Endoscopic management of Barrett’s esophagus with dysplasia
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CHAPTER 2

ENDOSCOPIC RESECTION FOR TREATMENT OF HIGH-GRADE DYSPLASIA AND EARLY CANCER IN BARRETT’S ESOPHAGUS

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Review Uptodate, May 2014
Barrett’s esophagus (BE) is thought to be a complication of longstanding gastroesophageal reflux, resulting in the replacement of the normal squamous lining of the distal esophagus by columnar epithelium containing specialized intestinal metaplasia.

Endoscopic surveillance is recommended for patients with Barrett’s esophagus because of its malignant potential in the hope of detecting dysplasia before it progresses to adenocarcinoma. Esophagectomy has traditionally been recommended for patients found to have high-grade dysplasia or early cancer. Endoscopic therapy has been proven to be a safe, effective, and less invasive alternative to surgery for treating such patients.

Endoscopic resection (ER) is an endoscopic approach in which the neoplastic epithelium is excised, thus allowing for a definitive histologic diagnosis, while also potentially being curative. ER has been applied not only to Barrett’s esophagus with high-grade dysplasia but also to early cancer in which the risk of lymph node involvement or hematogenous dissemination is low enough to justify a relatively conservative approach compared with esophagectomy.¹⁻⁸

• Several studies have demonstrated that ER is safe and effective for complete resection of superficial lesions, and offers the advantage of histopathologic verification.⁹⁻¹²

• Prior ER does not impair subsequent ablative therapy (eg, photodynamic therapy [PDT], argon plasma coagulation [APC], or radiofrequency ablation [RFA]) for treatment of larger areas of residual Barrett’s mucosa. Ablative therapy alone provides no specimen for histopathologic evaluation.

• ER is considered the cornerstone of endoscopic management, and ablative techniques are mainly used as an adjunct to ER.¹³

The experience with ER in patients with Barrett’s esophagus who have high-grade dysplasia (HGD) or early cancer (EC) is discussed here. Photodynamic therapy, radiofrequency ablation, a general approach to Barrett’s esophagus, and other treatment options for superficial esophageal cancer are presented separately.

**EVALUATION FOR ELIGIBILITY**

There are three major considerations in the evaluation of patients with Barrett’s esophagus (BE) who have high-grade dysplasia or early cancer: histopathologic evaluation, the endoscopic work-up, and staging of the lesions.

**HISTOPATHOLOGIC EVALUATION** Esophageal neoplasia is usually classified according to the internationally accepted Vienna classification.¹⁴ The Vienna classification is based upon the histopathologic evaluation of endoscopically acquired biopsies:

• Category 1: no dysplasia
• Category 2: indefinite for dysplasia
• Category 3: low-grade intraepithelial neoplasia (low-grade adenoma/dysplasia)
• Category 4: high-grade intraepithelial neoplasia (high-grade adenoma/dysplasia, noninvasive carcinoma or suspicion of invasive carcinoma)
• Category 5: invasive epithelial neoplasia (intramucosal carcinoma, submucosal carcinoma, or beyond)

The distinction between categories 4 and 5 can be difficult since it depends in part upon the size, location, depth, and number of biopsies. In category 4, there is no obvious invasion beyond the epithelial basal membrane. Category 5 is subdivided based upon whether there is invasion into the lamina propria or muscularis mucosa (category 5.1, also referred to as intramucosal cancer) or into the submucosa (category 5.2, also referred to as submucosal cancer).

Another problem with the diagnosis of dysplasia in Barrett’s epithelium is the interobserver reliability among pathologists. As a result, it is helpful to achieve a consensus (ie, from more than one pathologist) in categorizing such specimens. A consensus diagnosis has better predictive value regarding prognosis and may revise the original diagnosis, which can have implications for subsequent management. These observations underlie the recommendation that a second, experienced pathologist should confirm the diagnosis of high-grade dysplasia.

ENDOSCOPIC EVALUATION  Patients diagnosed with high-grade dysplasia (HGD) or early cancer (EC) in Barrett’s esophagus should undergo an endoscopic work-up in a center with expertise in evaluating such patients. The reasons for this are threefold:

• Evaluation at a specialized center helps assure that a second, experienced endoscopist can confirm the findings of the initial endoscopy, making a false positive diagnosis less likely. Up to 40 percent of patients who are diagnosed with HGD have no dysplasia at follow-up endoscopies. If the diagnosis of HGD is confirmed in biopsies obtained on a separate occasion, the chance of over diagnosis and unnecessary treatment should be reduced.

• Evaluation at a specialized center permits detection of synchronous lesions elsewhere in the Barrett’s esophagus that might otherwise be left untreated. This is especially important if endoscopic therapy is being considered.

• Specialized centers often have integrated expertise in gastrointestinal pathology, endoscopy, and surgery, and the experience to offer advanced endoscopic techniques such as ER.

Early neoplastic lesions in Barrett’s esophagus are often difficult to detect with standard video endoscopy. Although a number of techniques have been proposed to increase the accuracy of endoscopic imaging (such as chromoendoscopy, magnification endoscopy, and optical coherence tomography), none is used routinely in clinical practice. Three general rules should be followed in the endoscopic evaluation of patients being considered for ER:

• Use the best endoscope available
• Have a vigilant eye for detecting mucosal abnormalities
• Use a systematic, meticulous approach

Use the best endoscope available  High-resolution endoscopy may have higher sensitivity for the detection of early BE neoplasia compared with standard video endoscopy systems. Because early BE neoplasia often presents as flat lesions with only subtle mucosal abnormalities, most experts agree that high-resolution endoscopy is the preferred method for the endoscopic evaluation of BE.

