Overview of endoscopic resection of gastrointestinal tumors

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INTRODUCTION

Endoscopic resection (ER) is an endoscopic alternative to surgical resection of mucosal and submucosal neoplastic lesions and intramucosal cancers [1]. ER includes endoscopic mucosal resection (EMR), which involves snare resection of dysplastic lesions, and endoscopic submucosal dissection (ESD) in which endoscopic tools are used to dissect lesions from the submucosa. ER offers both diagnostic and therapeutic capability. Lesions limited to the mucosa and the superficial layers of the submucosa appear to be the most amenable to endoscopic cure.

This topic will provide an overview of ER for gastrointestinal tumors. Additional information on ER for the removal of superficial esophageal cancer, high-grade dysplasia in patients with Barrett's esophagus, early gastric cancer, and large colon polyps can be found elsewhere. (See "Management of superficial esophageal cancer" and "Barrett's esophagus: Treatment of high-grade dysplasia or early cancer with endoscopic resection" and "Early gastric cancer: Epidemiology, clinical manifestations, diagnosis, and staging" and "Endoscopic removal of large colon polyps".)

LESION CLASSIFICATION

The greatest experience with ER has come from Japan, where the Japanese Society for Gastroenterological Endoscopy (JSGE) has developed a classification system based upon visual and endosonographic features. The system was developed in an attempt to codify the indications and outcomes related to ER [2]. Although it was developed for early gastric cancer, it can also be applied to epithelial cancers at other sites in the gastrointestinal tract. The system recognizes four types of early endoluminal cancers (table 1 and figure 1):

- Type I lesions are polypoid or protuberant and are subcategorized as:
  - Ip – pedunculated
  - Ips/sp – subpedunculated
  - Is – sessile
- Type II lesions are flat and are further subcategorized as:
  - IIa – superficial elevated
  - IIb – flat
  - IIc – flat depressed
  - IIc+IIa lesions – elevated area within a depressed lesion
  - IIa+IIc lesions – depressed area within an elevated lesion
- Type III lesions are ulcerated
- Type IV lesions are lateral spreading

Another classification system, the Paris system, was proposed at a consensus development meeting held in Paris in 2002 [3]. Superficial lesions (type 0) can be classified as polypoid, nonpolypoid or excavated (table 2 and figure 2):

- Type 0-I lesions are polypoid are subcategorized as:
  - Type 0-Ip – protruded, pedunculated
  - Type 0-Is – protruded, sessile
- Type 0-II lesions are nonpolypoid and are subcategorized as:
  - Type 0-IIa – slightly elevated
  - Type 0-IIb – flat
  - Type 0-IIc – slightly depressed
- Type 0-III lesions are excavated

INDICATIONS

The indications for ER include the treatment of early esophageal, gastric, and colon cancers. Endoscopists in the United States are increasingly utilizing ER techniques as commercially available devices become easier to use, such as band assisted mucosectomy devices. ER is also used to treat dysplasia in the setting of Barrett's esophagus and for the removal of large colon polyps. (See "Barrett's esophagus: Treatment of high-grade dysplasia or early cancer with endoscopic resection" and "Endoscopic removal of large colon polyps", section on 'Endoscopic mucosal resection techniques'.)

Esophageal cancer — ER can be done successfully in patients with superficial esophageal cancer [4-13] or with high-grade dysplasia (HGD) in Barrett's esophagus (BE) [4,14,15]. (See "Management of superficial esophageal cancer" and "Barrett's esophagus: Surveillance and management" and "Barrett's esophagus: Treatment of high-grade dysplasia or early cancer with endoscopic resection".)

For patients with esophageal cancer or high-grade dysplasia, ER is being used in conjunction with ablation including radiofrequency ablation (RFA), argon plasma coagulation (APC), and cryotherapy ablation techniques [16]. If nodular adenocarcinoma or HGD confined to the mucosa or superficial submucosa is identified, then ER and further ablation of flat Barrett's mucosa may be appropriate treatment for curative intent. However, if invasion into the deep sub-mucosa is identified, then other treatment options should be considered given the high rate of nodal metastases (17 percent in one study) [17,18]. (See "Barrett's esophagus: Treatment with radiofrequency ablation".)

Esophageal cancers are amenable to ER using standard EMR technique if they (table 3) [4,19,20]:

- Have a diameter of ≤2 cm
- Involve less than one-third of the circumference of the esophageal wall
- Are limited to the mucosa of the esophagus (corresponding to a T stage of T1a) (table 4)

Larger esophageal lesions may still be effectively treated with ER [21].

Gastric cancer — Studies suggest that ER is an effective treatment for early gastric adenocarcinoma including lesions that are confined to the mucosa and those extending to the superficial submucosa. The criteria for selecting patients with early gastric cancer for endoscopic resection are discussed separately. (See "Early gastric cancer: Treatment, natural history, and prognosis", section on 'Endoscopic therapies'.)

ER has been used for treating gastric subepithelial tumors, such as gastrointestinal stromal tumors, leiomyomas, and neuroendocrine tumors. Efficacy of ER for such tumors is related to the lesion's layer of origin and ER technique. Lesions confined to the muscularis mucosa and submucosa may be resected en bloc by endoscopic mucosal resection (EMR) and, if they are greater than 1 cm in size, by endoscopic submucosal dissection (ESD). However, lesions originating from the deeper layers such as muscularis propria may require full thickness ER or submucosal tunneling ER (STER) to achieve R0 resection. In a study with 37 patients with gastric subepithelial tumor who had ESD, complete en bloc resection was achieved in 30 patients (81 percent) [22]. Higher resection rates were associated with tumors in the submucosa compared with the muscularis propria (100 versus 68 percent). No recurrences were reported for patients who had complete resection after a median follow-up of 21 months. However, in study of 90 patients who underwent ER primarily for gastric or small bowel gastrointestinal stromal tumors (one patient had an esophageal tumor), complete resection with negative margins was achieved in 23 patients (26 percent) [23]. After a mean follow-up of 46 months, there were two recurrences (both had microscopic margins positive for tumor). In a study including 454 patients with gastric GIST (≤5 cm in size), ER with ESD or submucosal tunneling was associated with lower rates of achieving R0 resection compared with surgical resection (62.7 versus 98.5 percent) [24]. After a median follow up ranging from 41 to 48 months, no recurrence or distant metastases occurred in either treatment group.

