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# Endoscopic Resection for Early Cancers of the Esophagus and Stomach

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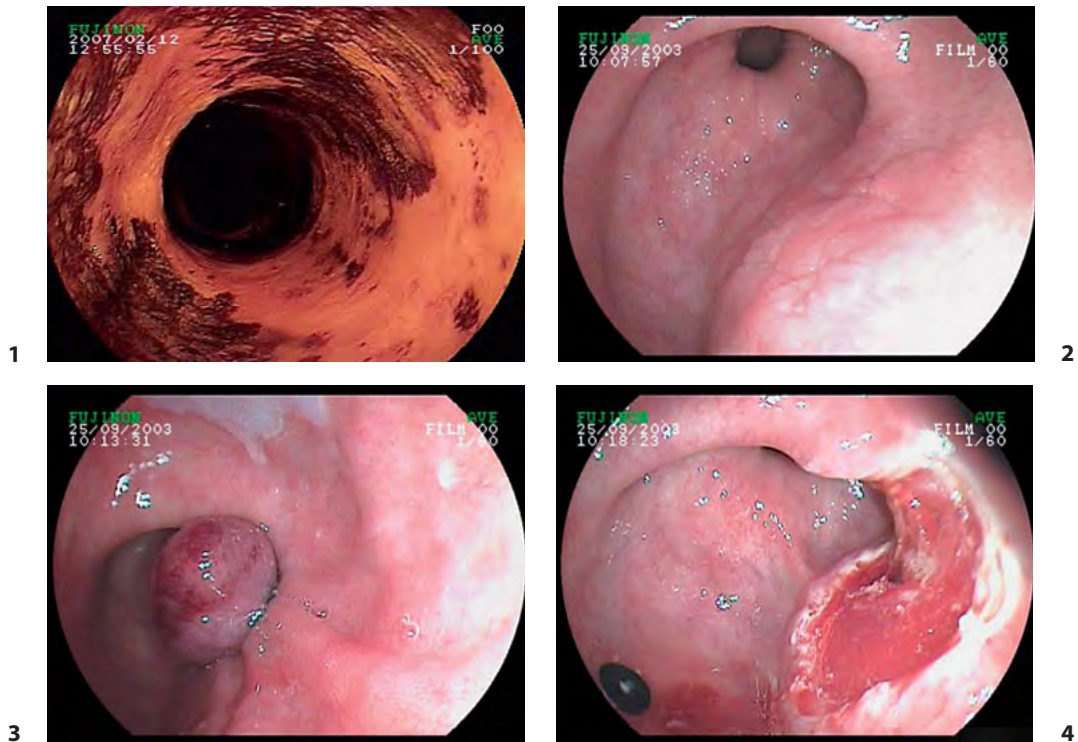
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## Abstract

The advent of endoscopic resection (ER) techniques has enabled gastroenterologists to remove premalignant and early neoplastic lesions throughout the gastrointestinal tract. The indications and techniques of ER are discussed in this article. Before it is performed, accurate evaluation of patients and careful staging of the lesions is mandatory. After ER of the neoplasia, histological assessment of the entire specimen with detailed histological analysis of layer infiltration is crucial. The first long-term follow-up studies of large numbers of patients confirm the excellent effectiveness of ER for well-differentiated mucosal lesions without lymphatic or blood vessel invasion.

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Detection of early neoplasias in the gastrointestinal tract has become more frequent as a result of improved endoscopic imaging technology, surveillance programs, and the increasing experience of endoscopists. For many years, radical esophageal resection or gastrectomy was considered to be the treatment of choice for early neoplasias. However, especially in the esophagus surgical resection is associated with significant mortality and morbidity. For these reasons local treatment methods have been introduced and investigated in several studies on cancers that carry a negligible risk of lymph node metastasis. In general, patients are ideal candidates for endoscopic treatment if they are at no risk of lymph node metastasis or lower risk for developing lymph node metastasis compared with the risk of mortality from surgery. This risk of lymph node involvement depends on the location of the neoplasia within the gastrointestinal tract and the depth of tumor invasion. Endoscopic resection (ER) is a promising therapeutic option for removal of superficial gastrointestinal tract carcinomas. Unlike ablative methods such as photodynamic therapy, argon plasma coagulation, or radiofrequency ablation, ER allows complete pathological assessment of the resected specimen including the depth of cancer invasion, degree of cellular differentiation of the cancer, and involvement of lymphatics or vessels. This pathological staging is crucial as it allows the risk of lymph node metastasis to be predicted and refinement of further treatment. There are various ER techniques, of which the most commonly used methods are discussed here.