Have a vigilant eye  Up to 80 percent of patients referred for evaluation of HGD or
EC without visible abnormalities will have at least one visible abnormality detected in their BE upon endoscopic inspection by expert endoscopists. Although early BE neoplasia generally presents as subtle flat lesions that can be difficult to detect, most state-of-the-art endoscopes are capable of revealing these abnormalities when viewed by highly experienced endoscopists. Thus, familiarity with the endoscopic appearance of early Barrett’s neoplasia is essential for its diagnosis.

Perform a systematic endoscopic inspection. The detection of gross mucosal abnormalities such as elevations, ulcerations, and nodularities is relatively easy. By comparison, the detection of subtle abnormalities requires a more careful and thorough inspection, making a systematic approach imperative.

After intubation of the esophagus, the esophagus should be carefully cleaned to remove any mucus or saliva. Simple water flushes usually are sufficient but spraying acetylcysteine (1 percent) can be helpful if there is excessive or viscous mucus. It is important to suction all gastric secretions to prevent reflux into the esophagus that could interfere with inspection.

The endoscope should be gradually withdrawn to examine the BE segment for mucosal irregularities and to describe the extent of BE. One system for doing so uses the validated Prague C & M criteria, which assess the circumferential and maximum extent of the visualized BE segment. After initial inspection, the inflated esophagus should be gradually deflated to reveal any irregularities that may have flattened during inflation, making them more difficult to see. Special attention should be paid to the area between 12 and 6 o’clock in the endoscopic view, where the majority of neoplastic lesions are found. In addition, if a hiatal hernia is present, it is important to inspect the transition of the BE into the hiatal hernia in the retroflexed position, since abnormalities in this area are easily overlooked in the antegrade view.

The Seattle biopsy protocol is recommended for mapping Barrett’s esophagus with HGD. Targeted biopsies are obtained from all visible abnormalities and random four-quadrant biopsies are taken every 1 cm starting from the top of the gastric folds up to the most proximal extent of the BE (squamocolumnar junction).

• The importance of random biopsies every 1 cm rather than every 2 cm was demonstrated in a study in 45 patients with BE and HGD. The authors calculated that using a standard protocol would have missed 50 percent of cancers that were detected by the 1 cm protocol.

Based upon the above observations, inspection and classification of all visible lesions should be followed by biopsies from each visible abnormality and then random four-quadrant biopsies. The biopsies should always start distally, working upwards to minimize bleeding that obscures visualization. We follow the rule “look longer, biopsy less” since, in our experience, the diagnosis of HGD or EC can be made in 80 to 90 percent of patients with these lesions by targeted biopsies after a thorough inspection. However, random four-quadrant biopsies are still required, since 10 to 20 percent of lesions are missed with targeted biopsies alone.

In addition, the American Society for Gastrointestinal Endoscopy has issued guidelines that recommend endoscopic resection for the treatment and staging of nodular BE and suspected intramucosal adenocarcinoma.

ENDOSCOPIC RESECTION AS STAGING PROCEDURE. We consider ER to be both a reasonable treatment option and also the final step in the diagnostic work-up of
patients with HGD or EC in BE. In one study, interobserver agreement about the presence of neoplasia was significantly better on ER specimens than biopsy specimens. This approach is consistent with 2013 guidelines from the American Society for Gastrointestinal Endoscopy that recommend endoscopic resection for the treatment and staging of nodular BE and suspected intramucosal adenocarcinoma. If the endoscopic appearance of the lesion does not raise suspicion for deep submucosal infiltration, the lesion may be removed by ER.

The most important predictor of lymph node metastasis is the penetration depth of the tumor. Endoscopic resection of the most suspicious area in the Barrett’s segment, followed by histopathologic evaluation of the resected specimen, permits assessment of infiltration depth and estimation of the risk for local lymph node metastasis.

OTHER STAGING PROCEDURES Among patients diagnosed with HGD or EC, other imaging techniques could be considered to evaluate tumor infiltration depth, local lymph node status, and metastatic spread. Endoscopic ultrasonography (EUS) and computerized tomography (CT) scan are the most widely used techniques.

Endoscopic ultrasound EUS is the most accurate technique for locoregional staging of esophageal cancer. However, EUS is less reliable for T- and N-staging in patients with HGD and EC than in patients with more advanced esophageal cancer. In addition, accuracy is influenced by the experience of the endosonographer. High frequency miniprobe may improve the accuracy of T-staging compared with standard EUS, but the accuracy of N-staging appears to be inferior to standard EUS because, while it is higher resolution, the visualization is more superficial.

- T-staging (depth of invasion) – Differentiating mucosal lesions from lesions infiltrating into the submucosa is much more difficult in BE than in the squamous esophagus for the following reasons:
  - The crypts and villi present in BE are more heterogeneous than the layered architecture of squamous epithelium.
  - BE neoplasia can be associated with significant inflammatory changes and the presence of a double muscularis mucosae.
  - Most Barrett’s lesions are located in the distal esophagus close to the cardia, where EUS interpretation is known to be difficult.

There appears to be limited added value of EUS for determining T-staging once tumor depth has been estimated by endoscopic inspection of the lesion of interest by an expert endoscopist.