Thus, the decision to use of ER for subepithelial lesions is informed by multiple factors including lesion's layer of origin and size, histology of the lesion (risk of metastatic disease), advanced endoscopist availability, and patient's operative risk. (See "Local treatment for gastrointestinal stromal tumors, leiomyomas, and leiomyosarcomas of the gastrointestinal tract".)

Colorectal cancer — ER can be used in the treatment of colorectal cancers, including adenocarcinoma and rectal carcinoid tumors. (See "Staging, treatment, and post-treatment surveillance of non-metastatic, well-differentiated gastrointestinal tract neuroendocrine (carcinoid) tumors", section on 'Rectum'.)

Inject-and-cut methods of EMR for colonic neoplasms have been reported in many series, with complete en bloc removal rates of 86 to 97 percent [25-27]. (See 'Endoscopic resection techniques' below.) Factors associated with incomplete removal include size greater than 2 cm and a large sessile configuration. A modified needle-knife demarcation technique has also been employed. In a series of 32 patients with large (>3 cm) sessile neoplasms, the needle-knife technique had a 100 percent success rate. (See 'Endoscopic submucosal dissection' below.) [28].

According to the JSGE, colonic neoplasms that may be amenable to EMR include (table 3) [20]:

- JSGE type I lesions that are less than 3 cm in diameter
- JSGE type IIa lesions that are less than 3 cm in diameter
- JSGE type IIb lesions that are less than 5 mm in diameter
- JSGE type IIc+IIa lesions that are less than 1 cm in diameter
- JSGE type IIa+IIc lesions that are less than 1 cm in diameter
- JSGE type IV lesions that are less than 3 cm in diameter

Depressed lesions may have invasion into the submucosa, even when they are small, and deep invasion is a contraindication to EMR. The Paris classification notes that deep invasion is more likely when [3]:

- The lesion diameter is >15 mm
- The border of an elevated or depressed lesion (Paris type 0-IIa or 0-IIc, respectively) presents as a smooth circle without indentations
- The lesion fails to lift after injection with saline into the submucosa

When determining whether a lesion is amenable to EMR, we consider the presence of any of the criteria for deep invasion identified in the Paris classification, especially the failure to lift, to be contraindications to any mucosal resection method.

In addition to EMR, ESD is being used in the treatment of colon polyps and cancers [29]. In a meta-analysis of 14 studies of patients undergoing ESD for large polyps, successful en-bloc polyp resection was achieved in 85 percent of procedures [30]; in 75 percent of the procedures, the resection margins were histologically negative for adenoma. Other studies of patients with colorectal neoplasms including cancers have found complete resection rates of 75 to 89 percent [31,32]. (See "Endoscopic removal of large colon polyps", section on 'Endoscopic submucosal dissection techniques'.)

ENDOSCOPIC ULTRASOUND IN ENDOSCOPIC RESECTION

Endoscopic ultrasound (EUS) is a sensitive in vivo method for determining the depth of tumor penetration and thus aids with the selection of patients who have lesions that are amenable to ER. On the other hand, ER may allow for more precise determination of the depth of tumor invasion compared with EUS [33]. The role of EUS for identifying patients who are candidates for ER is discussed elsewhere. (See "Endoscopic ultrasound in esophageal cancer" and "Endoscopic ultrasound (EUS): Use of miniprobes for evaluating gastrointestinal lesions" and "Management of superficial esophageal cancer" and "Barrett's esophagus: Treatment of high-grade dysplasia

or early cancer with endoscopic resection" and "Early gastric cancer: Epidemiology, clinical manifestations, diagnosis, and staging".)

ENDOSCOPIC RESECTION TECHNIQUES

Endoscopic mucosal resection techniques — The techniques for endoscopic mucosal resection (EMR) can be broadly divided into two groups: suction (suck-and-cut) and non-suction (lift-and-cut) techniques. Regardless of the resection technique, submucosal injection is often used to separate mucosal and submucosal lesions from the muscularis propria (figure 3); however, EMR in the esophagus is increasingly performed without submucosal injection.

Submucosal injection — Submucosal injection to create an undermining submucosal fluid cushion (SFC) may decrease the incidence of perforation during EMR. Puckering or non-lifting of the lesion during injection also suggests invasion of the muscularis propria [34].

Normal saline can be used but is absorbed quickly. To overcome this limitation, hypertonic saline, 50 percent dextrose, 10 percent glycerol, 5 percent fructose, a fibrinogen mixture, sodium hyaluronate, and hydroxypropyl methylcellulose (HPMC), hydroxyethyl starch 6 percent, have all been used [35-39]. One preferred SFC solution is HPMC because it is widely available, less expensive than sodium hyaluronate, and appears to be as effective as sodium hyaluronate [40,41]. At least 10 to 40 mL of solution should be injected for an effective SFC [42-45]. Injections are performed using an injection needle at one or multiple sites adjacent to the lesion in an attempt to lift the lesion away from the muscularis propria. An automated pump designed for rapid and uniform submucosal injection (ERBE USA, Inc., Marietta, GA) is also commercially available [46].

Some studies suggest that 50 percent dextrose may be superior to normal saline for use as a lasting (more than five minutes) SFC during prolonged procedures [47]. However, a potential concern with 50 percent dextrose was raised in one study in which it was more likely to be associated with postpolypectomy electrocoagulation syndrome than the combination of saline and epinephrine [47]. (See "Postpolypectomy coagulation syndrome".)

In a study comparing various solutions, the duration of the SFC was shortest with normal saline or normal saline plus epinephrine (less than three minutes), was slightly longer with 50 percent dextrose and glycerine (four minutes), and was longest with hyaluronic acid (22 minutes) [34].

Preliminary animal and human experiences have been reported that suggest that adding MESNA (sodium 2-sulfanylethanesulfonate) to the SFC may enable resection of flat lesions by further enhancing the ability to separate the mucosa from the submucosa [48,49].

In a trial of 80 patients with colonic lesions sized 20 to 100 mm, the use of succinylated gelatin for submucosal injection resulted in lesion removal in fewer pieces and less time compared with normal saline. This solution is not available in the United States [50].

We typically use hetastarch mixed with methylene blue and dilute epinephrine for ER procedures. Several proprietary submucosal injectate solutions have become commercially available. Based on clinical experience, these injectate solutions are more useful than saline in terms of lesion lift and duration of effect.