**Fig. 1.** Chromoendoscopy with iodine solution in early squamous cell cancer of the esophagus. **Fig. 2.** Endoscopic finding of early Barrett's cancer. **Fig. 3.** Pseudopolyp created during a ligation procedure for early Barrett's cancer (suck-and-cut ER). **Fig. 4.** Endoscopic finding after suck-and-cut ER of early Barrett's cancer.

### Technique and Accessories

Before performing ER, identification of the margins of a lesion is crucial to avoid incomplete resection. For this purpose, conventional chromoendoscopy, e.g. with lugol iodine (squamous cell carcinoma; fig. 1), acetic acid (early Barrett's cancer), or indigo carmine with or without acetic acid (early gastric cancer), are widely used. However, virtual chromoendoscopy techniques like Fujinon intelligent chromoenhancement [1] and narrow-band imaging [2] have also been successfully applied.

There are two different concepts for ER: lesions can either be removed en bloc or piecemeal. Endoscopic resections are commonly performed with the 'suck-and-cut' technique. With this method, mucosa and submucosa are sucked into a cap or tube, and the pseudopolyp created in this way is resected using a diathermy snare (fig. 2–4). The procedure can be performed either with the cap or ligation device. Cap-assisted ER involves the injection of fluid, usually saline or diluted epinephrine, into the submucosa to lift the neoplastic area away from the muscularis propria. The lifted area of mucosa and submucosa is then suctioned into a transparent plastic cap attached to the end of the endoscope, and a cautery snare set inside the plastic cap is closed. Marking the periphery of the lesion with electrocautery before ER helps to determine the lesions margins after submucosal injection for precise direction of ER. Alternatively, the 'suck-and-cut' technique can

be applied using a standard ligation device to capture the lesion and make it into a polypoid lesion by deploying the band underneath. However, this technique requires repeated withdrawal and the introduction of the endoscope for band ligation and subsequent resection. A novel multiband mucosectomy device (Duette®, Cook Ireland Ltd, Limerick, Ireland) has recently been proposed. Since a polypectomy snare can be passed through the ligator handle, ligation and subsequent resection can be performed immediately without removal of the endoscope. A randomized study showed no significant difference between the 'suck-and-ligate' technique and the 'cap-assisted' technique concerning complications and size of the specimen obtained [3].

The major drawback of ER with the suck-and-cut technique appears to be that only small lesions with a diameter of <20 mm can be resected en bloc with tumor-free lateral margins. Larger lesions can usually be resected completely by piecemeal resections, but this method appears to be associated with a higher recurrence rate because of small neoplastic residues resulting from insufficient overlapping of the resection areas [4, 5]. Therefore, a new resection technique called endoscopic submucosal dissection (ESD) was developed to remove large lesions en bloc allowing more accurate histological evaluation of the lateral and basal margins of the lesion [6]. Standard ESD consists of three main steps. First, the lesion margins are marked by electrocautery, and fluids (e.g. hyaluronic acid or glycerol) are injected into the submucosal layer to separate it from the muscular layer. Second, circumferential cuts are made around the lesion. Then, special endoscopic knives (e.g. insulated tip-knife, hook knife, or flush knife) are used to dissect the submucosal layer underneath the carcinoma in order to obtain a large resection specimen with the neoplasia resected en bloc. The size of the resected specimen obtained with ESD can extend to >10 cm in diameter, but this fascinating new method is associated with several problems and disadvantages. First of all there is a substantial complication rate, including bleedings (8–38%) and perforations (ranging from 4% in non-ulcerated cancers to up to 54% in cases with ulceration) [4–6]. Moreover, ESD requires long procedure times of up to several hours and has a slow learning curve and a high degree of operator dependency. This might be the reason for the fact that even in Japan, the reported en bloc R0 resection rate for gastric neoplasias varies between 55% [7] and more than 95% [8]. At present, ESD has mostly been applied for early gastric carcinoma, and there are only a few reports on cases with early squamous cell cancer or cancer of the esophagogastric junction treated with ESD.