- N-staging (nodal status) – In the work-up and staging of patients with early neoplasia, N-staging is of crucial importance, since positive lymph nodes will exclude patients from endoscopic treatment. EUS has a high negative predictive value (>95 percent) for the absence of tumor infiltration into the deeper wall layers and local lymph nodes. Ultimately, however, the best method for assessment of the risk of lymph node involvement is not EUS, but assessment of the depth of infiltration of the lesion after endoscopic resection.

CT scanning The value of computed tomography (CT) scanning lies mainly in the detection of distant metastases. The risk for distant metastases is very low in patients with HGD or EC who show no signs of deep submucosal infiltration or suspi-
cious lymph nodes on EUS. Thus, the value of CT is limited in such patients.  

Other radiographic modalities  Other imaging techniques, such as positron emission tomography (PET) scanning and magnetic resonance imaging (MRI), do not have a role in the work-up of patients with esophageal HGD or EC.

ENDOSCOPIC RESECTION TECHNIQUES

A variety of endoscopic resection techniques have been described for the esophagus, primarily for esophageal squamous neoplasia.

ESTABLISHED TECHNIQUES

Endoscopic resection-cap  The most widely practiced endoscopic resection technique for the treatment of Barrett’s neoplasia is the endoscopic resection-cap technique after submucosal lifting (figure 1 and picture 1). The target lesion is first lifted by injection of a fluid, which may be saline or diluted epinephrine (1:100,000), into the submucosal layer. Subsequently, a transparent cap is attached to the endoscope. The cap has a distal ridge that allows positioning of a crescent-shaped endoscopic resection-snare. The lesion is sucked into the cap, thus creating a pseudopolyp that is immediately captured by forcefully closing the pre-positioned endoscopic resection-snare. The lesion is then removed using electrocoagulation.

Figure 1 Schematic drawing showing the consecutive steps of the endoscopic resection-cap procedure of a focal lesion in a Barrett’s esophagus  
(A and B) A transparent cap is attached to the distal tip of the endoscope and the target lesion is lifted by injection of a fluid, usually diluted epinephrine (1:100,000), into the submucosal layer, using a standard sclerotherapy needle. (C and D) After removal of the needle, a crescent shaped snare is positioned into a distal ridge within the cap. The lesion is sucked into the cap thus creating a pseudopolyp that is immediately captured by forcefully closing the pre-positioned EMR-snare. (E) The lesion is removed using electrocoagulation. EMR: Endoscopic mucosal resection
Endoscopic resection of an early cancer in a Barrett’s esophagus

(A) A 4-cm long segment of Barrett’s esophagus with a large island of squamous mucosa in its center. (B) A detailed view of a lesion at the 3 o’clock position. (C) Same lesion shown in the retroflexed position. (D) The lesion has been delineated by placing coagulation markers at its outer surface. (E) The lesion has been elevated by injection of diluted epinephrine solution through a standard sclerotherapy needle. (F) A transparent cap has been attached to the distal tip of the endoscope and a crescent shaped snare is positioned into the distal ridge of the cap. (G) Using the coagulation markers for orientation, the lesion is identified and subsequently sucked into the cap. (H) After closure of the snare, the resulting pseudo-polyp, including the lesion, is pushed outside the cap and removed using electrocoagulation. (I) The created EMR wound shown in the antegrade position; there is still some mucosal swelling due to the submucosal lifting. (J) EMR wound shown in the retroflexed position, no markers can be identified indicating an endoscopically complete resection; note the mucosal whitening due to the vasoconstrictive effect of the epinephrine solution used for submucosal lifting. (K) The EMR specimen is subsequently removed from the stomach using retrieval net and pinned down on paraffin to prevent shrinking and curling. (L) Microscopic view of the specimen showing a well differentiated cancer infiltrating into the deeper layers of the muscularis mucosae, there is no infiltration into the submucosa.

EMR: endoscopic mucosal resection

Endoscopic resection-caps are available with different diameters and have either a straight or an oblique shape. The largest en bloc resections are achieved with a large caliber flexible cap that, despite its large outer diameter of 18 mm, can be relatively easily introduced into the esophagus due to its flexibility. Using this technique, lesions with a diameter of more than 2 cm can be removed en bloc.
An alternative approach (the “suck-band-and-ligate” technique) does not require submucosal injection (picture 1). A reusable variceal ligation device is used to suck the lesion into the ligation cap, allowing it to be captured with a rubber band. The endoscope is then removed, the ligation device is disassembled, and the endoscope is reintroduced to remove the created pseudopolyp with a standard polypectomy snare.

These two techniques were compared in a prospective randomized trial of 100 consecutive endoscopic resections in 72 patients with early stage esophageal cancer. Fifty endoscopic resections were performed with the “suck-band-and-ligate technique” without prior submucosal injection and 50 resections were done with the endoscopic resection-cap technique after submucosal injection of a diluted epinephrine solution. No significant differences were observed between the two groups with regard to size of the resected specimens (ligation group: 16.4 x 11 mm versus cap group: 15.5 x 10.7 mm). There was one minor episode of bleeding in each group and no severe complications occurred.