Suction methods — Once the lesion has been lifted away from the muscularis propria by the SFC, it is suctioned up and resected [51]. This technique is most commonly performed with a transparent cap affixed to the tip of the endoscope (also known as cap-assisted EMR, EMRC) [52]. This cap is placed over the lesion and suction is applied, drawing the lesion into the cap. The lesion is then resected with a snare placed through the endoscope into the cap (figure 4). To decrease the risk of perforation, two groups have recommended injecting a sufficient volume of saline (20 to 40 mL) to raise the lesion with controlled suction and snaring at the middle of the SFC rather than the base [53,54].

A variation of the suction technique is the band and snare procedure, which in many cases does not require submucosal injection. During the band and snare procedure, tissue is banded using an esophageal variceal banding device and then snared off in the standard fashion (figure 5 and picture 1) [52,55,56]. Commercial EMR kits designed for this technique are available. A large channel endoscope may be helpful since it facilitates generation of adequate suction prior to resection.

Non-suction methods — Non-suction methods use a grasping device to pull the lesion away from the muscularis propria, after which a snare is used to resect the specimen. These were the first techniques used for EMR and are technically more challenging than the suction methods described above. Non-suction methods include: strip biopsy (lift-and-cut), strip biopsy (cutting method), strip biopsy (using a partial hood), endoscopic double-snare polypectomy, endoscopic resection with local saline epinephrine injection, and endoscopic resection with local sodium hyaluronate injection [43,57-61].

Widespread EMR — The widespread EMR (WEMR) technique is intended for resection of surface lesions larger than 2 cm at the esophagogastric junction [62]. WEMR can potentially benefit patients with high-grade dysplasia in Barrett's esophagus. It may also minimize the 5 to 47 percent residual or recurrent lesion rate associated with piecemeal resection of colonic polyps larger than 2 cm [63,64]. (See "Endoscopic removal of large colon polyps".)

A mucosal strip is created using a prototype porcelain ball-tipped needle-knife. The proximal and lateral margins of the strip are separated from the underlying tissue after a sufficient SFC is created. The mucosa is then stripped off its cushion moving in a distal direction using a grasping forceps. Next, the strip of mucosa, which is still attached at its distal end, is released into the gastric cavity and resected using a snare and forceps with the endoscope in retroflexion. WEMR can be technically challenging to perform and demands multiple maneuvers of the endoscopist.

WEMR can be partial or circumferential. However, the circumferential method has been associated with an increased incidence of stricture formation [11].

Endoscopic submucosal dissection — Endoscopic submucosal dissection (ESD) is a specialized ER technique that uses a modified needle knife (ESD-knife) to remove the lesion by dissecting through the submucosa [65-69]. It offers the potential to remove mucosal and submucosal tumors en bloc irrespective of size of the lesion. The greatest experience with ESD has been in treatment of early gastric cancer [65,66,70,71], but it has also been applied to lesions in the colon [67,72-74], the esophagus [68,75-80], the esophagogastric junction [81], and duodenum [82-84]. (See "Early gastric cancer: Treatment, natural history, and prognosis", section on 'Endoscopic submucosal dissection'.)

Technique — Several steps are required to perform ESD. First, the lesion and the margin are studied using narrow band imaging (NBI) or chromoendoscopy. (See "Chromoendoscopy".)

Next, the circumference of the lesion is marked at 3 to 5 mm from the margin with cautery or argon plasma coagulation. Submucosal injection is performed under the markings. Circumferential incision guided by the markings is performed with the ESD-knife, creating a mucosal flap and access for submucosal dissection. Submucosal solution is again injected under the incised mucosal flap and the ESD knife is used to perform cautery dissection strand-by-strand until the entire lesion is released from its submucosal attachment. The submucosal dissection step tends to be the most challenging, often requiring management of exposed submucosal vessels and continuously maintaining the endoscope within the submucosal plane (avoiding incising the dysplastic tissue [superficial] and the muscularis propria [deep] to the dissection plane).

Various electrocautery settings may be used for both incision and dissection steps of the procedure. Special devices, such as a transparent cap attached to the tip of the endoscope, can provide better control of the dissection step. A variety of ESD-knives are available and selection of the knife is largely dependent on the operator's experience and preference (picture 2) [85].

While the technique has shown promise in highly experienced hands, adverse events related to the procedure and incomplete tumor removal have been described [74,77,81,86-88]. The technique requires advanced skill levels and focused training to acquire these skills.

Hybrid endoscopic submucosal dissection — A modification of standard ESD technique includes a simplified hybrid approach (hybrid ESD) where the lesion is marked and incised using above-mentioned ESD technique with only partial submucosal dissection followed by EMR using snare resection of the lesion. This method minimizes the amount of submucosal dissection, which tends to be the most challenging and time-consuming part of the procedure. Hybrid EMR technique still allows for en bloc resection of lesions much greater in size compared with those resected using standard EMR [89].

Comparative efficacy — Studies comparing ESD with EMR have suggested that ESD is associated with improved outcomes.

- A meta-analysis of 15 studies found that ESD, compared with EMR, had higher en bloc and curative resection rates (OR 13.9 and 3.5, respectively), as well as lower rates of local recurrence (OR 0.09) for malignant and premalignant lesions of the gastrointestinal tract [86]. Similar results were noted in two other meta-analyses [90,91].

- A subsequent study of 239 patients with early gastric cancer found that patients who underwent ESD had lower recurrence rates than patients who underwent EMR (4 versus 18 percent) [92].

- In a retrospective study of 300 patients with squamous cell cancer of the esophagus, patients who underwent resection with ESD had significantly higher en bloc resection rates and lower local recurrence rates compared with patients who underwent EMR (100 versus 53 percent and 1 versus 10 percent, respectively) [93].

LONG-TERM OUTCOMES

Follow-up studies suggest that ER in carefully selected patients can achieve long-term cure, although the number of patients reported is relatively small.

Esophagus — Follow-up data are available for patients who have undergone ER in the esophagus for cancer, high-grade dysplasia, or intestinal metaplasia. Several reports have suggested low mortality rates following ER of isolated lesions [4-12,18,94-97]. Five-year survival rates range from 76 to 100 percent. However, survival is lower in patients with multiple or

circumferential lesions or with lesions that extend beyond the lamina propria. Recurrences are seen in 3 to 32 percent of patients and can often be treated with local therapy [7,97-99].

- One of the largest studies with long-term follow-up included 402 patients with superficial esophageal squamous carcinoma [94]. The patients were treated either with EMR (48 percent) or ESD (52 percent) and were followed for a mean of 50 months (range 4 to 187). The overall one-year, three-year, and five-year survival rates were 99, 94, and 84 percent, respectively. Survival was highest among patients whose tumors did not invade beyond the lamina propria (five-year survival rate of 91 percent). The five-year survival rate was 71 percent both for patients with involvement of the muscularis mucosa and for patients with involvement of the submucosa.

