Review Article

Endoscopic or Surgical Resection for Gastro-Esophageal Cancer

Ines Gockel, Albrecht Hoffmeister

Summary

Background: Early gastro-esophageal cancer is staged as m1 to m3 depending on the infiltration of the anatomical layers of the mucosa or, analogously, as sm1 to sm3 depending on the depth of infiltration into the submucosa. The risk of lymph node metastases is low in mucosal carcinoma but increases with the depth of infiltration into the submucosa.

Methods: This review is based on pertinent publications retrieved by a selective search in MEDLINE, PubMed, the Cochrane Library, and the International Standard Randomised Controlled Trial Number (ISRCTN) registry.

Results: New technologies such as narrow-band imaging have improved the endoscopic diagnosis and staging of early gastro-esophageal cancer. The development of endoscopic submucosal dissection has led to a higher R0 resection rate, a lower risk of recurrence, and an increase in the number of endoscopic resections that are performed with curative intent. In squamous-cell carcinoma of the esophagus, surgical oncological esophagectomy is indicated if the cancer infiltrates into the third mucosal layer (T1a, m3) or deeper. In esophageal adenocarcinoma, the prevalence of lymph node metastases is low if the cancer is restricted to the mucosa and increases only when the submucosa is infiltrated. In the current German S3 guideline, endoscopic resection is recommended for intramucosal adenocarcinoma as long as there are no further histopathological risk factors. Lymph node metastasis in gastric carcinoma begins in the deep mucosal infiltration stage (m3). If certain special conditions ("extended criteria") are met, carcinoma expanding into the first submucosal layer (sm1) can be removed endoscopically. All further stages must be treated with total or subtotal gastrectomy with systematic D2 lymphadenectomy.

Conclusion: Borderline cases between endoscopic and surgical resection of early carcinoma of the esophagus or stomach must be managed with an interdisciplinary treatment algorithm. If there is a risk of lymph node metastasis, surgical oncological resection is indicated. Such resections of gastroesophageal cancer in the locally advanced stage should always be part of a multimodal treatment approach.

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The Robert Koch Institute predicts that about 7400 persons (5700 men, 1700 women; incidence rising) will be diagnosed with esophageal cancer and about 14 700 (9100 men, 5600 women; incidence falling) with stomach cancer in Germany in 2018 (1). For many years surgical resection was the only curative treatment for malignancies of the esophagus and stomach, but endoscopic treatment of these cancers is becoming increasingly widespread. The seamless availability of diagnostic endoscopy in the industrialized nations means that malignant tumors are more often being detected at an early stage, rendering local endoscopic treatment technically feasible, provided the oncological situation permits. Two procedures—endoscopic mucosal resection and endoscopic submucosal resection (ESD)—have become established as techniques for removal of early-stage carcinomas. The complication rates of these procedures depend largely on the endoscopist's experience. For this reason, their use should be restricted to specialized centers.

At the point where the perioperative risk associated with oncologic surgery outweighs the survival advantage, endoscopic tumor resection becomes not only technically feasible but also medically preferable.

Nevertheless, endoscopic resection is often merely a diagnostic procedure. This is particularly the case when histological analysis of the resected tissue shows a high likelihood of metastasis or when complete excision is not possible by endoscopic means. In such cases it is advisable to proceed to surgical resection in the same session. The patient must be informed of this possibility before commencement of endoscopy. Every instance of endoscopic removal of a malignant tumor from the gastrointestinal tract should be followed by interdisciplinary discussions involving pathologists, surgeons, and endoscopists (tumor board) to decide on how best to proceed (repeat endoscopic resection, surgery, follow-up protocol). A second endoscopic resection should take place only in the case of lateral R1 resection, and then only if all the criteria expounded below are met. In the event of deep R1 resection at the basal resection margin, surgical treatment must always follow.