Multiband mucosectomy  Multiband mucosectomy (MBM) uses a modified variceal band ligator with six bands and a handle that allows passage of a hexagonal snare alongside the releasing wires for the bands. Suction is used to draw the lesion into the cap, a rubber band is deployed, and a polypoid lesion is created. The “polyp” can then be removed using a snare that is inserted through the biopsy channel during the procedure, thereby eliminating the need to remove the scope between banding and snare polypectomy. Multiple specimens can be removed during the procedure using this device (picture 2). A multiband mucosectomy device is now commercially available (Duette; Cook Medical, Limerick, Ireland).

This MBM technique has several advantages:

- As a modification of the “suck-band-and-ligate technique,” it does not require submucosal injection as with the endoscopic resection-cap technique. The reason is that the esophageal muscle layer will immediately retract when captured within a rubber band whereas, with the standard endoscopic resection-cap technique, it will remain captured in the forcefully closed endoscopic resection-snare.
- Multiple resections can be performed with the same snare.
- Pre-looping the endoscopic resection-snare in the ridge of the cap is not necessary.
- MBM does not require withdrawal of the endoscope between resections as is needed with the “conventional” suck-band-and-ligate technique. Since the instrument holds six rubber bands, up to six consecutive resections can be performed. This reduces the time and cost required for the procedure, while also reducing patient discomfort.

A prospective registration of 243 MBM procedures in patients with Barrett’s esophagus demonstrated that the technique is safe and effective. Complications occurring during the procedure (acute complications) were observed in 3 percent. Bleeding was the only acute complication, and in all cases it was managed endoscopically. No perforations occurred. Complications within 30 days of the procedure (early complications) included delayed bleeding (2 percent of procedures) that was managed endoscopically and stenosis (48 percent). Endoscopic complete resection was achieved in 91 percent of focal lesions.

In a case control study, 80 MBM procedures were compared with 86 endoscopic resection-cap procedures. The study showed that MBM was safe and effective for widespread endoscopic resection in Barrett’s esophagus. MBM appeared to be
quicker than endoscopic resection-cap, but the specimens removed with MBM were significantly smaller than with the endoscopic resection-cap technique. Following this case-control study, a multicenter randomized controlled trial was initiated to compare the endoscopic resection-cap technique and MBM for piecemeal resection of early neoplasia in Barrett’s esophagus. The trial included 84 patients (42 assigned to MBM and 42 to ER-cap) and found that procedure times and costs were significantly less with MBM versus endoscopic resection-cap (34 versus 50 minutes and 240 versus 322 euro, respectively). MBM resulted in smaller specimens than endoscopic resection-cap (18 versus 20 mm in longest dimension). There were no significant differences in maximum specimen thickness or the amount of submucosa resected. There were three perforations in the endoscopic resection-cap group and one perforation in the MBM group. The perforations in the endoscopic resection-cap group were treated endoscopically, whereas the perforation in the MBM group required surgical repair because of periesophageal scarring that prevented endoscopic closure.

Picture 2 Endoscopic images of a multi-band mucosectomy (MBM) in a patient with Barrett’s esophagus with a focal lesion with HGIN

(A) Overview of a 3 cm long segment of Barrett’s esophagus. (B) There is a subtle lesion in the center of the endoscopic image. (C) View after placement of electrocoagulation markers to delineate the lesion. (D) A transparent cap with six rubber bands at its outside (identical to a variceal six-shooter) has been attached to the distal tip of the endoscope (Wilson-Cook Medical, Limerick, Ireland). The two wires to which the rubber bands are connected pass through the working channel of the endoscope and are connected to the handle that allows release of the bands. (E) The area of interest is suctioned into the cap, without prior submucosal injection, followed by the release of one of the black rubber bands. (F) The modified handle of the MBM device allows passage of a hexagonal polypectomy snare alongside the wires of the ligator. The snare is closed either above or below the rubber band followed by cutting using electrocoagulation. (G) The wound after resection. (H) The specimen is retrieved for histological assessment. Histology showed HGIN. The lateral and deep resection margins were free of dysplasia. HGIN: high-grade intra-epithelial neoplasia.
MBM appears to be safe and fast for widespread ER in Barrett’s esophagus. Time and costs appear to be saved compared with endoscopic resection-cap, since submucosal lifting is not required and a single snare can be used for all resections. MBM does not appear to be associated with more complications than endoscopic resection-cap, despite lack of submucosal lifting. MBM results in significantly smaller sized resections, but the clinical relevance of this finding may be questioned, since there was no significant difference in the depth of resection between the two techniques.

NEW TECHNIQUES New endoscopic resection techniques continue to be explored. Japanese endoscopists have used specially designed needle-knives for en bloc dissection of large esophageal lesions, a technique known as endoscopic submucosal dissection. These dissection techniques are usually performed after submucosal injection with viscous substances such as hyaluronidate, which provide prolonged submucosal lifting. Experience is limited and a high level of endoscopic expertise appears to be required for their safe application.

In the future, different ER techniques may be combined. The endoscopic resection-cap technique or the needle-knife endoscopic dissection technique may be preferred for en bloc removal of focal lesions, while the other approaches may be used for removal of residual mucosa.

LEARNING CURVE Endoscopic resection (ER) is a technically demanding procedure that requires specific endoscopic expertise, both to resect lesions in a safe and effective manner, and to manage complications that may arise during ER procedures. However, studies on the learning curve of ER are limited, and most have assessed the learning curve of the endoscopic submucosal dissection (ESD) technique only. The majority of studies come from Asia and show that the experience and level of training in ESD of the endoscopist are associated with an increase in complete endoscopic resection rate and decreases in perforation rate and procedure time.