## Outcomes

### *Early Barrett's Adenocarcinoma*

Eligibility for ER of Barrett's cancer depends on risk stratification in accordance with known risk factors such as the infiltration depth of the carcinoma (mucosal layer of Barrett's epithelium is divided into four layers, m1–4), grade of differentiation, and lymph vessel or venous infiltration (fig. 5). A large series on patients with Barrett's carcinoma analyzed 350 resected lymph nodes in 41 patients with adenocarcinoma and found that the risk of lymph node involvement was 0% in patients with m1–4 compared to 16% in patients with submucosal infiltration [9]. Limitations for ER of early Barrett's carcinoma should be submucosal infiltration or infiltration of the muscularis mucosae in combination with another risk factor such as poor differentiation or lymph vessel infiltration (table 1).

Surgical series showed that also patients with Barrett's cancer invading the upper third of the submucosa (sm1) have a very low risk of lymph node metastasis [10, 11]. Therefore, the question arises whether also these cancers might be eligible for ER with a curative intent. This question

**Table 1.** Indications for ER in esophageal neoplasia

	Indication	Expanded indication <sup>1</sup>
Barrett's neoplasia	HGIN, carcinoma, size <20 mm, no risk factors <sup>2</sup> , macroscopic types I, IIa, b, c	Carcinoma >20 mm, multifocal cancer, sm1 infiltration without risk factors <sup>2</sup>
Squamous cell neoplasia	HGIN, mucosal cancer, no risk factors <sup>2</sup> , macroscopic types I, IIa, b, c	Lesion >20 mm, multifocal cancer

HGIN = High-grade intraepithelial neoplasia.

<sup>1</sup> ER only in highly experienced centers and/or under study conditions.

<sup>2</sup> Risk factors: lymph vessel invasion (L1), venous infiltration (V1), low tumor differentiation (G3).

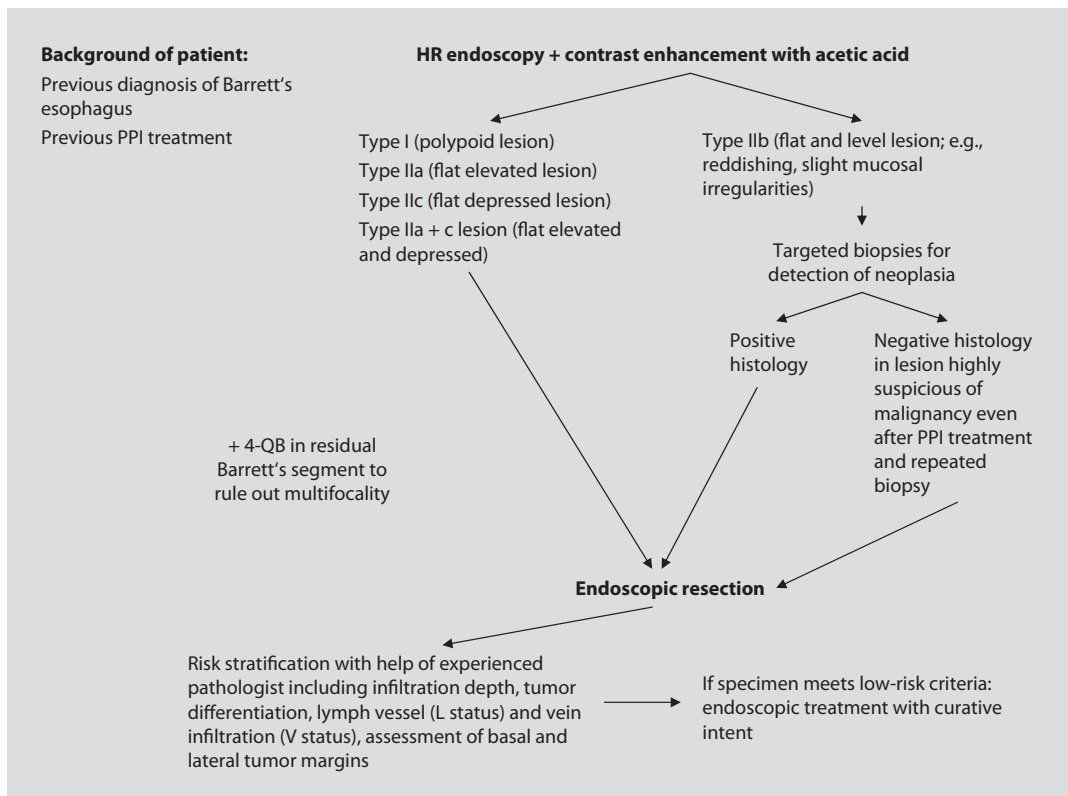
was answered by a recently published study [12]. ER was associated with favorable outcomes in submucosal Barrett's cancer meeting the following low-risk criteria: invasion not beyond sm1; absence of infiltration into lymph vessels/veins; histological grade G1/2, and macroscopic type I/II. It has to be pointed out that further trials are required before a general recommendation for ER in low-risk sm1 cancers can be given, and ER with a curative intent should only be carried out under study conditions in this group of patients.

