Barrett's esophagus: Treatment of high-grade dysplasia or early cancer with endoscopic resection

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INTRODUCTION

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. (See "Barrett's esophagus: Epidemiology, clinical manifestations, and diagnosis".)

Endoscopic surveillance is recommended for patients with BE 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 (HGD) or early cancer. (See "Barrett's esophagus: Surveillance and management".)

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 BE with HGD 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, argon plasma coagulation or radiofrequency ablation) 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 BE who have HGD or early cancer is discussed here. Radiofrequency ablation, a general approach to BE, and other treatment options for superficial esophageal cancer are presented separately. (See "Barrett's esophagus: Treatment with radiofrequency ablation" and "Barrett's esophagus: Surveillance and management" and "Management of superficial esophageal cancer".)

PRETREATMENT EVALUATION

The pretreatment evaluation of patients with Barrett's esophagus (BE) who have high-grade dysplasia (HGD) or early cancer includes the endoscopic work-up, staging of the lesions, and histopathologic evaluation.

Endoscopic evaluation — Patients with BE should undergo a careful endoscopic evaluation to detect possible visible lesions. If a visible lesion is found, a patient should be referred for further work-up in a center with expertise in diagnosis and treatment of BE. If no visible lesion is found, random biopsies according to the Seattle protocol should be obtained, and if these show dysplasia (either low- or high-grade dysplasia, confirmed by an expert pathologist), the patient should be referred to an expertise center for further work-up. The reasons for this are:

- 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 [14]. 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.

- Visible lesions in patients with BE and low-grade dysplasia (LGD) may be missed. In a study including 248 patients initially diagnosed with flat BE and LGD, restaging by an expert center demonstrated a visible lesion with HGD or cancer in 45 patients (18 percent) [15].

- Evaluation at a specialized center permits detection of synchronous lesions elsewhere in the BE 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 endoscopic resection (ER).

Early neoplastic lesions in BE 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. (See "Chromoendoscopy" and "Magnification endoscopy" and "Barrett's esophagus: Evaluation with optical chromoscopy" and "Optical coherence tomography in the gastrointestinal tract".)

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 [16,17]. 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 early cancer without visible abnormalities will have at least one visible abnormality detected in their BE upon endoscopic inspection by expert endoscopists [16,18]. 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 [19]. 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 [20]. 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 BE with HGD [21]. 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 [21]. 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 early cancer can be made in 80 to 90 percent of patients with these lesions by targeted biopsies after a thorough inspection [22]. However, random four-quadrant biopsies are still required since 10 to 20 percent of lesions are missed with targeted biopsies alone.

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 a visible lesion and HGD or early cancer in BE [23-25]. In one study, interobserver agreement about the presence of neoplasia was significantly better on ER specimens than biopsy specimens [24]. This approach is consistent with guidelines from the American Society for Gastrointestinal Endoscopy that recommend ER for the treatment of visible lesions and suspected intramucosal

adenocarcinoma [26]. 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 predictors of lymph node metastasis are the penetration depth of the tumor, differentiation grade, and presence of lymphovascular invasion [27]. ER 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.

Among patients diagnosed with HGD or early cancer, other imaging techniques could be considered to evaluate tumor infiltration depth, local lymph node status, and metastatic spread. Endoscopic ultrasonography and computerized tomography (CT) scan are the most widely used techniques. Staging of and treatment strategies for superficial esophageal cancer are discussed separately. (See "Management of superficial esophageal cancer".)

Other staging methods — Endoscopic ultrasound (EUS) has a central role in the initial staging of esophageal cancer. However, EUS is less reliable for T- and N-staging in patients with HGD and early cancer than in patients with more advanced esophageal cancer. The role of EUS for T staging and subsequent management of superficial tumors has been controversial and is discussed in more detail separately. (See "Endoscopic ultrasound in esophageal cancer" and "Management of superficial esophageal cancer", section on 'Initial assessment'.)

The value of CT scanning lies mainly in the detection of distant metastases. The risk for distant metastases is very low in patients with HGD or early cancer who show no signs of deep submucosal infiltration or suspicious lymph nodes on EUS. Thus, the value of CT is limited in such patients.