A study from the Netherlands has evaluated the implementation of a structured training program for esophageal ER. The training program of six teams consisting of an endoscopist, an endoscopy nurse, and a pathologist is aimed at controlled implementation and centralization of ER procedures in the Netherlands. Training resulted in a high success rate of complete endoscopic resection of lesions, although the observed perforation rate of 5 percent suggested that performing 20 ER procedures is insufficient to reach the peak of the learning curve in ER for a single endoscopist. ER should only be performed by trained endoscopists with experience in screening, imaging, and treatment of patients with early Barrett’s neoplasia. Integrated expertise in surgery and histopathology at these expert centers is preferable. A minimum case load per year may be recommended.
ACID SUPPRESSION FOLLOWING ENDOSCOPIC RESECTION

Patients should be treated with adequate acid suppression to allow the endoscopic resection wounds to heal with neosquamous epithelium and probably also to reduce local scarring. Most centers treat patients with high dose proton pump inhibitors (we use esomeprazole 40 mg twice daily).

The wounds generally heal in three to six weeks depending upon the size of the resected area. No studies have evaluated the mucosal regenerative pattern after ER. In our experience, healing proceeds from proximal to distal with regeneration starting from the edges.

PATHOLOGIC ASSESSMENT

Interpreting endoscopic resection (ER) specimens of Barrett’s neoplasia may be more difficult than specimens obtained from squamous lesions. The tissue architecture with crypts and villi differs from the layered architecture in squamous mucosa, making it more difficult to discern a clear transition between wall layers. This problem is further increased by the presence of a double muscularis mucosae in many patients with BE. Because the deeper muscle layer represents the true muscularis mucosae, lesions infiltrating through the superficial muscularis mucosae should NOT be considered as submucosal invading cancers.

To further complicate matters, complete histologic assessment is generally not available during the procedure. As a result, the endoscopist cannot make real-time decisions regarding the adequacy of tissue resection. A pilot study suggested that real-time frozen sections can provide histologic assessment that correlates well with permanent sections, but experience is limited.

Many early lesions in Barrett’s esophagus (BE) are associated with severe inflammation that is due to the accompanying reflux disease and may hamper histological assessment. Similarly, because endoscopic resection involves the use of electrocoagulation, the deep and especially the lateral resection margins often have extensive coagulation artifacts, complicating histologic evaluation compared with surgical resection specimens.

The ability to treat early cancer (EC) with ER underscores the important nuances of histopathologic assessment. However, making important distinctions between high-grade dysplasia (HGD) and invasive cancer (and its depth of invasion) may not be straightforward. In an illustrative report, the interobserver reliability for distinguishing Barrett’s esophagus with HGD from intramucosal cancer in surgical specimens was poor (kappa statistic 0.42). It was somewhat better for distinguishing intramucosal and submucosal cancer (kappa statistic of 0.71).

PATHOLOGIC SUBCLASSIFICATION The terminology and classification of early esophageal cancers have evolved and are outlined in the 2010 TNM staging system of the AJCC (American Joint Committee on Cancer)/UICC (International Union Against Cancer).

Early esophageal cancers are those that are classified as Tis (high-grade dysplasia, which includes all noninvasive neoplastic epithelial that was formerly called carcinoma.
in situ) or T1 tumors. T1 tumors are further split into T1a and T1b subcategories, depending upon the depth of invasion (table 1). However, this classification by itself is inadequate to distinguish differences in lymph node involvement among T1a and T1b esophageal cancers. A more comprehensive subclassification scheme has been proposed for early esophageal cancers and is useful for determining prognosis and selecting treatment (figure 2). According to this classification, mucosal tumors are divided into three types based upon 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 AJCC stage definition, while both M2 and M3 tumors would be considered T1a lesions.

Tumors invading the submucosa are subclassified as follows:

- SM1 – Penetrates the shallowest one-third of the submucosa (<500 microns)
- 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.

Table 1 T stage definitions for esophageal cancer (both squamous cell and adenocarcinoma)

<table>
<thead>
<tr>
<th>Primary tumor (T)*</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx</td>
<td>Primary tumor cannot be assessed</td>
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<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>High-grade dysplasia³</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor invades lamina propria or muscularis</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor invades lamina propria or muscularis</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor invades submucosa</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades muscularis propria</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invades adventitia</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor invades adjacent structures</td>
</tr>
<tr>
<td>T4a</td>
<td>Resectable tumor invading pleura, pericardium, or diaphragm</td>
</tr>
<tr>
<td>T4b</td>
<td>Unresectable tumor invading other adjacent structures, such as aorta, vertebral body, trachea, etc.</td>
</tr>
</tbody>
</table>

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.

³High-grade dysplasia 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.
For Barrett’s neoplasia, ER is considered appropriate therapy for lesions limited to the superficial mucosal layers (M1 and M2 tumors) because these tumors have low rates of lymph node metastasis (<3 percent). There is less consensus, however, with regard to lesions that extend to the muscularis mucosa (M3 tumors), yet most centers consider this an accepted indication for endoscopic treatment of early Barrett’s neoplasia, whereas for squamous neoplasia M3 lesions are a relative indication.

