Esophageal Cancer

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Esophageal cancer is diagnosed in about 400,000 patients per year, which makes it the ninth most common malignancy worldwide and sixth on the list of cancer mortality causes. It is important to realize that it is somewhat difficult to determine its true incidence because cancer in the distal esophagus, particularly around the gastroesophageal (GE) junction, may be classified as esophageal cancer or as gastric cardia cancer.

For the purpose of this review, esophageal squamous cell carcinoma (ESCC) is defined as a tumor in the squamous epithelium that lines the normal esophagus. Adenocarcinomas are tumors that are located at the interface of the distal esophagus and proximal stomach and are subdivided into esophageal adenocarcinoma (EAC) and gastric cardia adenocarcinoma. EAC usually develops in Barrett’s esophagus (BE) (Siewert type I). Gastric cardia adenocarcinomas are tumors that arise in the cardia (Siewert type II) or subcardia (Siewert type III). Siewert type II and III tumors often extend proximally across the GE junction, causing dysphagia. In this review, predominantly ESCC and EAC are considered.1

The prognosis of esophageal cancer has slightly improved over the last few years in patients eligible to undergo a surgical resection; however, the 5-year survival rate in the resected group is still not higher than 30% to 35%.2,3 For all patients who have esophageal cancer, the 5-year survival rate does not exceed 20%. Early detection and treatment offers the best chance for cure.

This article reviews the epidemiology and pathogenesis of esophageal cancer. In addition, endoscopic diagnosis and staging methods of esophageal cancer are discussed. Curative treatment options for esophageal cancer (early esophageal neoplasia and advanced esophageal cancer) are reviewed. Finally, the most frequently used palliative methods for incurable esophageal cancer are summarized.

EPIDEMIOLOGY

The incidence of esophageal cancer is high in Western Europe, south-central Asia, eastern Africa, and parts of South America. In the Western world, the incidence is...
highest in the United Kingdom, France, Ireland, and the United States, with a higher incidence in men than in women, particularly in France and Slovakia.\textsuperscript{4}

There has been a large increase of EAC in so-called “developed countries” and a modest decrease of ESCC. Rates of EAC have been increasing in the United States, the United Kingdom, Scandinavia, France, Switzerland, Denmark, Italy, Slovakia, the Netherlands (restricted to men), Australia, and New Zealand.\textsuperscript{5–7}

This increase in rates of EAC may be partly due to a diagnostic shift. Tumors arising around the GE junction used to be classified as cardia adenocarcinomas; therefore, an increase in EAC could appear if tumors at or near the GE junction are increasingly being identified as esophageal in origin. Cardia adenocarcinoma rates, however, would then diminish to a similar extent, which has not occurred.\textsuperscript{8} Rates may also increase with an earlier endoscopy-based diagnosis, but the stage distribution has not changed over time, and survival consistently has been poor, even for patients diagnosed with localized disease.

The increase in incidence of EAC could also be real. A cohort study using a large general practice database in the Netherlands showed that the incidence of EAC increased from 1.7 in 100,000 (95% confidence interval [CI], 0.3–5.4) in 1997 to 6.0 in 100,000 (95% CI, 3.3–10.2) in 2002 ($R^2 = 0.87$). Similarly, the incidence of BE, the main precursor of EAC, increased from 14.3 in 100,000 (95% CI, 8.6–22.4) in 1997 to 23.1 in 100,000 (95% CI, 17.2–30.6) in 2002 ($R^2 = 0.87$). The increase in the incidences of EAC and BE was independent of the number of upper endoscopies performed, because this number decreased from 7.2 in 1000 (95% CI, 6.7–7.7) to 5.7 in 1000 (95% CI, 5.4–6.1) in the same time period.\textsuperscript{9}

These observations suggest that the increase of EAC is real and may reflect changes in the prevalence of risk factors. It is interesting to note that the mortality from esophageal cancer shows the same patterns.\textsuperscript{4} Due to the increased incidence and the limited improvement in survival of patients who have esophageal cancer, mortality rates have been increasing in most countries.

**PATHOGENESIS**

The question regarding which individuals are at highest risk of developing esophageal cancer is important because it may help to identify those at highest risk of developing this malignancy.