Furthermore, this review sets out to delineate the indications for endoscopic versus surgical tumor resection and describe how borderline cases should be managed. Here too, the decision on the best treatment for a tumor is taken on an individual basis in full consideration of

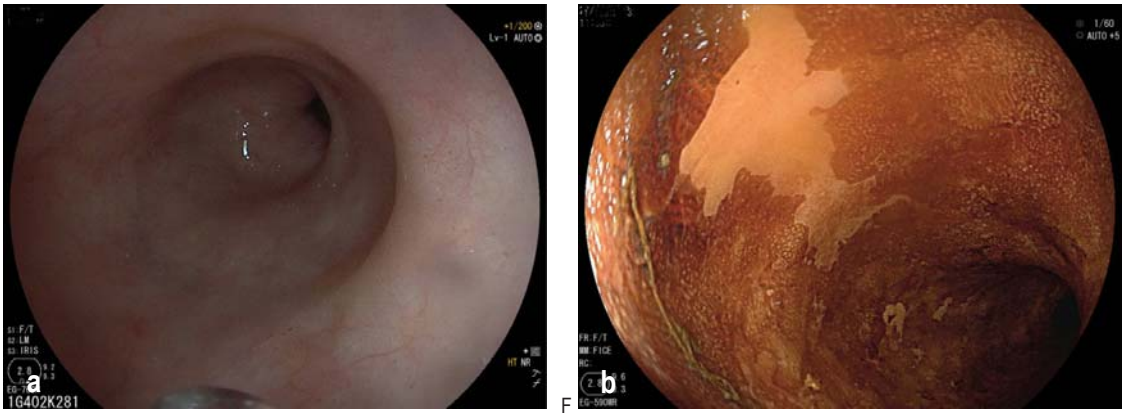

Figure 1: High-grade intraepithelial neoplasia of the squamous epithelium as precursor of squamous cell carcinoma: a) conventional white light endoscopy; b) chromoendoscopy with Lugol solution

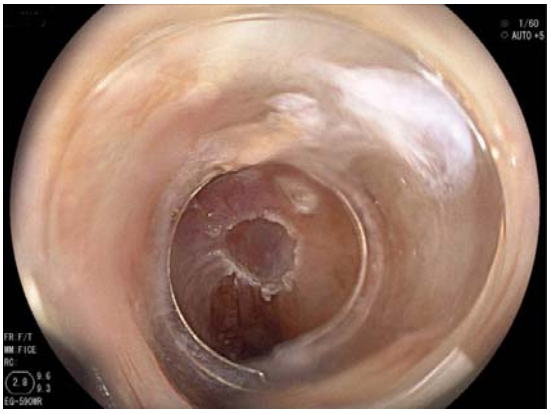

Figure 2: Same patient as in *Figure 1* after endoscopic mucosal resection of the affected area

each patient's specific circumstances. In a patient whose comorbidities greatly increase the risks involved in surgery, for instance, it may be advisable to adjust the boundaries between endoscopic and surgical treatment presented below, or to administer systemic treatment for an early-stage tumor.

Squamous cell carcinoma of the esophagus

Squamous cell carcinoma of the esophagus is completely different from adenocarcinoma with regard to etiopathogenesis, tumor biology, comorbidity, surgical risks, and prognosis (2, 3). The best-known risk factors are chronic alcohol consumption and smoking (3). Mucosal or submucosal esophageal cancer with or without lymph-node metastases (corresponding to Tis or T1 in the 2017 TNM classification of the *Union internationale contre le cancer* [UICC] [4]) is defined as superficial.

Endoscopic treatment

Before endoscopic treatment of a squamous cell carcinoma or its precursor, intraepithelial neoplasia, it is essential to determine how far the tumor has spread. This is a precondition for any attempt at curative treatment. Alongside the necessary systematic work-up, diagnostic endoscopy is needed to determine the precise size and extension of the esophageal lesion. Chromoendoscopy with Lugol solution is helpful in this regard *(Figure 1)*. According to one systematic review and meta-analysis, endoscopy with narrow band imaging is also feasible and in fact superior to chromoendoscopy for differentiation from other mucosal lesions (5). Preinterventional endoscopic ultrasonography (EUS) has limitations at this stage of disease (6). EUS may underestimate the extent of early neoplasia, but should nevertheless be carried out to exclude more advanced disease.