Esophagectomy is generally preferred for lesions that invade the submucosa (SM1, SM2, and SM3 tumors) given the significantly higher rates of lymph node metastasis associated with these lesions (table 2). Some groups have suggested that ER may be appropriate for lesions that penetrate into the superficial submucosal (SM1 tumors with submucosal penetration <500 microns). The reason ER may be an option is that these lesions may have a low risk of positive lymph nodes, provided that they do not show poorly differentiated cancer or lymphovascular invasion. However, most centers consider SM1 tumors to be an indication for surgery and reserve ER for patients who are considered to be at high surgical risk. More studies are required before strong management advice can be given with regard to these lesions.

The above considerations underscore the importance of specialized referral centers where expert pathologists are available. This topic is discussed in detail elsewhere.

**EFFICACY**

An understanding of the efficacy of endoscopic resection (ER) for management of high-grade dysplasia (HGD) or early cancer (EC) in Barrett’s esophagus (BE) is evolving. The available evidence suggests that ER for these conditions has an initial success rate comparable to surgical treatment, but with fewer complications.
The rate of complete remission (ie, successful removal of the HGD or EC with ER) is variable, ranging from 59 to 99 percent in different studies.\(^9,12,55-60,62-66\) In a systematic review that included 11 studies of patients with BE who underwent endoscopic mucosal resection (EMR), complete eradication of HGD or EC was achieved in 95 percent of patients, and complete eradication of all Barrett’s mucosa was achieved in 89 percent.\(^67\) Higher degrees of success are seen in patients with lower risk lesions, which are defined as macroscopic types I (protruded type), IIa (flat elevated type), IIb (flat type), and IIc (flat depressed type); a lesion diameter up to 20 mm that is limited to the mucosa; and histologically well to moderately well differentiated tumors.

Recurrence of carcinoma or the development of metachronous malignancies has been described in 6 to 30 percent of patients.\(^9,12,55-59,61,62,65,66\)

Multiple factors have been associated with recurrence:  
- Larger lesion diameter  
- Long-segment BE  
- Removal of the lesion with piecemeal resection  
- Failure to perform adjunctive ablative therapy (photodynamic therapy, argon plasma coagulation, or radiofrequency ablation)  
- Presence of multifocal neoplasia  
- An elapsed time of more than 10 months prior to achieving complete remission  
- The presence of residual dysplasia  

### Table 2 Lymph node invasion in surgical resection specimens of patients with early cancer in Barrett’s esophagus

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of patients</th>
<th>Selection criteria</th>
<th>Number of lymph nodes resected</th>
<th>Positive lymph node in T1m</th>
<th>Survival in T1m</th>
<th>Positive lymph node in T1sm</th>
<th>Survival in T1sm1N1</th>
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<td>Peters</td>
<td>17</td>
<td>Preoperative HGD/early cancer*</td>
<td>0/4 HGD</td>
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<td>100% 5-yr</td>
<td>1/2</td>
<td>--</td>
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<td>Ruol (1997)</td>
<td>26*</td>
<td>Postoperative</td>
<td>0/4</td>
<td>94% 5-yr†</td>
<td>8/22 37% 5-yr</td>
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<tr>
<td>Nigro (1999)</td>
<td>37</td>
<td>Postoperative</td>
<td>41†</td>
<td>1/15 T1m</td>
<td>--</td>
<td>6/12 T1sm</td>
<td>--</td>
</tr>
<tr>
<td>Van Sandick (2000)</td>
<td>32</td>
<td>Postoperative diagnosis pT1</td>
<td>13‡</td>
<td>0/12</td>
<td>100% 3-yr</td>
<td>6/20 50% 3-yr</td>
<td></td>
</tr>
<tr>
<td>Stein (2000)</td>
<td>94</td>
<td>Postoperative</td>
<td>21 and 19§</td>
<td>0/38</td>
<td>90% 5-yr‡</td>
<td>10/56 60% 5-yr</td>
<td></td>
</tr>
<tr>
<td>Rice (2001)</td>
<td>122</td>
<td>Postoperative</td>
<td>+ IHC</td>
<td>0/38 HGD</td>
<td>95% 5-yr</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>Fernando (2002)</td>
<td>28</td>
<td>Preoperative</td>
<td>0/17 HGD</td>
<td>2/53 T1m</td>
<td>80% 5-yr</td>
<td>6/31 TxN1</td>
<td></td>
</tr>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16†</td>
<td>0/6 T1m</td>
<td>100% 1-yr</td>
<td>1/5</td>
</tr>
</tbody>
</table>

HGD: high-grade dysplasia

*Pre-operative work-up: no review histology, Seattle biopsy protocol, EUS not mentioned, inclusion: 1985-1993

†For T1m/sm no.

£ Median

§Mean

‡Pre-operative work-up: review histology, four-quadrant biopsies in 64%, EUS in 57%


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The rate of complete remission (ie, successful removal of the HGD or EC with ER) is variable, ranging from 59 to 99 percent in different studies.\(^9,12,55-60,62-66\) In a systematic review that included 11 studies of patients with BE who underwent endoscopic mucosal resection (EMR), complete eradication of HGD or EC was achieved in 95 percent of patients, and complete eradication of all Barrett’s mucosa was achieved in 89 percent.\(^67\) Higher degrees of success are seen in patients with lower risk lesions, which are defined as macroscopic types I (protruded type), IIa (flat elevated type), IIb (flat type), and IIc (flat depressed type); a lesion diameter up to 20 mm that is limited to the mucosa; and histologically well to moderately well differentiated tumors.