Histopathologic evaluation — Esophageal neoplasia is usually classified according to the internationally accepted Vienna classification [28]. 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 [29,30]. These observations underlie the recommendation that a second, experienced pathologist should confirm the diagnosis of HGD. (See "Barrett's esophagus: Surveillance and management".)

ENDOSCOPIC RESECTION

Techniques

Endoscopic resection-cap — The ER-cap technique is performed after submucosal lifting (figure 1 and picture 1) [31,32]. 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 ER-snare. The lesion is sucked into the cap, thus creating a pseudopolyp that is immediately captured by forcefully closing the pre-positioned ER-snare. The lesion is then removed using electrocoagulation. (See "Overview of endoscopic resection of gastrointestinal tumors".)

ER-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.

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. Multiple specimens can be removed during the procedure using this device (picture 2).

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 ER-cap technique. The reason is that the esophageal muscle layer will immediately retract when captured within a rubber band, whereas with the standard ER-cap technique it will remain captured in the forcefully closed ER-snare.
- Multiple resections can be performed with the same snare.
- Pre-looping the ER-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 (BE) 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 [32].

In a case control study, 80 MBM procedures were compared with 86 ER-cap procedures [33]. The study showed that MBM was safe and effective for widespread ER in BE. MBM appeared to be quicker than ER-cap, but the specimens removed with MBM were significantly smaller than with the ER-cap technique.

Following this case-control study, a multicenter randomized controlled trial was initiated to compare the ER-cap technique and MBM for piecemeal resection of early neoplasia in BE [34]. 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 ER-cap (34 versus 50 minutes and 240 versus 322 euro, respectively). MBM resulted in smaller specimens than ER-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 ER-cap group and one perforation in the MBM group. The perforations in the ER-cap group were

treated endoscopically, whereas the perforation in the MBM group required surgical repair because of periesophageal scarring that prevented endoscopic closure.

MBM appears to be safe and fast for widespread ER in BE. Time and costs appear to be saved compared with ER-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 ER-cap despite the 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.

Endoscopic submucosal dissection — Endoscopists have used specially designed needle knives for en bloc dissection of large esophageal lesions, a technique known as endoscopic submucosal dissection (ESD) [35-39]. The main advantage of ESD is that it allows for en bloc resection of lesions, but it is associated with a longer procedure time, a longer learning curve and possibly a higher risk of complications compared with endoscopic mucosal resection (EMR).

The European Society of Gastrointestinal Endoscopy guidelines recommend piecemeal EMR over ESD in most cases of Barrett's early neoplasia [40]. We reserve ESD for patients with a strong suspicion of submucosal invasion and for the resection of lesions with a large intraluminal component prohibiting a cap-based resection (ie, the intraluminal part of the lesion would fill the cap upon suctioning, and resection of the basal mucosal layers might be incomplete despite the absence of deep submucosal invasion). We perform ESD in approximately 25 percent of patients with early Barrett's neoplasia. (See "Overview of endoscopic resection of gastrointestinal tumors", section on 'Endoscopic submucosal dissection'.)

Data from mostly retrospective studies suggest that ESD is effective and safe for treating early Barrett's neoplasia [41,42]. In a meta-analysis of 11 studies including 1329 patients, ESD was associated with greater likelihood of en bloc resection and R0 resection (ie, resection with a negative margin) compared with EMR (odds ratio [OR] 47.3, 95% CI 23.9-93.57 and OR 6.2, 95% CI 2.5-15.2, respectively) [42]. ESD was associated with a lower risk of local recurrence after 16 months compared with EMR after 27 months of follow-up (OR 0.2, 95% CI 0.1-0.8). In a subsequent study including patients with HGD or mucosal cancer, ESD was associated with higher rates of en bloc resection and R0 resection compared with EMR (89 versus 43 percent and 73 versus 56 percent, respectively) [41]. ESD was associated with lower rates of recurrence after eight months compared with EMR after 16 months of follow-up (4 versus 31 percent).

When interpreting these studies, there are several important considerations such as possible selection bias related to retrospective study design and confounding factors. For example, data

may be impacted by endoscopist experience, differences in resection technique, and duration of follow-up. Because ESD is a technically challenging procedure, more advanced and experienced endoscopists typically perform ESD, whereas EMR is performed by less experienced endoscopists. In addition, EMR procedures were generally performed in earlier studies, whereas ESD was performed more often in subsequent studies. Over time, the quality of the endoscopic equipment and endoscopic therapy has improved. Lastly, follow-up time after ESD is generally shorter than EMR procedures, which may also introduce bias.

