of T1a cancers.[55-57] Potential complications of EMR are bleeding, perforation, and stricture formation. Delayed bleeding is rare, but immediate, postresection bleeding can occur in 10% of patients.[53,56,58] Perforation rates are reported to be less than 3%.[57,59,60] Rates of stricture formation vary depending on the circumference and length of mucosa removed by EMR, but can occur in up to 37% of cases.[61] The majority of strictures are successfully managed by endoscopic dilation.[61] ESD is not commonly performed in the United States and only recently has been introduced in

Europe. Reports from Japan of ESD for SCC of the esophagus show up to 100% en bloc resection rates and 80% curative resection rates.[62,63] One of these studies, a retrospective review of ESD versus EMR for the treatment of early SCC, reported higher en bloc resection (100% vs 53.3%; $P < .05$) and lower local recurrence rates (0.9% vs 9.8%; $P < .05$) with ESD.[63] ESD in the esophagus has been associated with perforation rates of 2% to 5%[61,62] and stricture rates between 5% and 17.2%.[63,64]

Ablation techniques for BE and intramucosal carcinoma include photodynamic therapy (PDT), cryotherapy, argon plasma coagulation (APC), heater probe treatment, and radiofrequency ablation (RFA). These techniques may be used alone or in combination with mucosal resection techniques, depending on the clinical scenario. PDT has been used successfully to manage high-grade dysplasia in BE, although strictures occur in approximately one-third of patients.[65] Data describing the use of PDT as the primary management of early esophageal cancer are limited to case series and case reports.[66,67] More often, PDT is used in combination with a second ablative or resection modality.[68,69] Successful therapy has been reported in a series of 38 patients with T1 SCC, demonstrating 87% complete eradication; however, there was an 18% recurrence rate of SCC observed in this study.[70] Cryotherapy has been reported in a small series of patients as an adjunct to endoscopic resection therapy. In a case series of 30 patients with high-grade dysplasia or intramucosal carcinoma, the use of cryotherapy downgraded or eliminated the neoplasia in 27 patients (90%).[71] Complications of cryotherapy include chest pain, dysphagia, and, rarely, perforation.[72] APC, heater probe, and RFA each have a limited role as monotherapy with curative intent for intramucosal carcinoma because of the superficial nature of these techniques.[73]

Endoscopic therapy of early esophageal cancer has recently been shown to result in similar cancer-free survival with lower morbidity when compared with surgical resection.[74] Das et al[75] analyzed the Surveillance, Epidemiology, and End Results (SEER) database and compared the long-term survival of 742 patients with TisN0M0 and T1N0M0 esophageal cancer treated with either endoscopic modalities (most commonly EMR) and surgical resection. Patients treated with endoscopic methods had similar median cancer-free survival compared with those treated with surgery (56 months vs 59 months, respectively; $P = .41$).[75] A more recent, single-center report by Zehetner et al[76] came to similar conclusions, demonstrating equivalent survival at 3 years (94%) in patients with high-grade dysplasia and intramucosal carcinoma treated with endoscopic resection and ablation compared with surgical resection.[76] In this report, morbidity associated with endoscopic treatment was significantly lower than with surgery (0% vs 39%; $P < .0001$). Patient selection for endoscopic therapy is complex, depending on tumor-specific, esophagus-specific, and patient-specific factors. A recent decision analysis concluded that

endoscopic therapy for early EAC associated with BE was more cost-effective, with similar quality adjusted life years gained at less expense, compared with surgical resection.[77]

Palliation

Nutritional deficiency and weight loss are significant concerns in patients with esophageal cancer. Esophageal obstruction and tracheoesophageal fistula formation are frequent complications. Endoscopic options for palliation include dilation, stenting, chemical or ablative debulking, and enteral feeding. When planning treatment, it is important to include the patient and caregiver in the discussion to ensure a complete understanding of the goals of the intervention. Dilation of obstructing esophageal masses rarely provides sustained relief of symptoms and is complicated by a high perforation rate.[78,79] More durable symptom relief can be obtained by esophageal stenting.[80] Self-expandable metal stents (SEMS) have been used since the 1990s to palliate malignancies. Current stent technology allows for the placement of partially and fully covered SEMS for the purpose of traversing a malignant obstruction or for covering a tracheoesophageal fistula.[80] Although SEMS provide more durable relief of dysphagia and are associated with decreased risk for perforation than dilation alone, SEMS provide no associated improvement in nutrition.[81] A randomized, prospective study comparing stenting to ablation with APC among patients with inoperable esophageal cancer demonstrated an overall improvement in quality of life in patients who were treated with stents; however, survival decreased by a mean of 40 days.[82] Stent complications include intolerable chest pain, perforation, migration, tumor ingrowth, bleeding, and fistula formation.[82,83] A randomized study comparing self-expandable plastic stents (SEPS) to SEMS for palliation of esophageal cancer demonstrated higher complication rates with SEPS than SEMS, although these differences did not reach statistical significance.[83] Rates of migration (11% vs 2%), tissue reaction, and bleeding were all higher in the SEPS group. SEMS were noted to have higher rates of tumor overgrowth, fistula formation, and food impaction. Improvements in dysphagia symptoms in the two groups were similar.

