

ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

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Insights Into Resection for Esophageal Adenocarcinoma



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G&H Could you briefly summarize the association between esophageal adenocarcinoma and gastroesophageal reflux disease?

DP Acid reflux can be either symptomatic or asymptomatic; however, in either event, it can lead to inflammatory changes typically in the distal esophagus and at the gastroesophageal junction. In some patients, acid reflux can lead to metaplasia, specifically intestinal metaplasia, which when present in the distal esophagus or gastroesophageal junction is known as Barrett esophagus (BE). Although most often nondysplastic, BE is the only identified histologic precursor to dysplasia or premalignant change that can lead to higher degrees of dysplasia and, in a subset of patients, to esophageal adenocarcinoma (EAC).

G&H What is the next step after EAC is detected?

DP The first step is to focus on staging, in other words, how extensive is the EAC. For EAC, staging with computed tomography is important to rule out metastatic disease. Endoscopic ultrasound (EUS) is used to determine TDNM staging (T for assessment of the tumor, D for depth of invasion, N for nodal status or presence of lymph node invasion, and M for metastatic or more distal spread). Essentially, T and M are the most important components detectable on EUS that help determine the next steps in the management of EAC. Although there are different EUS probes (the standard EUS endoscope probe or a miniprobe, which is a small catheter-based ultrasound probe that can be advanced through a standard

endoscope), for most cases of EAC, standard EUS is used to assess depth of invasion and nodal status and to provide a better sense of local/regional staging.

Other procedures that can be helpful for staging include chromoendoscopy using narrow-band imaging or other electronic chromoendoscopy modalities and dye-based chromoendoscopy. These techniques use either electronic means or chemical dyes to help determine the features of the tumor (eg, surface characteristics, size, and presence of ulceration) that may suggest a deeper invasive component of the lesion and that can correlate with other next steps in management and prognosis. EUS, however, remains the gold standard for evaluation of local/regional staging.

G&H What type of EAC is resectable endoscopically?

DP When discussing endoscopic resectability, the focus is on early EAC that is typically staged as T1. This stage can be subcategorized into more superficial invasion that is limited to the mucosal epithelium, T1a, or which extends through the lamina propria into the muscularis mucosa and more superficial levels of the submucosa, T1b. Generally, the T1 lesions are thought to be potentially resectable via endoscopic techniques.

There are different features and clues that help in determining the optimal means for endoscopic resection based on whether the lesion is T1a or T1b. For instance, an ulcerated lesion typically correlates with deeper submucosal invasion. Factors that may influence different endoscopic resection techniques include how well differentiated the cells of the tumor are, with moderately and

well-differentiated tumors having better outcomes, and how small the lesion is, typically, 20 mm (2 cm) or less. Staging, as noted, is largely dependent initially on EUS evaluation and is best accomplished by resecting the nodular component of the tumor and measuring the depth of invasion. A measurement of more than 500 μm suggests deeper invasion and a higher risk of lymphovascular involvement or invasion, lymph node metastasis, and higher-grade tumors, which have less well-differentiated cells and generally a less favorable outcome.

G&H What are the latest trends in resection techniques for EAC?

DP The mainstays for EAC resection are, for the most part, divided into 2 categories: endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). Both procedures were pioneered in Japan and elsewhere in Asia, and both are widely accepted. In the United States, this is true especially for EMR, although ESD, which has been well established in western Europe for quite some time, is being increasingly utilized in this country. The latest trends have to do with optimizing techniques for both EMR and ESD and the evaluation of the lesion itself, which may include use of artificial intelligence (AI). AI has been shown to be useful in assessing the surface features of the tumor, which can help predict, for instance, the grade of the tumor, as well as the likelihood of submucosal invasion.

G&H What factors determine which type of resection technique should be performed?

DP The type of resection technique performed depends on the individual center's experience as well as procedural volume and multimodal approaches to the diagnosis, staging, resection, and management of potential complications. Patients may have access to multiple options. However, in some areas, that may not be the case, so the first factors to consider are: what is the local expertise, and what is best for the patient with the physician and endoscopist involved in the patient's care. After that, there are a number of factors that can help determine which technique to use, including the size of the lesion, depth of invasion, grade, and whether ulceration is present. The goal, ideally, is to perform a complete en bloc resection with clear margins, also called R0 or curative resection. Whether EAC can be resected en bloc relies on several factors. The more well differentiated the tumor is, the better the outcome. Esophageal tumors are graded from G1 to G3, G1 being well differentiated, G2 moderately differentiated, and G3 poorly differentiated. En bloc resection has a higher rate of being achieved when there is less than 500

μm invasion into the submucosa.

When deciding between EMR and ESD, the lesion size, as indicated, is a factor. For lesions larger than 20 mm in early or T1 disease, the recommendation generally, where possible, is to perform ESD. Other factors that would favor ESD over EMR include lesions that are less well differentiated or ulcerated as well as lesions that have recurred after a prior resection. For example, ESD may be preferred when the margins are positive after EMR, when there is unclear margin integrity after piecemeal resection, and when there is deeper invasion.