Additional studies are needed to determine whether ESD is preferred for selected patients with neoplasia related to BE (eg, patients with lesions >2 cm), and randomized trials comparing ESD with EMR are ongoing [43,44].

Observational studies from specialized centers suggest that ESD is more effective for mucosal cancer than submucosal cancer. In a study including 138 patients with BE with bulky lesions or suspected submucosal invasion, the rates of successful en bloc and R0 resection after ESD were higher for patients with HGD/mucosal cancer compared with submucosal cancer (87 versus 49 percent) [45]. Among 34 patients with R1 resection (ie, microscopic detection of residual tumor), 10 patients (29 percent) had residual cancer detected at the initial follow-up endoscopy after ESD. Six patients who underwent surgery had no residual tumor. These data suggest that R1 resection is a challenging histologic assessment and may not consistently establish the presence of residual disease.

Learning curve — 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. (See 'Complications' below.)

However, studies on the learning curve of ER are limited, and most have assessed the learning curve of the 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 ER rate and decreases in perforation rate and procedure time [46-48].

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 ER 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 [49].

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 ER 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.

HISTOLOGIC ASSESSMENT

Interpreting endoscopic resection (ER) specimens of Barrett's neoplasia may be challenging. 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 Barrett's esophagus (BE) [50]. 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.

Many early lesions in BE are associated with severe inflammation that is due to the accompanying reflux disease and may hamper histologic assessment. Similarly, because ER involves the use of electrocoagulation, the deep and especially the lateral resection margins may have coagulation artifacts, complicating histologic evaluation compared with surgical resection specimens [45,51].

Histologic assessment relies on the extent of the resection; however, data suggests that resection specimens that lack submucosal tissue are common with ESD. In a study including 1685 digitized tissue sections from 76 patients with early cancer related to BE, rates of submucosal defects following ESD or EMR were 33 and 35 percent, respectively [52]. The findings related to ESD are somewhat unexpected because ESD allows for uniform deep submucosal dissection. Further studies are need to explore whether the presence of submucosal defects can be used as a quality indicator for proficiency in ESD.

The ability to treat early cancer 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 BE with HGD from intramucosal cancer in surgical specimens was poor (kappa statistic 0.42) [53]. It was somewhat better for distinguishing intramucosal and submucosal cancer (kappa statistic of 0.71). The distinction between HGD and mucosal cancer is not considered clinically relevant. The two conditions are difficult to distinguish histologically, and both carry a virtually absent risk of local lymph node metastases.

Assessment of disease extent and risk factors for nodal metastases are discussed in more detail separately. (See "Management of superficial esophageal cancer", section on 'Initial assessment'.)

Pathologic subclassification — The terminology and classification of early esophageal cancers have evolved and are outlined in the tumor node metastasis (TNM) staging system of the combined American Joint Committee on Cancer (AJCC)/Union for international Cancer Control (UICC) [54].

Early esophageal cancers are those that are classified as Tis (HGD, 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. (See "Clinical manifestations, diagnosis, and staging of esophageal cancer", section on 'TNM staging criteria'.)

A more comprehensive subclassification scheme has been proposed for early esophageal cancers and is useful for determining prognosis and selecting treatment (figure 2) [55]. 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 [55]:

- 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.

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 2).

Patients with invasive adenocarcinoma of the esophagus (into the submucosa and beyond) should be referred to an oncologist for staging and to discuss treatment options. The choice of treatment will depend on the patient's overall health and the stage of the cancer and may include chemoradiotherapy with or without esophagectomy, or even ER in highly selected cases. (See "Management of superficial esophageal cancer".)

EFFICACY

The rate of complete remission (ie, successful removal of the HGD or early cancer with ER) is high. In a systematic review that included 11 studies of patients with BE who underwent endoscopic mucosal resection, complete eradication of HGD or early cancer was achieved in 95 percent of patients, and complete eradication of all Barrett's mucosa was achieved in 89 percent [56]. 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.