- Similar results were noted in a study of 66 patients with esophageal adenocarcinoma who underwent endoscopic resection plus ablation for tumors that were thought to have shallow penetration into the submucosa (SM1) [100]. Complete endoluminal remission (CER) was achieved in 53 of 61 patients (87 percent) who could be evaluated (one patient was still undergoing endoscopic therapy, and four patients were lost to follow-up). Among patients with small (up to 2 cm) focal lesions, the CER rate was 97 percent. The CER rate was 77 percent for patients with larger or multifocal lesions. Long-term remission was achieved in 51 patients (84 percent of those evaluated, 77 percent of the original cohort) after a mean follow-up of 47 months. Among patients with small, focal lesions, the long-term remission rate was 90 percent, whereas it was 77 percent in patients with larger or multifocal lesions.

- In a study of 53 patients who underwent ESD for adenocarcinoma of the gastroesophageal junction, overall survival after a median follow-up of 6.1 years was 94 percent, and recurrence-free survival was 92 percent [96]. Recurrences were detected in three patients (6 percent). The recurrence rate was 17 percent among patients with noncurative resections (3 of 17), whereas there were no recurrences among the 36 patients with curative resections [96].

Long-term survival has also been described when ER has been combined with photodynamic therapy [8,100,101].

Outcomes with ER have also been compared with surgery for superficial esophageal cancer. A study using the National Cancer Data Base looked at 5390 patients who underwent treatment for a T1a (54 percent) or T1b (46 percent) esophageal cancer from 2004 to 2010; 3963 had surgical resection and 1427 were treated endoscopically [18]. Patients treated endoscopically had higher 30-day survival rates than those treated surgically (99.5 versus 96.5 percent), but 5-

year conditional survival (which excluded patients who died within 30 days of surgery) was lower in the ER group than in the surgery group (77 versus 88 percent). However, a substantial number of patients with T1b tumors were treated endoscopically (ranging from 7 percent in 2004 to 21 percent in 2010), so patient selection may have accounted for the worse long-term survival with ER, since patients with T1b tumors are at high risk for lymph node metastases. (See 'Esophageal cancer' above.)

Studies suggest that when EMR is used in patients with Barrett's esophagus (BE), the rates of complete eradication of intestinal metaplasia and dysplasia are 59 to 100 percent and 86 to 100 percent, respectively [14,95,99,102-107].

- One study examined 349 patients with BE undergoing EMR for HGD (61 patients) or early esophageal adenocarcinoma (288 patients) [99]. Complete eradication was attained in 97 percent. During a mean follow-up of 64 months, 22 percent of patients had a recurrence. Of these patients, 85 percent received further endoscopic treatment and achieved a second complete remission. Risk factors associated with recurrence included piecemeal resection (relative risk [RR] 2.4), long-segment BE (RR 1.9), no mucosal ablative therapies of BE after complete remission (RR 2.5), time to achieve complete remission of more than 10 months (RR 0.3), and multifocal neoplasia (RR 2.1). The analysis of data for 231 patients with early esophageal adenocarcinoma treated only by EMR demonstrated a long-term complete remission rate of 96 percent.

EMR has also been applied to patients with superficial isolated local disease after definitive chemoradiotherapy for more advanced esophageal cancer. In one such series of 16 patients, eight patients had local failures, five had metachronous cancers, and three had residual cancers following definitive chemoradiotherapy [108]. The three-year survival rate was 56 percent. Three of the patients with local failure and two of three patients with residual disease were alive and relapse-free for 21 to 48 months after the procedure.

Stomach — Recurrence appears to be uncommon following ER of gastric cancer when an adequate resection margin can be achieved. The use of ER for the treatment of early gastric cancer is discussed in detail elsewhere. (See "Early gastric cancer: Treatment, natural history, and prognosis", section on 'Endoscopic therapies'.)

Colon — Both EMR and ESD have been used in the colon.

EMR in the colon — Outcomes following EMR in the colon are good, particularly if the lesion can be removed en bloc. This issue was examined in a meta-analysis that included 31 observational studies and two randomized trials in which a total of 3422 adenomas or early carcinomas (mucosal invasion or submucosal invasion <1 mm [sm1]) were removed using EMR

[109]. There were 503 recurrences (15 percent, 95% CI 12-19 percent). The risk of recurrence was higher following piecemeal resection than it was following en bloc resection (20 versus 3 percent). Retreatment at follow-up endoscopy was reported for 351 recurrences, with a subsequent recurrence rate of 21 percent. The mean number of endoscopic treatments needed to eradicate the original lesion was 1.2.

In one of the studies included in the meta-analysis, there were no cases of advanced colorectal cancer or metastasis after a mean follow-up of 4.5 years among 100 patients who had a total of 125 flat and depressed colorectal lesions [110]. The lesions included invasive cancer (3), carcinoma in situ (7), adenomas (91), hyperplastic polyps (21), and nonspecific abnormalities (3).

A study not included in the meta-analysis included 390 patients who underwent endoscopic resection of submucosal invasive T1 tumors [sm1 to sm3] [111]. EMR alone was used in the treatment of 249 patients, whereas 141 were teated with surgery. Unfavorable outcomes (locoregional tumor relapse, lymph node metastasis, distal metastasis, or death related to advanced colorectal cancer) were seen in 39 patients overall (10 percent) and in 17 patients treated with EMR alone (7 percent). Factors associated with unfavorable outcomes included incomplete tumor resection at the time of endoscopic resection (OR 2.6), lymphatic invasion (OR 7.8), and the presence of a poorly differentiated tumor (OR 3.4).

EMR has also been evaluated in patients with rectal carcinoids with good success rates. In a retrospective study of 304 patients with tumors that were 20 mm or less in diameter, complete resection was achieved in 268 patients (88 percent) based upon endoscopic appearance and in 183 (60 percent) based on pathologic evaluation [112]. Of the 85 patients with complete resection based upon endoscopic evaluation but incomplete resection based on pathologic assessment, residual tumor was detected in eight at follow-up endoscopy (9 percent). Overall, local recurrence developed in two patients (0.6 percent). The three-year survival rate for patients treated endoscopically was 100 percent.