The risk of lymph-node metastases rises with increasing infiltration of deeper layers. For purposes of precise characterization, the depth of infiltration of the mucosa or submucosa is assessed. Depending on which layers within the mucosa are affected, the tumor is classified as m1, m2, or m3. The degree of submucosal infiltration is analogously described as sm1, sm2, or sm3. The risk of lymph-node metastases is low for m1 and m2 mucosal cancers. Further independent factors predicting lymph-node metastasis are tumor size exceeding 2 cm, poor differentiation, and invasion of lymph vessels (7).

Endoscopic resection of squamous cell carcinoma is recommended (8, 9) for m1 and m2 tumors less than 2 cm in size with differentiation grade G1/G2 and no invasion of blood or lymph vessels (L0, V0). Whether the resection takes the form of mucosal or submucosal dissection *(Figures 2 and 3)* depends on the size of the tumor and the expertise of the center.

Surgical intervention

To date there are no valid preinterventional diagnostic procedures (endosonography, computed tomography [CT], positron emission tomography/CT) that can be relied upon to identify potential lymph-node metastases of superficial esophageal cancer (mucosal and submucosal infiltration = pT1a, b) with sufficient accuracy.

Surgical studies on resected specimens of superficial squamous cell carcinoma have found that a fairly high

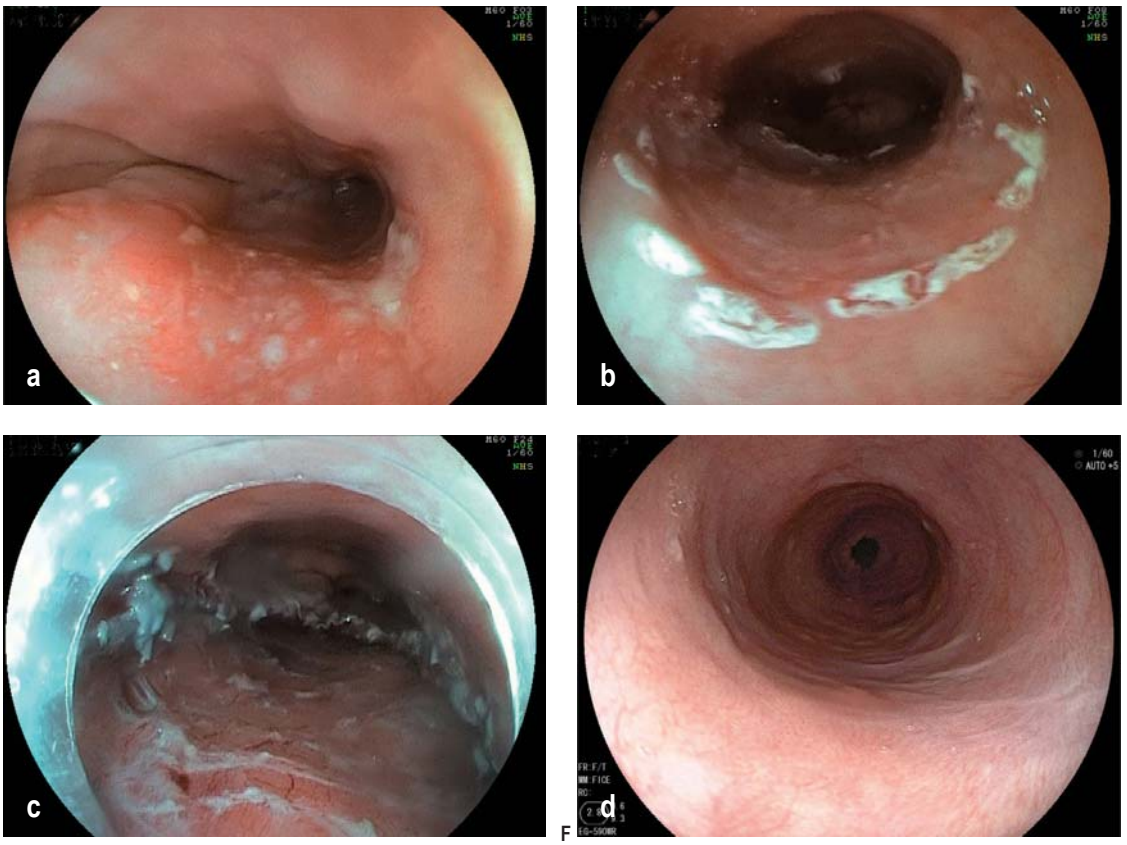

Figure 3: Endoscopic submucosal dissection (ESD): a) mucosal squamous cell carcinoma before treatment; b) marking of the area for resection; c) resected area after successful ESD; d) scar formation 5 months after ESD