Recurrence of carcinoma or the development of metachronous malignancies has been described in 6 to 30 percent of patients.\(^9,12,55-59,61,62,65,66\)

Multiple factors have been associated with recurrence:

- Larger lesion diameter
- Long-segment BE
- Removal of the lesion with piecemeal resection
- Failure to perform adjunctive ablative therapy (photodynamic therapy, argon plasma coagulation, or radiofrequency ablation)
- Presence of multifocal neoplasia
- An elapsed time of more than 10 months prior to achieving complete remission
- The presence of residual dysplasia
In most cases, recurrences can be successfully managed endoscopically. One of the largest studies to look at the efficacy of ER for patients with early adenocarcinoma of the esophagus included 1000 patients who were followed for a mean of 56.6 months. Complete remission was achieved in 96 percent of patients. Recurrent or metachronous lesions developed in 140 patients (15 percent) and were successfully treated endoscopically in 115 (82 percent of those with recurrence or metachronous lesions). Overall, the long-term complete remission rate was 94 percent.

The ideal candidate for ER has a solitary, small (ie, <2 cm diameter), flat type lesion (usually a combination of types IIa, IIb, and IIc) that is limited to the mucosa. Histopathologic differentiation may be less important for most cases, since the vast majority of these early lesions will be classified as high-grade dysplasia or well differentiated cancers. Tumors that are poorly differentiated or undifferentiated tumor differentiation is associated with adverse outcomes in studies using univariate analysis, but these studies usually included patients with more advanced lesions. In multivariate analyses, tumor differentiation has NOT been identified as an independent risk factor for lymph node metastasis or tumor recurrence. This finding may be related to the fact that most undifferentiated tumors have already invaded the submucosa at the time of diagnosis. However, reliable data on the relevance of histopathologic differentiation are sparse, especially given the small number of early, undifferentiated lesions in the available studies.

Because of the risk for recurrence, patients treated with endoscopic resection require regular endoscopic follow-up to detect recurrent lesions. In most studies, patients are followed every three months during the first year and annually thereafter. Alternatively, the residual Barrett segment could be treated endoscopically.

ENDOSCOPIC RESECTION AS PART OF ENDOSCOPIC THERAPY

An important drawback of endoscopic resection (ER) monotherapy for high-grade dysplasia (HGD) or early cancer (EC) in Barrett’s esophagus (BE) is the high recurrence rate of 30 percent within five years during follow-up; therefore, eradication of the residual Barrett’s mucosa should be recommended.

Endoscopic ablative therapy with radiofrequency ablation (RFA) or photodynamic therapy (PDT) allows treatment of the whole Barrett’s segment in one session, which may permit treatment of larger areas and/or be associated with a lower recurrence rate. Studies of RFA have reported impressive success rates when used in combination with ER for removal of visible abnormalities, both in the short- and long-term. PDT has been investigated as monotherapy for HGD and EC in BE as well as an adjuvant treatment after ER; however, serious complications such as stricture occurred frequently, and 15 percent of patients who received PDT ultimately developed esophageal cancer. Complete ER of the whole Barrett’s segment (picture 3) may also be used as endoscopic therapy. This so called stepwise radical endoscopic resection (SRER) technique offers the potential to remove the entire area of dysplastic and metaplastic tissue and has several advantages over ablative therapy.

- It allows complete removal of the whole mucosa at risk for malignant progression.
- It provides tissue samples for optimal histopathologic diagnosis.
• It may reduce the likelihood of persistent and/or induced genetic abnormalities that are associated with the progression of BE to adenocarcinoma.

Several series have demonstrated the feasibility and safety in experienced hands of ER of the entire Barrett’s segment, even in patients with a long segment of BE. 64,70-73

As examples:
• A series of 21 patients with HGD or EC underwent two sessions each of ER to remove the entire Barrett’s segment. 72 This was performed with a polypectomy snare after a submucosal injection of 10 to 15 mL of saline. There were no severe complications and none of the patients developed a stricture. In three patients, histology revealed that resection of an EC was incomplete; one patient underwent surgery (no residual tumor was found in the surgical resection specimen), and the other two patients underwent chemoradiotherapy. All three were alive without residual disease at follow-up.

Of the 18 patients with successful eradication of neoplasia, two (11 percent) showed recurrence of HGD during follow-up and were successfully retreated with endoscopic resection. Five patients had residual islands of Barrett’s mucosa embedded in the neosquamous mucosa, with low-grade dysplasia present in three of the five.

• Another series included 39 patients with HGD or EC in BE who underwent radical endoscopic resection using the endoscopic resection-cap technique after sub-
mucosal lifting (median of three sessions). All of the Barrett’s mucosa was removed in 33 (89 percent) of the patients, four patients had small isles of Barrett’s mucosa buried beneath the neosquamous mucosa (all had received argon plasma coagulation), and two could not complete the therapy due to unrelated comorbidities. There were two complications (one asymptomatic perforation and one delayed bleeding) and 10 patients (26 percent) developed dysphagia that responded to dilation. After a median of 11 months follow-up, there were no cases of recurrent neoplasia or Barrett’s mucosa.

In a single-center United States series, 107 patients with HGD or EC in BE were treated with endoscopic resection to remove the BE segment, either in a radical approach (single session) or in multiple treatment sessions. In a per-protocol analysis (eg, excluding patients who underwent surgery after ER or discontinued treatment for other reasons) 79 of 80 patients (99 percent) were treated successfully. Durability data were available for 74 patients who were followed for a median of 33 months; 74 of 74 patients (100 percent) had complete remission of HGD or EC, and 53 of 74 patients (72 percent) had complete remission from intestinal metaplasia.