ESD in the colon — Studies are looking at long-term outcomes in patients who undergo ESD for the treatment of colonic lesions and suggest good long-term outcomes for patients with low-risk colon lesions that are completely removed with ESD. Outcomes are not as good for patients with rectal lesions or lesions with high-risk features [113,114]. (See "Endoscopic removal of large colon polyps", section on 'Endoscopic submucosal dissection techniques'.)

A retrospective study examined 549 patients with submucosal colon cancer and 209 patients with submucosal rectal cancer who underwent ESD with complete removal of the cancer [113]. Patients were divided into three groups: those with low-risk lesions who underwent ESD alone, those with high-risk lesions who underwent ESD alone, and those with high-risk lesions who

underwent surgery. Low-risk lesions were those that were completely resected, were well- or moderately-differentiated adenocarcinoma, lacked vascular invasion, and had a depth of submucosal invasion <1 mm. All other lesions were considered high-risk.

Median follow-up was 60.5 months. Among those with low-risk lesions, recurrence rates were 0 and 6.3 percent for colon and rectal cancers, respectively. The five-year recurrence-free survival rates were 96 and 90 percent, respectively. For those with high-risk lesions treated with ESD, the recurrence rates were 1.4 and 16 percent, respectively, with five-year recurrence-free survival rates of 96 and 77 percent, respectively. Among those with high-risk lesions who underwent surgery, the recurrence rates were 1.9 and 4.5 percent respectively, with five-year recurrence-free survival rates of 97 and 95 percent, respectively.

ADVERSE EVENTS

In experienced hands, ER is a safe procedure that can be performed on outpatients. However, a variety of adverse events have been described, including stricture formation, bleeding, and perforations.

Esophagus — In one report of 87 ERs, immediate adverse events were observed in 13 percent of procedures, including mediastinal emphysema (suggesting perforation, 3 percent) and ulcer bleeding (10 percent) [11]. Late adverse events were seen in 7 percent, including esophageal stricture due to scarring (6 percent) and ulcer bleeding after five days (1 percent).

A similar perforation rate was noted in a series of 143 patients with tumors of the esophagogastric junction treated with ESD. In that series, six patients (4 percent) suffered perforations [81]. No patients required surgical repair for the perforation, but two were treated with closed thoracic drainage for pneumothorax. The cap technique with submucosal injection and the ligation technique without submucosal injection had similar safety in a randomized controlled trial [115]. (See 'Endoscopic resection techniques' above.)

In a series of 681 patients undergoing EMR for Barrett's esophagus, there were no perforations. Bleeding developed in eight patients, all but one of whom were treated endoscopically [116]. Symptomatic strictures developed in seven patients and were all treated successfully with endoscopic dilation. Of note, however, the procedures were carried out in an endoscopy unit that specialized in the treatment of Barrett's esophagus, so the results may not be generalizable to other centers.

Strictures typically are seen in patients who had a mucosal defect involving more than three-fourths of the esophageal circumference [11,117]. Triamcinolone injection at the time of

resection may decrease the risk of stricture formation [118]. Strictures are typically treated with esophageal balloon dilation. In a small retrospective series, treating with esophageal balloon dilation plus an oral steroid was associated with a reduced need for esophageal balloon dilation compared with esophageal balloon dilation alone, though randomized trials are needed to confirm this finding [119]. The treatment of refractory strictures may include injecting depo-type corticosteroids such as triamcinolone into the stricture following dilation. (See "Endoscopic interventions for nonmalignant esophageal strictures in adults", section on 'Refractory strictures'.)

Stomach — In a series of patients undergoing EMR, immediate bleeding was observed in 4 out of 14 cases [120]. The bleeding was controlled with injection therapy, monopolar electrocoagulation, ligation with a detachable snare, and endoscopic clipping. In another report, delayed bleeding (occurring from 6 to 166 hours after the procedure [median 33 hours]) was observed in 25 of 476 patients (5 percent). The only independent risk factor associated with delayed bleeding was immediate bleeding [121]. Bleeding can be difficult to control. We have found endoscopic application of an endoscopic clip to be a reliable and safe method for controlling bleeding.

In a study of ESD for 1192 gastric neoplasms, there were 1166 ESD-induced ulcers, with bleeding in 62 cases (5.3 percent) [122]. There were 30 cases (2.6 percent) of early bleeding and 32 cases (2.7 percent) of late bleeding. A specimen size of >40 mm was a risk factor for bleeding overall, and antithrombotic drug therapy was a risk factor for delayed (but not early) bleeding.

Perforation has also been described and is more common with ESD. A meta-analysis found that the perforation rate for ESD was 4.5 percent, compared with 1.0 percent for EMR [90]. Treatment of a perforation generally requires open or laparoscopic surgery, although endoscopic clipping can be used for small perforations [123,124]. Factors that have been associated with an increased risk of perforation with ESD include tumor location in the upper stomach and tumor size >20 mm [125].

Colon — Adverse events seen with endoscopic resection in the colon include bleeding, perforation, and post endoscopic submucosal dissection electrocoagulation syndrome. In one series of patients undergoing EMR, bleeding occurred in 7 out of 29 patients (24 percent) [120]. No patients developed perforation. Bleeding and perforation occurred in one patient each in a series of 23 patients undergoing EMR with a suction method for lateral spreading tumors of the colon [53]. Both adverse events were successfully treated by endoclipping.

Perforations have been reported in up to 10 percent of patients undergoing ESD for colorectal neoplasms, though frequently they can be managed by endoscopic clipping and conservative

treatment [31,32,74,126-129]. However, surgery is still required in some cases. Even for uncomplicated cases, prolonged hospital stays of up to five days are common following ESD [130].

- In a study that included 297 patients who underwent ESD for colorectal neoplasms, there were 14 perforations (5 percent) and five cases of postprocedural bleeding (2 percent) [126]. One of the perforations required treatment with emergency surgery, whereas the other adverse events were managed endoscopically.

- A study of ESD for colorectal neoplasms examined 310 consecutive lesions in 290 patients removed using ESD [31]. Perforations occurred during the procedure in 5 percent of the procedures and after the procedure in 0.3 percent. All of the perforations that occurred during the procedure were treated successfully with endoscopic clipping. Two percent of the procedures were complicated by bleeding.

- Another study of ESD for colorectal neoplasms included 1111 lesions in 1090 patients [32]. Perforation occurred in 5 percent of patients, and bleeding occurred in 1.5 percent. Tumor size of 50 mm or greater was an independent risk factor for adverse events, as was a lower number of ESDs performed at an institution.