rate of lymph-node metastasis can be expected even in mucosal cancer (pT1a) from infiltration depth m3 (10). Stage pT1a, m1 tends not to be associated with lymph-node metastasis, and stage pT1a, m2 only rarely, so these tumors are potential candidates for oncologically adequate endoscopic resection (7, 10–13). From stage pT1a, m3 onward, oncological esophageal resection is indicated. A study of our own patients with oncologically resected pT1 esophageal cancers showed that pV status and tumor size in multivariate analysis were significant predictors of potential lymph-node metastases; the cut-off point for tumor size was 20 mm (14). Oncologically resected submucosal squamous cell carcinomas showed lymph-node involvement in 27% of cases for infiltration depth sm1, 38% for sm2, and as many as 54% for sm3 (15). The prognosis of superficial squamous cell carcinoma of the esophagus is far worse than that of adenocarcinoma (16). The reason is the more aggressive tumor biology exhibited by squamous cell carcinoma. Multivariate analysis in the study by Stein et al. showed that only the histological tumor type and the presence of lymph-node metastases were independent predictors of long-term survival (16). The 5-year survival rate was 83.4% for patients with early adenocarcinoma versus 62.9% for squamous cell carcinoma, and 48.2% for patients with versus 79.5% for those without lymph-node metastases (16).

The outcome in patients treated surgically subsequent to endoscopic therapy of early squamous cell carcinoma of the esophagus (17) led to the recommendation of radical oncological esophageal resection with systematic two-field lymph-node dissection, even if it were technically feasible to perform endoscopic submucosal dissection of pT1b squamous cell carcinoma.

Adenocarcinoma of the esophagus

Chronic exposure of the distal esophagus to acidic gastric contents can bring about Barrett's esophagus, a change in the mucosal cells, which in turn may lead to esophageal adenocarcinoma (18, 19). The factors predisposing to Barrett's esophagus are, together with reflux disease and overweight, smoking and male sex. Barrett's esophagus is more likely to occur after eradication of gastric *Helicobacter pylori* infection

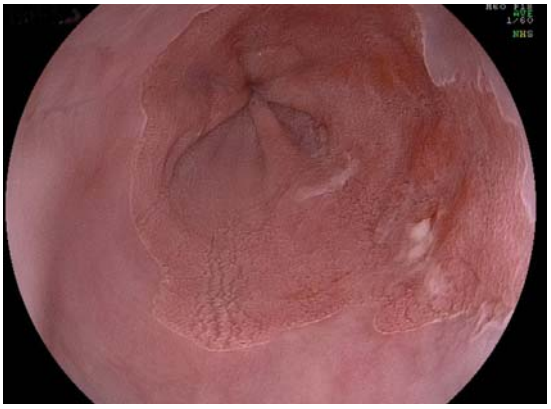

Figure 4: Chromoendoscopy with acetic acid: early-stage carcinoma in Barrett's mucosa, chromoendoscopy with 1.5% acetic acid

BOX

Indications for endoscopic resection of esophageal adenocarcinoma (9)

- **Mucosal cancer**
  - L0
  - V0
  - No ulceration
  - Grade G1 or G2
- **Submucosal cancer**
  - pT1sm1; <500 µm depth of infiltration
  - <20 mm
  - L0
  - V0
  - No ulceration
  - Grade G1 or G2

(18–22). Barrett's esophagus occurs much more frequently than was previously thought, but progression to adenocarcinoma much less frequently. Population-based studies show that the cancer risk of Barrett's esophagus is between 0.10% and 0.15% per year and that patients with Barrett's esophagus rarely die of esophageal adenocarcinoma (23, 24). Compared with the normal population, the relative risk of adenocarcinoma for patients with Barrett's esophagus is 11.3 (95% confidence interval [8.8; 14.4] (25). Histologically, the most important risk factor for esophageal adenocarcinoma as a result of Barrett's esophagus is demonstration of intraepithelial neoplasia/dysplasia (25).