While there are only a few cases reports on the successful performance of ESD in patients with Barrett's neoplasia, reports on suck-and-cut ER show very promising results. In several studies, complete remissions of more than 95% have been achieved [13] with no mortality due to Barrett's neoplasia during a 5-year follow-up [14]. However, recurrences or metachronous neoplasia in up to 20–30% [13, 14] represent the major problem with endoscopic therapy in early Barrett's neoplasia, although successful repeat endoscopic treatment is possible in almost all patients. The reasons for the high rate of recurrence appear to be undetected neoplasia in the residual Barrett's segment after treatment and, more importantly, the fact that residual Barrett's metaplasia appears to have an increased risk of malignant transformation in these patients. Ablative therapy, e.g. by argon plasma coagulation or radiofrequency ablation, of the residual Barrett's segment is used in order to reduce recurrence rates.

Although ER is a very safe procedure for resection of esophageal neoplasias, a few complications have been reported. Early complications include perforation (<0.5%) and bleeding (14%) [15]. However, in most cases intra-procedural bleeding is easily controlled by epinephrine injection or metal clip application (or a combination of both). Esophageal stenosis followed ER in 0–30% of cases [13–15] with circumferential resection being a major risk factor.

#### *Squamous Cell Cancer of the Esophagus*

Compared to early Barrett's cancer, the risk of lymph node metastasis appears to be higher in patients with squamous cell neoplasia. The mucosal layer of the esophageal squamous epithelium can be divided into three layers (m1–3). Intraepithelial cancers (m1) and cancers invading the lamina propria (m2) are associated with almost no risk of lymph node metastasis [16–18]. The risk appears to be higher with cancers invading the lamina muscularis propria (m3), in the range of 0–10% [16], and with cancers invading the submucosa (50–55%) [17]. Most interestingly, it was shown that even in m3/sm1 tumors, lymph node metastasis was absent if the



**Fig. 5.** Algorithm for the detection and endoscopic resection of early Barrett's cancer.

resected specimen did not show lymphatic or blood vessel permeation [16]. Several studies have shown that ER for mucosal squamous cell cancer with low risk of lymph node metastasis is safe and effective. Our group reported a series of 65 patients with high-grade intraepithelial neoplasia and mucosal squamous cell cancer. With ER, complete response was achieved in 95% [19]. However, after successful ER there is a considerable risk of metachronous lesions ranging from 20 to 30% [19, 20]. A recent publication by Fujishiro et al. [21] has reported on ESD in 58 patients with early esophageal squamous cell carcinoma. Complete resection (R0) was possible in 78%. Complications observed in this series included perforations in 7% and strictures in 16% of the cases. In conclusion, ER or ESD of squamous cell carcinoma is indicated for neoplasias with m1 or m2 invasion. Patients with a squamous cell neoplasia invading the muscularis mucosa (m3) should only be treated endoscopically if no further risk factors for lymph node metastasis are present (table 1). In case of submucosal invasion, patients should always be treated using surgery or radiochemotherapy. It remains unclear whether a combination of ER and radiochemotherapy represents an adequate treatment for patients with submucosal invasion or otherwise higher risk of lymph node metastasis, and further studies are needed in order to answer this question.

### *Gastric Carcinoma*

In Japan, ER and ESD are well established alternative treatments to surgery for early gastric carcinoma [22]. Traditionally, indications for endoscopic therapy include well-differentiated

**Table 2.** Expanded criteria for ER in early gastric cancer

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Mucosal cancer  
Differentiated adenocarcinoma  
No lymphatic-vascular invasion (L0)  
If ulcer finding: tumor size <3 cm  
Without ulcer findings: regardless of tumor size

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Undifferentiated mucosal cancer  
L0  
Without ulcer findings  
Tumor <2 cm

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sm1 invasion, < 500 µm  
Differentiated adenocarcinoma  
L0  
Tumor <3 cm

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elevated or flat adenocarcinomas of <20 mm in size, and small (<10 mm) depressed lesions without ulcerations. A large database involving more than 5,000 patients who underwent gastrectomy with meticulous R2 level lymph node dissection [23] showed that the incidence of lymph node metastasis of early gastric cancer was negligible in intramucosal cancers and small (<3 cm) cancers infiltrating the upper third of the submucosa (sm1). Based on these data, extended criteria for endoscopic therapy of early gastric carcinoma were proposed (table 2). Recently, long-term outcomes of ER for small differentiated mucosal early gastric carcinomas of <20 mm in size have been reported in comparison to those of surgical treatment [24]. In the report, the disease-specific 5- and 10-year survival rates were both 99%.