In addition to the risk of local recurrence, the reported risk of developing HGD or early cancer in BE that persists after ER of a visible lesion ranges from 15 to 30 percent during the subsequent three to five years [12,57-59]. Endoscopic eradication therapy using radiofrequency ablation is typically used to treat BE in such patients, and this is discussed separately. (See "Barrett's esophagus: Treatment with radiofrequency ablation".)

Multiple factors have been associated with recurrence [12,60-64]:

- 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 the vast majority of cases, recurrences can be successfully managed endoscopically [64].

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 [64]. 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.

ENDOSCOPIC RESECTION AS PART OF ENDOSCOPIC THERAPY

An important drawback of endoscopic resection (ER) monotherapy for high-grade dysplasia (HGD) or early cancer in Barrett's esophagus (BE) is the relatively high recurrence rate of 15 to 30 percent within five years during follow-up; therefore, eradication of the residual Barrett's mucosa is usually performed. (See 'Efficacy' above.)

Endoscopic ablative therapy with radiofrequency ablation (RFA) allows treatment of the entire Barrett's segment in one session. 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 [65,66]. Selecting patients with HGD or early cancer for focal ER followed by ablative therapy using RFA is discussed in more detail elsewhere. (See "Management of superficial esophageal cancer", section on 'Endoscopic therapy' and "Barrett's esophagus: Treatment with radiofrequency ablation".)

COMPLICATIONS

Serious complications related to endoscopic resection (ER) techniques are rare, though complications such as stricture formation are common if large areas of Barrett's mucosa are resected [9,67-69]. Studies have shown that the risk of complications increases with piecemeal resection and the degree of involvement of the mucosa [68,70]:

- 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 [9,45,57,61,64,69,71-73]. 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. The risk of bleeding has been associated with the number of resections. In an analysis of 3827 ER procedures using multiband mucosectomy, a higher number of resections was associated with increased bleeding risk (OR, 1.15; 95% CI, 1.06-1.25) [73].

- Perforation has been reported with an estimated incidence <1 to 5 percent [45,64,69,70,73]. The risk of perforation is increased during piecemeal resection [70].

- Strictures have been reported in 2 to 88 percent of patients undergoing ER for BE [45,65-69,73-75]. The size/length of the mucosal defect and the degree of circumferential involvement by the BE predict stricture formation [68,74,76]. In a study of 73 patients who underwent ER 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 [74].

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: Barrett's esophagus".)

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: Barrett's esophagus (The Basics)")
- Beyond the Basics topics (see "Patient education: Barrett's esophagus (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **General principles** – Patients with high-grade dysplasia (HGD) or early cancer should be referred to specialized centers that have integrated expertise in gastrointestinal endoscopy, imaging, surgery, oncology, and histopathology. (See "Management of superficial esophageal cancer".)

  The pretreatment evaluation of patients with Barrett's esophagus (BE) who have HGD or early cancer includes endoscopic evaluation, staging of the lesions, and histopathologic evaluation. For patients with a visible lesion in BE, endoscopic resection (ER) serves as both diagnostic modality and therapeutic intervention. (See 'Pretreatment evaluation' above.)

- **Techniques** – Endoscopic techniques for resecting visible lesions in patients with BE include ER-cap technique, multiband mucosectomy, and endoscopic mucosal dissection (ESD). (See 'Techniques' above.)

- **Histologic assessment** – 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. However, in patients who undergo ER and the histology of the lesion shows HGD or cancer but with good differentiation and absence of lymphovascular invasion, ER is regarded as a curative intervention. (See 'Endoscopic resection as staging procedure' above and 'Histologic assessment' above.)

- **Follow up** – Patients treated with ER require regular endoscopic follow-up to detect recurrent lesions or, alternatively, the remaining BE segment is treated with ablation therapy. (See 'Efficacy' above and "Barrett's esophagus: Treatment with radiofrequency ablation".)

- **Adverse events** – ER is a safe procedure with a low risk for complications. The most common complications from ER are bleeding and esophageal stricture formation, both of which can generally be addressed endoscopically. (See 'Complications' above.)