Endoscopic treatment

The technique for endoscopic treatment of esophageal adenocarcinoma largely corresponds to that for squamous cell carcinoma. Chromoendoscopy with acetic acid is used to assess tumor spread *(Figure 4)*. The risk of lymph node metastases is greater if the tumor extends to the submucosa (26). Endoscopic resection proceeds according to the criteria shown in the *Box* (9).

The therapeutic strategy for esophageal adenocarcinoma often has to include a plan for dealing with precursor intraepithelial neoplasias in existing areas of Barrett's mucosa. In long-segment Barrett's esophagus, for instance, Kastelein et al. have reported a rate of 25% per year for progression of high-grade intraepithelial neoplasias to cancer (27). Low-grade intraepithelial neoplasias in Barrett's esophagus should also be endoscopically eradicated, because all intraepithelial neoplasias pose a risk and the techniques are becoming increasingly widespread and safe (28). Following successful resection of neoplasias in an area of Barrett's esophagus, the German S3 guideline recommends ablation of the non-neoplastic mucosa in the corresponding area to lower the rate of metachronic neoplasias (9). This thermic removal of the Barrett's epithelium is accomplished by means of endoscopic radiofrequency application (29). Alternatively, Barrett's epithelium can be ablated by means of argon plasma coagulation (APC). This more widely available and less costly procedure is used particularly often for shorter segments of Barrett's esophagus (9).

Surgical intervention

The risk of unanticipated lymph node metastases in patients with Barrett's adenocarcinoma confined to the mucosa is 1–2%, lower than the reported mortality rate for the operation (30). A nonrandomized controlled comparison of endoscopic resection and oncological esophagectomy in mucosal Barrett's adenocarcinoma revealed no significant difference with regard to the prognosis (overall survival and disease-free survival) (31). However, the recurrence rate was higher in the endoscopic resection group, so follow-up visits are mandatory (31). On the other hand, morbidity and mortality were higher in the surgical group than after endoscopic resection (31). Surgical resection of Barrett's esophageal adenocarcinoma following endoscopic resection should always be considered in the presence of the following findings (9, 32–35):

- Infiltration of lymph or blood vessels (L1 or V1)
- Poor differentiation (grade ≥ G3)
- Submucosal infiltration ≥ 500 µm
- Residual tumor at the basal resection margin (R1 basal).

Moreover, surgical treatment is indicated whenever endoscopic resection encounters technical difficulties and/or the endoscopic lifting sign (good raising of the lesion from the underlying tissues) is absent, as well as in the event of repeated recurrences after presumed curative endoscopic resection (36).

TABLE

Treatment options in mucosal and submucosal stomach cancer (from e3)

Infiltration	Mucosal (T1a)				Submucosal (T1b)	
Histology	**Nonulcerated**		**Ulcerated**		**sm1**	**sm2**
Diameter	≤ 2 cm	>2 cm	≤ 3 cm	>3 cm	≤ 3 cm	Any diameter
Intestinal type	ER	Extended indications ER	Extended indications ER	D2 gastrectomy	Extended indications ESD	D2 gastrectomy
Diffuse type	Consider gastrectomy	D2 gastrectomy	D2 gastrectomy	D2 gastrectomy	D2 gastrectomy	D2 gastrectomy

ER, endoscopic resection; ESD, endoscopic submucosal dissection

The decision whether to opt for endoscopic resection followed by monitoring or proceed immediately to surgical management is not always clear-cut. In surgical specimens of surgically resected superficial Barrett's adenocarcinoma the boundary between absence and presence of lymphogenic metastasis has been reported to lie between m4 (carcinoma infiltration of the original muscularis mucosae) and sm1, although the borderline for detectable lymph node metastases between these two layers is certainly not sharply defined (36). This is just as true for the distinction between sm1 low risk (good differentiation, L0, V0) and sm1 high risk (poor differentiation, L1, V1). The individual patient's risk profile with regard to a two-cavity intervention is thus crucial in determining the indications. Problems are also caused by the difficulty of distinguishing between mucosal and submucosal or low-risk and high-risk sm1 Barrett's adenocarcinomas by means of endosonography or other imaging modalities, so that "diagnostic endoscopic resection" is often the best choice.