The risk of local recurrence after ER varies between 2 and 35%, and the recurrence rate correlates with the number of resected specimens [22]. However, large studies show that cases of local recurrence could all be cured by repeated endoscopy or surgery [5, 6, 22]. In Western countries, experience with ER for early gastric cancer is still limited, not least due to the fact that the disease is relatively rare. Recently, it was shown that ER can also be effectively used for early gastric cancer in the West, but it is associated with a relevant risk of complications [25]. In this study from our group including 43 patients, the rate of minor complications (not Hb-relevant bleeding) and major complications (Hb-relevant bleeding, perforation) was 18 and 15%, respectively. All complications were managed conservatively. During a mean follow-up of 57 months, recurrent or metachronous lesions were observed in 29% of patients. All lesions were successfully treated by repeated endoscopic treatment. No tumor-related deaths occurred during follow-up.

## Staging

Accurate staging is mandatory before ER and ESD of gastric or esophageal cancer. The most important part of the staging procedure is careful evaluation of the neoplasia (table 3) and the borders of the lesion using a high-resolution endoscope and searching for multifocal neoplasia. While for staging of esophageal squamous cell cancer chromoendoscopy with iodine solution is helpful (fig. 1), for adenocarcinoma of the esophagus acetic acid spraying or virtual

**Table 3.** Japanese classification of gastric carcinoma

Type of lesion	Classification
Polypoid	Type I
Flat and slightly elevated	Type IIa
Flat and level	Type IIb
Flat and depressed	Type IIc
Flat and slightly elevated and depressed	Type IIa + c
Ulcerated	Type III

chromoendoscopy with Fujinon intelligent chromoenhancement or narrow-band imaging have shown promising results.

As mentioned above, the critical importance of accurately determining the depth of invasion of a small esophageal carcinoma is the link between depth of invasion and the likelihood of lymph node metastasis. Endoscopic ultrasound is not only recommended to exclude lymph node metastasis, but also to determine infiltration depth. In the esophagus, it has been shown that the accuracy of EUS for T staging is excellent for differentiating T1 and T2 tumors but poor for distinguishing between the important stages of T1m and T1sm [26, 27]. The only method currently available to accurately determine the depth of invasion is diagnostic ER. Histopathologic workup of the specimen determines if the patient can be safely treated with ER or needs to be referred to surgery for esophageal resection. Concerning T and N staging, EUS is considerably superior to computed tomography in the majority of studies. The major aim of computed tomography is to exclude distant metastases.

### Algorithm

An algorithm for the detection and ER of early Barrett's cancer is shown in figure 5. The macroscopic classification of early neoplastic lesions is shown in table 3.

### Conclusions

Advanced endoscopic imaging techniques have made early diagnosis of early cancer in the upper gastrointestinal tract easier. This has opened a new chapter in minimal invasive mucosal cancer therapy with fast evolving ER techniques. Especially for early neoplasias of the esophagus, ER and ESD show excellent results and compare very favorably with surgical resection of the organ which carries substantial mortality (5–20%) and morbidity (up to 50%) rates.

It is important to emphasize that after successful ER or ESD a close follow-up program is crucial for surveillance because of the known risk of metachronous or recurrent lesions. En bloc resection with ESD appears to be an attractive new treatment method not only for early gastric, but also for patients with early esophageal malignancy. In terms of complete tumor resection and local cancer recurrence, ESD has proven to be superior to ER. However, only a few experts worldwide have the skills to apply ESD, and the technique is too time-consuming to be implemented to a great extent in daily practice. Therefore, novel techniques and new devices

have to be invented to enable safe en bloc resections within certain time limits. In order to minimize complications and optimize the effectiveness of ER, this treatment approach should only be carried out by experienced endoscopists in an appropriate environment (high-volume center).

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