Another adverse event that has been described in patients undergoing ESD in the colon or rectum is post endoscopic submucosal dissection electrocoagulation syndrome. Post endoscopic submucosal dissection electrocoagulation syndrome develops when electrical current applied during the procedure extends past the mucosa into the muscularis propria and serosa, resulting in a transmural burn without perforation. Symptoms include fever, rebound tenderness, and marked leukocytosis. In a series with 82 patients who underwent ESD in the colon or rectum, post endoscopic submucosal dissection electrocoagulation syndrome was reported in 33 patients (40 percent) [131]. Risk factors for PEECS on multivariable analysis included lesion size larger than 3 cm and a resection site other than the rectosigmoid colon.

Bacteremia — Transient bacteremia with *Streptococcus salivarius* and *Corynebacterium* species was reported in 2 of 38 patients (5 percent) who underwent cap-assisted EMR for upper gastrointestinal lesions [132]. The positive cultures after 10 minutes were negative when repeated after four hours. The authors concluded that routine antibiotic prophylaxis for EMR was not indicated.

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: Gastric cancer".)

SUMMARY

- Endoscopic resection (ER) is an endoscopic alternative to surgical resection of mucosal and submucosal neoplastic lesions and intramucosal cancers. ER includes endoscopic mucosal resection, which involves snare resection of dysplastic lesions, and endoscopic submucosal dissection in which endoscopic tools are used to dissect lesions from the submucosa. Endoscopic resection offers both diagnostic and therapeutic capability. (See 'Introduction' above.)

- The largest experience, mostly from Japanese reports, has been in the treatment of gastric and esophageal neoplasms. The role of ER for staging and treating dysplastic Barrett's in conjunction with mucosal ablative techniques like radiofrequency ablation is growing. ER is also being used in the treatment of colonic neoplasms. (See 'Indications' above.)

- The techniques for endoscopic mucosal resection can be broadly divided into two groups: suction (suck-and-cut) and non-suction (lift-and-cut) techniques. Regardless of the resection technique, a submucosal fluid cushion (SFC) is highly desirable to separate mucosal and submucosal lesions from the muscularis propria. (See 'Endoscopic resection techniques' above.)

- Endoscopic submucosal dissection is a modified ER technique which utilizes a specialized electrocautery knife to incise and dissect the lesion through the submucosa. It offers the potential to remove mucosal and some submucosal tumors en bloc without size limitations. (See 'Endoscopic submucosal dissection' above.)

- Follow-up studies suggest that ER in carefully selected patients can achieve long-term cure, although the number of patients reported is relatively small. (See 'Long-term outcomes' above.)

- In experienced hands, ER is a safe procedure that can be performed in an ambulatory setting. However, a number of adverse events have been described, including stricture formation, bleeding and perforations. (See 'Adverse events' above.)

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Topic 2673 Version 47.0

GRAPHICS

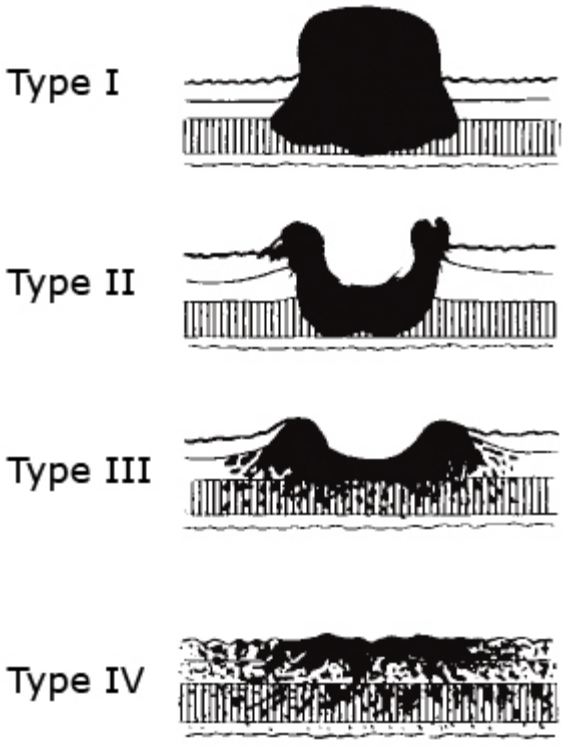
Japanese Society for Gastroenterological Endoscopy classification system of early endoluminal cancers

Type	Subclasses
I: Polypoid/protuberant	Ip: Pedunculated
	Ips/sp: Subpedunculated
	Is: Sessile
II: Flat	IIa: Superficial elevated
	IIb: Flat
	IIc: Flat depressed
III: Ulcerated	
IV: Lateral spreading tumor	

Japanese Gastric Cancer Association. Japanese Classification of Gastric Carcinoma. 2nd English Edition. Gastric Cancer 1998; 1:10.

Graphic 71003 Version 2.0

Japanese Society for Gastroenterological Endoscopy classification of early endoluminal cancers



This is also known as the Borrmann Pathologic Classification of Gastric Cancer.

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Graphic 82731 Version 7.0

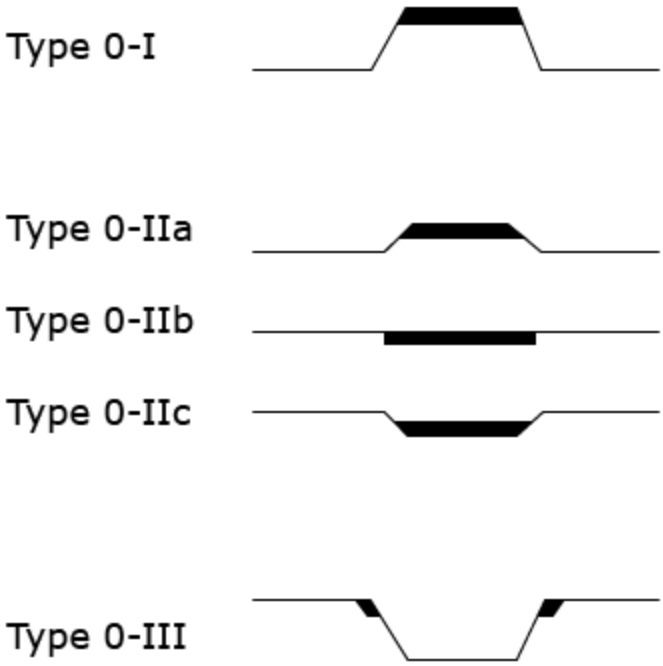
Paris classification system of superficial gastrointestinal neoplastic lesions

Type	Subclasses
0-I: Polypoid	0-Ip: Protruded, pedunculated
	0-Is: Protruded, sessile
0-II: Nonpolypoid	0-IIa: Slightly elevated
	0-IIb: Flat
	0-IIc: Slightly depressed
0-III: Excavated	

The Paris endoscopic classification of superficial neoplastic lesions: Esophagus, stomach and colon: November 30 to December 1, 2002. Gastrointest Endosc 2003; 58(6 suppl):S3.