In our own efforts to establish a model for prediction, we found that the predictors of lymphogenic metastasis were ranked as follows: grade 3 differentiation; sm3 infiltration; lymphovascular (L1) and microvascular (V1) infiltration; sm2 and sm1 infiltration (37). The risk of lymph-node metastases and lymphovascular invasion increases with tumor infiltration into deeper submucosal layers (14, 38, 39).

Gastric carcinoma

Gastric carcinoma is among the five most commonly occurring cancers in both men and women in Europe (40), and ranks equally highly for mortality (40). In international comparisons of age-standardized incidence and mortality, German men rank second and German women fifth (1).

Endoscopic treatment

As with esophageal carcinoma, there are defined criteria to follow when deciding on the indications for endoscopic treatment *(Table)*. For stomach cancer, however, one has to distinguish between absolute and extended indications for endoscopic resection (e1–e4). The extended criteria should be used only in clinical studies.

Resection of early tumors by means of endoscopic submucosal dissection yields a higher en-bloc resection rate, a higher rate of complete resection, and a lower recurrence rate than endoscopic mucosal resection (e5).

Surgical intervention

For stomach cancer, lymph-node metastasis begins with infiltration of the deep mucosal layer, m3 (e6), where the risk of spread to the lymph nodes has been stated as 13% (e6). In the case of the extended indications for endoscopic submucosal dissection, the cut-off point is infiltration of the submucosa to a depth of no more than 300 µm (e7). All other submucosal stages (sm1 and Laurén diffuse type, tumor diameter ≥ 3 cm; sm2, Laurén intestinal and diffuse type, any diameter; and all sm3 tumors) necessitate oncological gastrectomy with systematic D2 lymphadenectomy (e3). The proximal safety margin—in accordance with the German S3 guideline on stomach cancer—should be 5 cm for Laurén intestinal type tumors and 8 cm for the diffuse type (e3, e8).

The following risk factors have been identified for lymph-node metastasis in the mucosal type: tumor size, undifferentiated tumor type, lymphogenic and perineural invasion, and tumor ulceration (e9).

The overall risk of lymphogenic metastasis in the presence of submucosal tumor infiltration is reported as circa 25% (e10). The likelihood of lymph-node metastases is not necessarily correlated with the depth of infiltration.

Problems arise when the endoscopic resection is piecemeal rather than en-bloc. It is then harder to assess whether R0 resection has been achieved. Piecemeal resection increases the risk of local recurrence, the reported rate of which ranges from 2% to 35% (e11). Recurrences after endoscopic submucosal dissection must be distinguished from synchronic and metachronic lesions.

Submucosal stomach cancer in a high-risk surgical candidate can, as a "compromise," be treated with laparoendoscopic (full-thickness wall) resection (e12). On oncological criteria this seems to represent a useful, low-risk option.

Key messages

- Both endoscopic mucosal resection and endoscopic submucosal dissection have become established as techniques for removal of early-stage carcinomas from the upper gastrointestinal tract.
- The methods and indications for curative endoscopic treatment versus surgery are laid down in national and international guidelines. These reflect the risk of lymphogenic metastasis and/or recurrence, on the basis of defined tumor infiltration depths and further histopathological characteristics.
- Decisions on how to proceed in borderline cases between endoscopy and surgery require a differentiated interdisciplinary treatment algorithm together with careful assessment of each individual patient's risk profile including comorbidities.
- In early-stage carcinomas it is often expedient to start with endoscopic resection, which may turn out to have been merely a diagnostic intervention. Options for further management include endoscopic monitoring, endoscopic reintervention, and surgical resection.

Conflict of interest statement
Prof. Hoffmeister has received payments for lectures and the preparation of scientific meetings from the Falk Foundation.

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► **Supplementary material**
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