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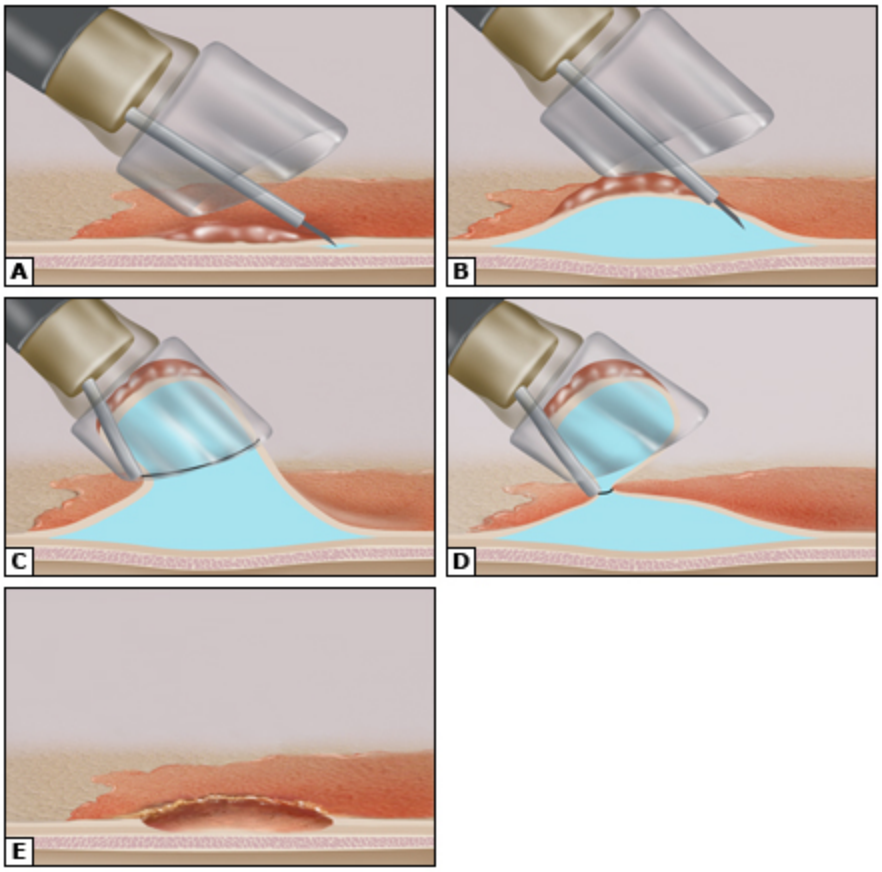
Topic 2651 Version 36.0

GRAPHICS

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.

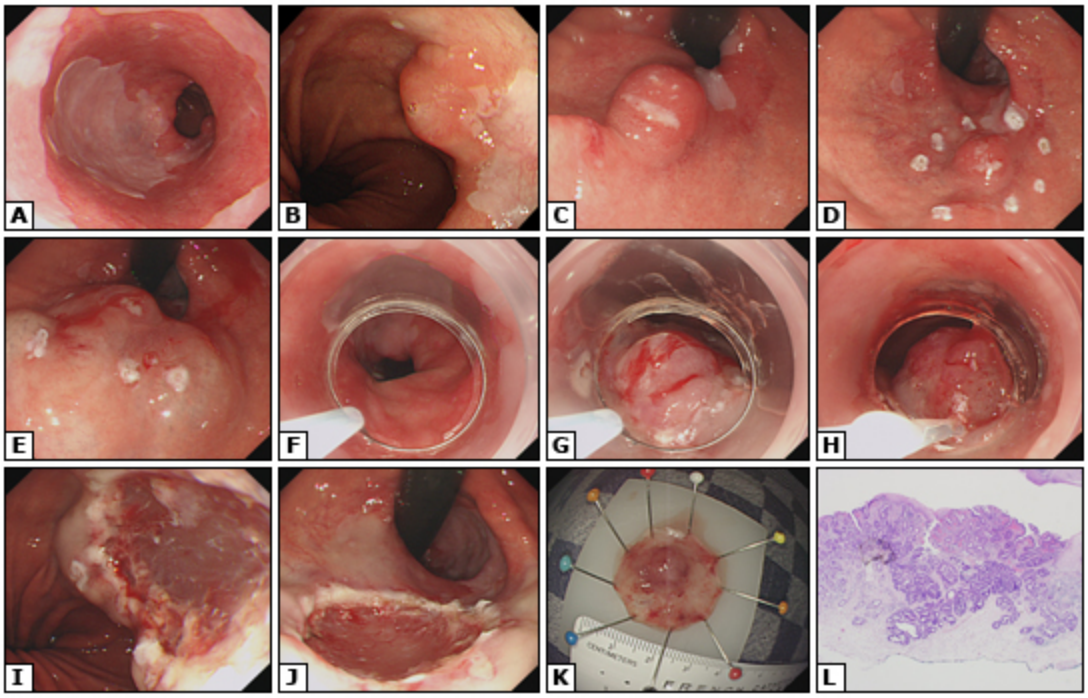
(C and D) After removal of the needle, a crescent shaped snare is positioned into a distal ridge within the cap. The lesion is sucked into the cap thus creating a pseudo-polyp that is immediately captured by forcefully closing the pre-positioned EMR-snare.