For EAC of less than 20 mm that is well differentiated or moderately differentiated, G1 to G2, with no ulcerated component or suggestion of scarring or fibrosis, if the lesion can be lifted off the wall of the esophagus with a submucosal injection, then either EMR or ESD might be appropriate. For such lesions, there is debate over which procedure to perform, and whether one is superior to the other is not clear. Although both EMR and ESD are likely somewhat equivalent in this regard, ESD might have a slight advantage. However, each case will have different factors that determine which technique is used. ESD is a technically challenging procedure that can take hours to complete, whereas EMR is a somewhat simpler technique. For smaller lesions and those that have a low risk of deeper invasion, EMR is considered acceptable, especially if an en bloc resection can be performed. Again, for any lesion that is larger than 20 mm, that does not lift well from the esophageal mucosa with a submucosal injection, or that has scarring, fibrosis, or deeper invasion correlating with a higher risk of lymph node metastases, ESD is generally favored.

G&H How common are the complications associated with EAC resection?

DP Both EMR and ESD are quite safe when performed by a skilled operator. As endoscopists gain more experience with ESD, the risk of complications is likely to decrease. The procedures have relatively similar rates of hemorrhage, perforation, stricture, and stenosis. Studies have reported a perforation risk up to 1.6% for EMR, and between 2.6% and 6.9% for ESD. Again, the risk depends on the center or volume of procedures. The risk of a delayed perforation from ESD is very uncommon, approximately up to 1.3%. Both techniques have been associated with postresection stricture and stenosis from the inflammatory healing response. The likelihood of these complications depends on the size of the lesion and extent of the resection. For resection of a lesion that is less than 50% of the circumference of the esophageal lumen, stricture risk is low, approximately 0.7%. For resection of a lesion involving between 50% and 75% of the esophageal

lumen circumference, the stricture rate is approximately 27%. In the event of a truly large lesion involving more than 75% of the circumference of the esophageal lumen, the stricture rate is quite high, approximately 94%.

G&H What are the determinants of long-term survival after surgery?

DP Higher rates of long-term survival are related to R0 resections and are more common with en bloc removal either by EMR or ESD. Long-term survival is largely dependent on the tumor stage, whether there is lymphovascular invasion, the tumor grade, how well differentiated the cells are, and whether the resection is complete. ESD has higher rates of R0 resection compared with EMR, especially when EAC is removed en bloc. When piecemeal resection is performed, either intentionally or unintentionally, it is more difficult to assess the margins. Lymph node metastasis, other local or regional spread, and obviously metastatic disease, of course, also determine longevity. The risk of lymph node metastasis in a curative endoscopic resection is lower than the risk of perioperative mortality associated with esophagectomy. In experienced hands, endoscopic resection techniques are generally well tolerated and safe, with good outcomes. The complications, such as bleeding and stricture, can typically be managed endoscopically.

G&H What does surveillance after EAC resection entail?

DP Surveillance after resection of EAC is part of a multidisciplinary discussion such as within an institutional tumor board, in which colleagues from gastroenterology, surgery, radiology, medical oncology, radiation oncology, and other relevant specialties collaborate on decision-making in each case. In the case of a noncurative resection of a well- or moderately differentiated lesion less than 20 mm (2 cm), with no signs of deep mucosal invasion, no ulceration, and no prior resection in that area, either EMR or ESD may be performed. A noncurative resection means that the margins are not clear, or the depth is greater than anticipated. The tumor board may consider ESD if EMR was performed first, for example, or another endoscopic technique or potentially surgical intervention. Surveillance after a curative resection depends on the T staging. Ideally, the recommendation is to have at least 2 expert gastrointestinal pathologists who concur on the initial staging. Curative resection of a relatively superficial T1a lesion into deeper levels of the mucosa alone (M1 to M3) typically requires endoscopic surveillance every 6 months for 2 years after resection and then annually, unless recurrent cancer is detected.

Deeper T1b lesions into the superficial submucosa (SM1) typically require surveillance with endoscopy at 3-, 6-, and 12-month intervals, then every 6 months for 2 years, and thereafter annually. EUS to assess the lymph node status and rule out metastatic disease and, generally, cross-sectional chest and abdominal imaging for the subsequent 3 to 5 years can be considered. For all lesions during surveillance after resection, any residual Barrett tissue or intestinal metaplasia can be removed using an ablative technique, such as radiofrequency ablation or argon plasma coagulation. Of course, along the surveillance pathway, there are additional discussions with the patient and shared decision-making that occur in the context of an ongoing multidisciplinary discussion.

G&H What is the focus of research on this topic?

DP Current research is focused on the individualized care and profile for each patient. Researchers are trying to figure out optimal recommendations for endoscopic resection plans paired with different ablation techniques for residual Barrett tissue based on the histologic grade of the tumor, depth of invasion into the submucosa, lymphovascular invasion, and risk for lymph node metastases for each patient. In addition, researchers are looking at how use of molecular clinical biomarkers can optimize surveillance frequency and duration, and how long surveillance should be continued after endoscopic resection. As mentioned, the use of AI to look at tumor surface patterns may help determine the tumor grade and assess the invasion depth, which correlates with the risk of invasive disease. These advances could help match the procedure (ESD vs EMR) to each patient, as well as determine whether adjunctive therapies may be needed down the line. Essentially, all of this research is part of coordinated effort to help determine the patient's risk profile and, therefore, the optimal resection technique and postresection surveillance plan that is tailored for the individual patient.

Disclosures

Dr Poppers is a consultant for Castle Biosciences, Lucid Diagnostics, and Regeneron/Sanofi.

Suggested Reading

di Pietro M, Trudgill NJ, Vasileiou M, et al. National Institute for Health and Care Excellence (NICE) guidance on monitoring and management of Barrett's oesophagus and stage I oesophageal adenocarcinoma. *Gut*. 2024;73(6):897-909.

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