Graphic 50239 Version 5.0

Paris classification system of superficial neoplastic lesions of the gastrointestinal tract



Paris classification system of superficial neoplastic lesions of the esophagus, stomach, and colon. Type 0-I lesions are polypoid (protruded or pendunculated); type 0-II lesions are nonpolypoid and may be slightly elevated (IIa), flat (IIb), or slightly depressed (IIc); type 0-III lesions are excavated.

Based on data from: The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach and colon: November 30 to December 1, 2002. Gastrointest Endosc 2003; 58(6 suppl):S3.

Graphic 61277 Version 3.0

Japanese Society for Gastroenterological Endoscopy criteria for endoscopic mucosal resection (EMR) of early endoluminal cancers

Cancer	JSGE type	Criteria for EMR
Early gastric cancer	I	Less than or equal to 2 cm
	IIb and IIc	Less than or equal to 1 cm
	Intestinal type adenocarcinoma	Limited to the mucosa
Esophageal cancer	I, IIa, IIb, IIc	Diameter of less than or equal to 2 cm
		Involvement of less than one-third of the circumference of the esophageal wall
		Limitation to the mucosa of the esophagus
Colon cancer	I	Less than 3 cm
	IIa	Less than 3 cm
	IIb	Less than 5 mm
	IIc + IIa	Less than 1 cm
	IIa + IIc	Less than 1 cm
	IV	Less than 3 cm

Raju GS, Waxman I. High-frequency US probe sonography-assisted endoscopic mucosal resection. Gastrointest Endosc 2000; 52:S39.

Graphic 61975 Version 2.0

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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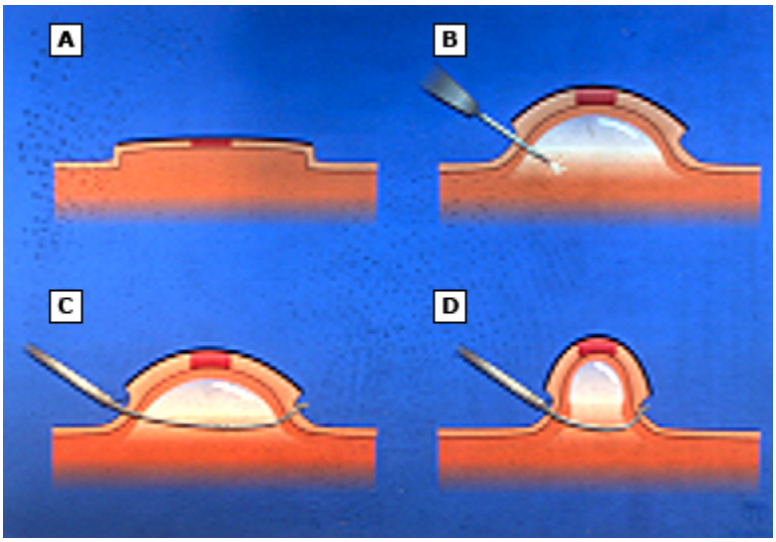
Graphic 111221 Version 9.0

Cartoon depicting the use of saline injection prior to endoscopic mucosal resection



(A) Simulated dysplastic lesion (red mark depicts dysplasia).

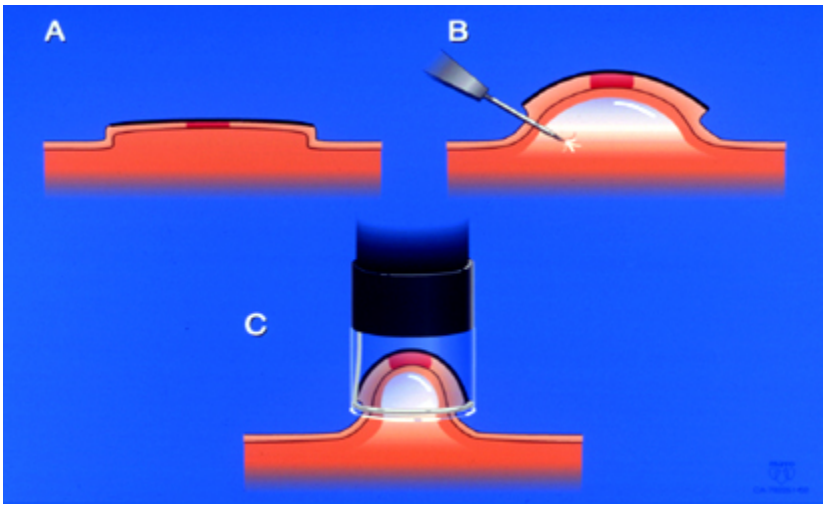
(B) Isolation of the lesion with submucosal fluid injection.

(C, D) Snare excision of isolated dysplastic lesion.

Courtesy of Christopher Gostout, MD.

Graphic 65182 Version 3.0

Cartoon illustrating the cap-assisted suction technique for endoscopic mucosal resection

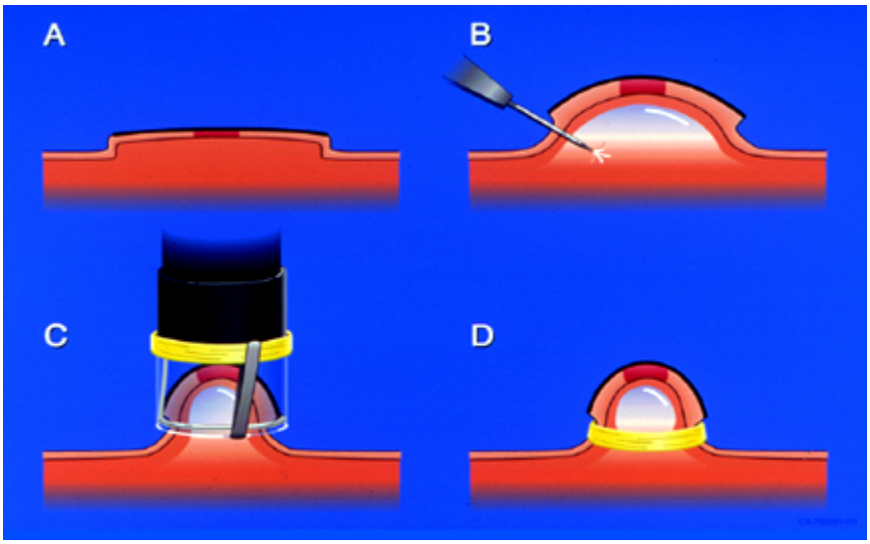


A submucosal saline injection (B) is used to raise the lesion (A), which is aspirated into a hood and permits snare excision of the isolated lesion (C).