In the largest multicenter series reported thus far, 169 patients with HGD or EC in BE up to 5 cm were treated with stepwise radical endoscopic resection to remove all neoplasia and Barrett’s mucosa. According to an intention-to-treat analysis, complete eradication of all neoplasia and all intestinal metaplasia by the end of the treatment phase was reached in 98 and 85 percent of patients, respectively. One patient had progression of neoplasia during treatment and died of metastasized adenocarcinoma (0.6 percent). After median follow-up of 32 months (interquartile range 19 to 49 months), complete eradication of neoplasia and intestinal metaplasia was sustained in 95 and 81 percent of patients, respectively. Acute, severe complications occurred in 1.2 percent of patients, and 50 percent of patients developed symptomatic stenosis.

In the only randomized trial to date in which SRER was compared with focal ER followed by radiofrequency ablation, 47 patients were included who had HGD or EC in BE up to 5 cm. Twenty-five patients received stepwise radical ER, and 22 patients received ER plus RFA. Complete eradication of all neoplasia (CE-neo) and all intestinal metaplasia (CE-IM) at the end of the treatment phase was similar in both groups (CE-neo 100 versus 96 percent, and CE-IM 92 versus 96 percent, respectively). The stenosis rate was higher in the SRER group than in the ER plus RFA group (88 versus 14 percent), which resulted in significantly more therapeutic sessions in the SRER group (six versus three procedures), mainly due to dilatations. After a median follow-up of 24 months (interquartile range 18 to 29 months), a single patient in the SRER group had a recurrent cancer at the neosquamocolumnar junction, which could be removed with ER.

The role of the stepwise radical endoscopic resection technique seems limited to select patients in the treatment of HGD or EC in Barrett’s esophagus. Although the SRER technique is equally effective and has potential advantages over ablative therapy, the results from the randomized trial indicate that SRER is associated with a much higher rate of stenosis than ER plus RFA. We would therefore advise to use the SRER technique only for patients with more extensive lesions in BE up to 5 cm.
Serious complications with the endoscopic resection (ER) techniques described above are rare, though complications such as stricture formation are common if large areas of Barrett’s mucosa are resected. \(^9,64,77,78\) Studies have shown that the risk of complications increases with piecemeal resection and the degree of involvement of the mucosa: \(^77,79\)

- **Bleeding** occurs in 0 to 46 percent of cases (depending in part on how it is defined) and can usually be managed easily with endoscopic methods. \(^9,57,59,60,66,78,80\) We suggest that immediate bleeding be regarded as a complication only if it results in clinical consequences such as a drop in the hemoglobin level, the need for blood transfusions, or clinical signs of recurrent bleeding after the endoscopic procedure.

- **Perforation** has been reported with an estimated incidence <1 to 5 percent. \(^66,78,79\) The risk is increased during piecemeal resection. \(^79\)

- **Strictures** have been reported in 2 to 88 percent of patients undergoing ER for Barrett’s esophagus (BE). \(^64,75-78,81,82\) The size/length of the mucosal defect and the degree of circumferential involvement by the BE predict stricture formation. \(^77,81,83\) In a study of 73 patients who underwent endoscopic resection for BE with high-grade dysplasia or intramucosal carcinoma, symptomatic strictures developed in 25 percent. Strictures were more common if the BE involved more than 50 percent of the esophageal circumference (odds ratio [OR] 4.2, 95% CI 1.3-14). There was a trend toward tobacco use also increasing the risk (OR 3.3, 95% CI 0.93-12). Strictures arising after ER usually resolve with dilation. \(^81\)

**SUMMARY AND RECOMMENDATIONS**

- In patients with high-grade dysplasia or early mucosal cancer complicating Barrett’s esophagus, we suggest endoscopic resection (ER) rather than surgery or ablative therapy, provided an experienced endoscopy is available and if the endoscopic appearance of the lesion does not raise suspicion for deep submucosal infiltration. ER should only be performed by trained endoscopists with experience in screening, imaging, and treatment of patients with early Barrett’s neoplasia (Grade 2C).
- ER is particularly useful in patients with nodular lesions.
- ER aids in histopathologic diagnosis, since it permits assessment of depth of infiltration and estimation of the risk for local lymph node metastasis. However, histopathologic interpretation of ER specimens may not be straightforward.
- Patients with high-grade dysplasia or early cancer should be referred to specialized centers that have integrated expertise in gastrointestinal endoscopy, imaging, surgery, and histopathology.
- Patients treated with ER require regular follow-up to detect recurrent lesions. In most studies, patients are followed every three months during the first year and annually thereafter.
- Optimal techniques for performing ER alone or in conjunction with other
endoscopic approaches are evolving. Combined with radiofrequency ablation, excellent eradication rates have been reported. Stepwise radical ER is associated with a higher rate of stenosis, and its use should be limited to patients with more extensive lesions.

- The most common complications from ER are bleeding and esophageal stricture formation, both of which can generally be addressed endoscopically.
REFERENCE LIST


Prasad GA, Wu TT, Wigle DA, et al. Endoscopic and surgical treatment of mucosal (T1a) esophageal adenocarcinoma in Bar-