(E) The lesion is removed using electrocoagulation.

EMR: endoscopic mucosal resection.

Graphic 62474 Version 4.0

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 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.

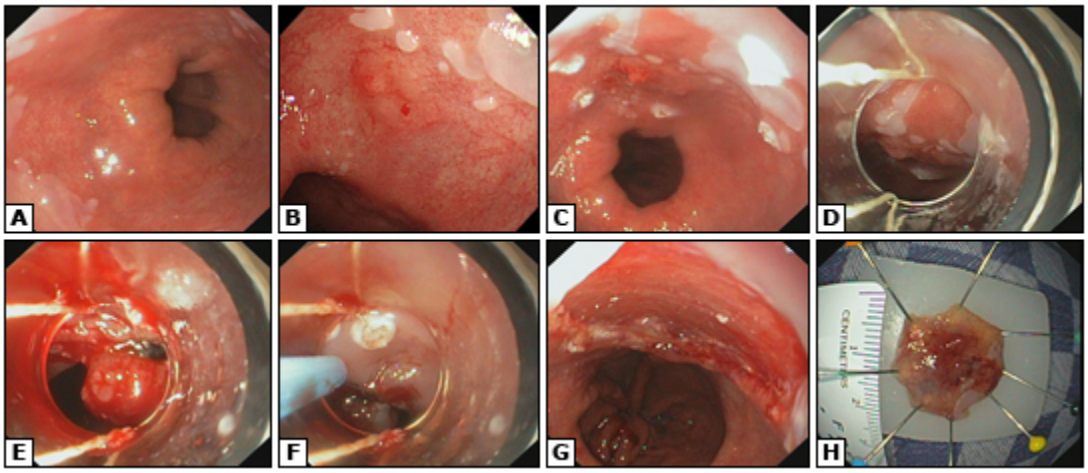
(K) The EMR specimen is subsequently removed from the stomach using retrieval net and pinned down on paraffin to prevent shrinking and curling.

(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.

Graphic 74236 Version 4.0

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 intraepithelial dysplasia.

Graphic 53386 Version 5.0

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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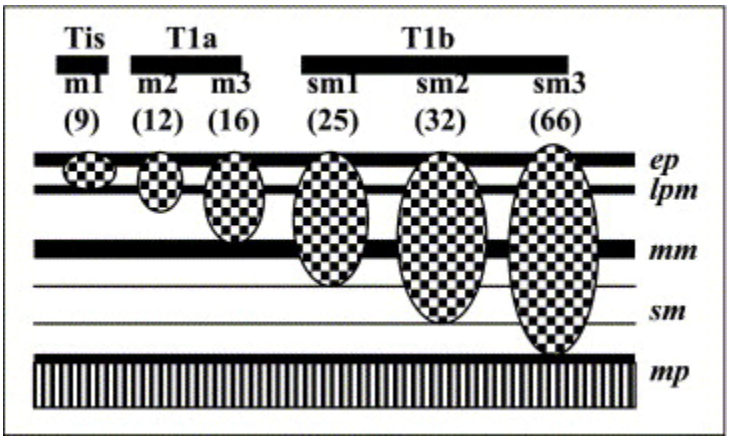
Graphic 111221 Version 9.0

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

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

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