Courtesy of Christopher Gostout, MD.

Graphic 76963 Version 3.0

Cartoon depicting the band and snare technique for endoscopic mucosal resection



The lesion (A) is raised with a submucosal injection (B). The banding hood is used to deploy a band ligation (C), which encapsulates the lesion (D).

Courtesy of Christopher Gostout, MD.

Graphic 53182 Version 3.0

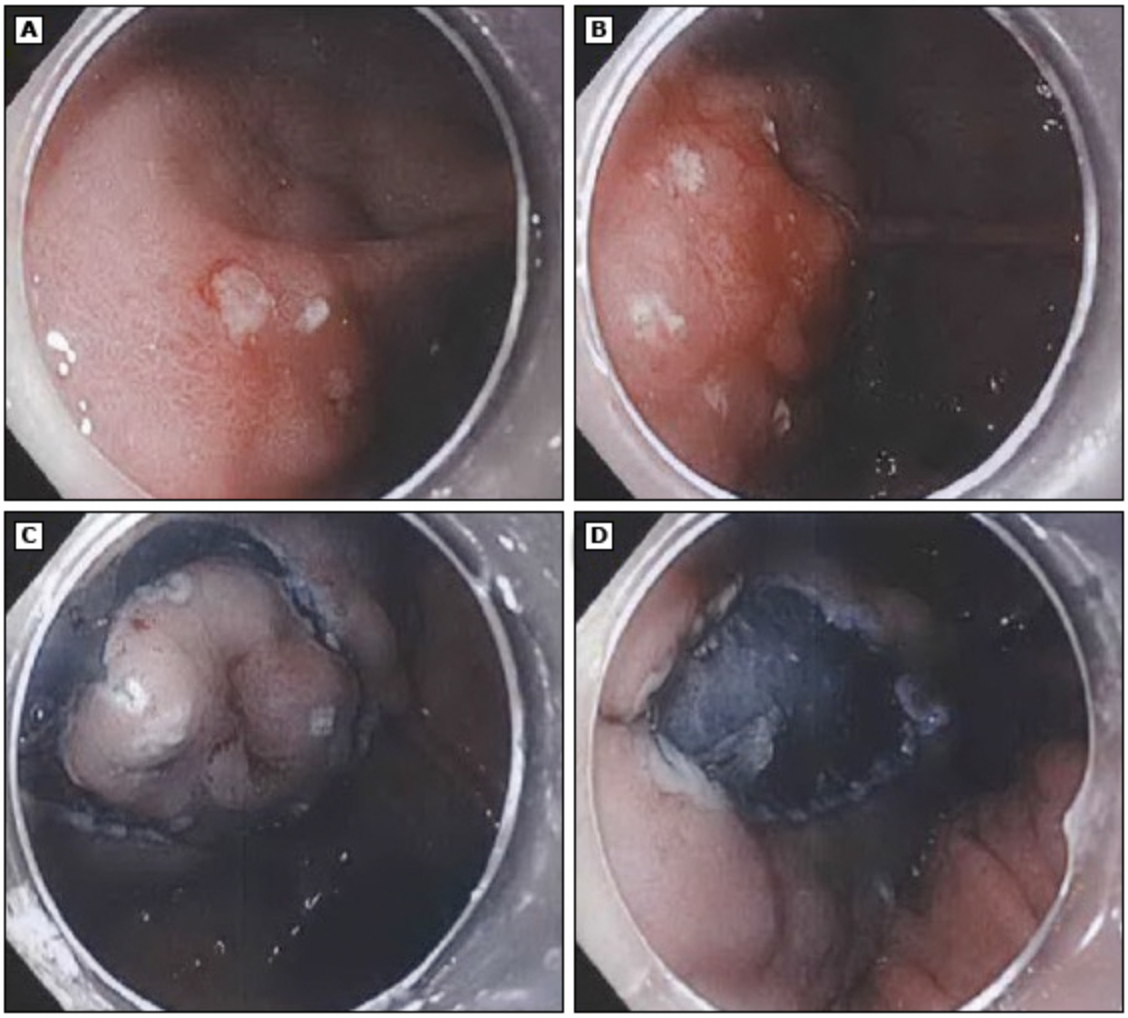
Picture demonstrating the band and snare technique for endoscopic mucosal resection

The top panels show the lesion ensnared with a variceal band ligator. A polypectomy snare is used to remove the tissue (lower left panel), leaving the residual mucosal defects (lower right panel).

Courtesy of Christopher Gostout, MD.

Graphic 50649 Version 3.0

Endoscopic submucosal dissection technique



Panel A shows careful endoscopic assessment of the focally ulcerated neoplastic lesion located in the mid gastric antrum. Narrow band imaging was also used but is not shown.

Panel B shows circumferential cautery marking at 5 mm from the margin of the lesion.

Panel C shows submucosal incision around the lifted lesion following the submucosal injection with methylene blue containing solution.

Panel D shows successful en bloc dissection of the lesion. Pathologic specimen revealed intramucosal cancer with no involvement of the lateral and vertical margins.

Courtesy of Eugene Zolotarevsky, MD.

Graphic 113286 Version 1.0

Contributor Disclosures

Naresh T Gunaratnam, MD No relevant financial relationship(s) with ineligible companies to disclose. **Eugene Zolotarevsky, MD** Consultant/Advisory Boards: Boston Scientific [Endoscopic retrograde cholangiopancreatography]. All of the relevant financial relationships listed have been mitigated. **John R Saltzman, MD, FACP, FACG, FASGE, AGAF** No relevant financial relationship(s) with ineligible companies to disclose. **Kristen M Robson, MD, MBA, FACG** No relevant financial relationship(s) with ineligible companies to disclose.

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