A tracheoesophageal fistula can develop from tumor penetration or as a complication of radiation therapy. SEMS can be used to palliate malignant tracheoesophageal fistulae by sealing the esophagus from the airway and preventing aspiration of luminal contents. Successful closure of tracheoesophageal fistulae has been reported in up to 86% of patients with SEMS placement.[84,85] Airway compromise after SEMS placement for a tracheoesophageal fistula has been reported and careful evaluation of the patient with a multidisciplinary approach and concomitant airway management should be considered before the procedure.[81]

Endoscopic techniques also may be used to debulk an inoperable, obstructing tumor. These methods include chemical debulking, laser ablation, and PDT.[86] Debulking via tumor injection of absolute alcohol provides only a transient improvement in symptoms and must be repeated often.[87,88] Case reports have demonstrated limited benefit from the use of a combined epinephrine/cisplatin injectate.[89,90] Laser ablation with neodymium-doped yttrium aluminium garnet (Nd:YAG) has been used with some success. Successful restoration of luminal patency by using laser ablation has been reported in up to 97% of patients, but multiple sessions are required and despite the return of esophageal patency, reports of symptom improvement were disappointing.[91,92] A randomized study comparing Nd:YAG therapy to esophageal stenting for the palliation of esophageal cancer demonstrated improved median survival in patients treated with laser therapy (mean 125 vs 68 days; $P < .05$), but no improvement in quality of life or dysphagia scores. Laser therapy is complicated by esophageal perforation in up to 7% of cases.[93]

PDT has largely supplanted laser therapy for tumor debulking. A multicenter randomized trial comparing ND:YAG to PDT demonstrated equivalent efficacy in palliation of esophageal cancer with fewer serious complications in the PDT arm.[93] Moreover, studies have demonstrated superiority of PDT in debulking proximal or large tumor burdens.[94] PDT may be used to facilitate stenting or as a salvage therapy in obstructing malignancies.[95] PDT carries a higher complication rate when used after standard chemotherapy and radiation.[96] Salvage PDT after chemoradiation has been described in a few case series as a single treatment option demonstrating 5-year survival rates of up to 36%.[97,98] PDT combined with APC can improve dysphagia scores, but not quality of life, and was inferior to high-dose brachytherapy for both outcomes.[99]

Endoscopic placement of enteral feeding tubes (eg, gastrostomy tube) bypasses obstructing lesions of the upper GI tract in order to permit delivery of nutrition. The technique, as well as its indications and risks, are discussed elsewhere.[100] Consideration of potential operative intervention may impact the location of enteral feeding tube placement. Gastrostomy tube placement can complicate esophagectomy and gastric pull-up procedures. Malignant metastases at stoma sites have been reported in patients who have undergone endoscopically aided enteral access.[101]

RECOMMENDATIONS

1. We recommend EUS and FNA (when indicated), in conjunction with cross-sectional imaging, for the accurate staging of esophageal carcinoma. ⊕⊕⊕◯
2. We suggest that EMR or ESD be used for the treatment and staging of nodular BE and suspected intramucosal SCC and adenocarcinoma. ⊕⊕◯◯
3. We suggest that APC, heater probe, cryotherapy, or radiofrequency ablation not be used as monotherapy

with curative intent for mucosal esophageal cancer. ⊕⊕○○

4. We suggest that ablative techniques such as APC, heater probe, cryotherapy, or radiofrequency ablation may have a role in ablation of remaining high-risk tissue following resection. ⊕⊕○○

5. We recommend that esophageal stent placement is the preferred method for palliation of dysphagia and fistulae secondary to esophageal cancer because it provides immediate and durable relief in the majority of patients. ⊕⊕⊕○

6. We suggest that a variety of factors, including patient preferences, quality of life, and prognosis be addressed with the patient and family before initiating endoscopic palliation for esophageal malignancy. ⊕⊕○○

DISCLOSURE

Dr Fisher, consultant for Epigenomics Inc. All other authors disclosed no financial relationships relevant to this publication.

Abbreviations: APC, argon plasma coagulation; BE, Barrett's esophagus; EAC, esophageal adenocarcinoma; ESD, endoscopic submucosal dissection; ND:YAG, neodymium-doped yttrium aluminium garnet; PDT, photodynamic therapy; SCC, squamous cell carcinoma; SEMS, self-expandable metal stents; SEPS, self-expandable plastic stents.

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