**Exogenous Factors**

In the 1990s, two milestone articles on this topic were published. In 1995, Vaughan and colleagues\textsuperscript{10} published a case-control study of risk factors for esophageal cancer that was conducted among residents of western Washington. Information on body mass index (BMI), cigarette use, alcohol intake, and other risk factors was collected from 404 cases or their next of kin (including 298 EAC cases and 106 ESCC cases) and 724 control subjects. Together, the risk factors of obesity, cigarette smoking, and alcohol use accounted for approximately 50% of all EAC cases diagnosed over that period. In comparison, cigarette smoking and alcohol intake alone accounted for 87% of all ESCC cases.

In 1999, Lagergren and colleagues\textsuperscript{11} published a case-control study from Sweden. Information on the history of GE reflux was collected from 189 patients who had EAC and 262 who had cardia adenocarcinoma in the period 1995 to 1997. For comparison, 820 control subjects and 167 patients who had ESCC were interviewed. Among persons who had recurrent symptoms of reflux, odds ratios (ORs) were 7.7 (95% CI, 5.3–11.4) for EAC and 2.0 (95% CI, 1.4–2.9) for cardia adenocarcinoma. The more
frequent, more severe, and longer-lasting the reflux symptoms, the greater the risk. Among persons who had long-standing and severe symptoms of reflux, ORs were 43.5 (95% CI, 18.3–103.5) for EAC and 4.4 (95% CI, 1.7–11.0) for cardia adenocarcinoma. The risk of ESCC was not associated with reflux (OR, 1.1; 95% CI, 0.7–1.9).

BE is a recognized risk factor for EAC that has a 30 to 50 fold increased risk of developing this malignancy. It is not well known, however, which patients who have BE have the highest risk of malignant progression. The evidence suggests that significant risk factors for EAC in BE are male sex, Caucasian race, and GE reflux disease (GERD). Further details on BE are discussed in the article by Bird-Lieberman and colleagues found elsewhere in this issue.

De Jonge and colleagues performed a case-control study to determine additional risk factors for EAC in BE. They included 91 cases of EAC and 244 control subjects who had BE. Information on demographic, anthropometric, and lifestyle characteristics; family history; symptoms of GERD; and medication use was collected by a questionnaire. Cases more often were current smokers (OR, 3.7; 95% CI, 1.4–9.9), had a BMI greater than 25 assessed at age 20 years (OR, 2.6; 95% CI, 1.2–5.5), and more frequently had been working in a stooped posture at age 20 years (OR, 2.0; 95% CI, 1.1–3.9). In addition, cases experienced fewer symptoms of heartburn (OR, 0.3; CI, 0.2–0.5) and less frequently used proton pump inhibitors (OR, 0.1; CI, 0.05–0.2). These data confirmed that the risk of EAC in BE is related to risk factors for GERD.

BMI is a clearly a risk factor for EAC, but its distribution does not reflect the demographic distribution of this cancer (which is highest among white men). Corley and colleagues thus performed a case-control study with 206,974 members of the Kaiser Permanente Health Checkup cohort, whereby subjects received detailed questionnaires, a standardized examination including BMI and anthropometric measurements, and follow-up of EACs and cardia adenocarcinomas using registry data. In total, 101 cases of EAC, 105 of cardia adenocarcinoma, and 144 of ESCC were detected. Increasing abdominal diameter (25 cm versus <20 cm) was strongly associated with an increased risk of EAC (OR, 3.5; 95% CI, 1.3–9.3). Adjustment for BMI did not diminish this association (BMI-adjusted OR, 4.8; 95% CI, 1.1–20.1). The association was also not diminished by adjustment for GERD-type symptoms, although reflux-type symptoms were separately associated with abdominal diameter and with cancer risk. Abdominal diameter (25 cm versus <20 cm) was not associated with the risk of cardia adenocarcinoma (OR, 1.3; 95% CI, 0.4–4.2) or ESCC (OR, 0.8; 95% CI, 0.3–1.9).

It can be concluded that ESCC is predominantly associated with alcohol use and smoking. To a lesser extent, the same risk factors apply for EAC, but in addition, GERD and BE and their common risk factor abdominal obesity contribute to this malignancy. Because abdominal obesity is more common among men, this suggests that an increase in obesity may disproportionately increase EAC risk in men.

**Endogenous Factors**

Another way of understanding pathogenetic mechanisms of esophageal cancer is to identify gene expression profiles. Gene expression profiles (DNA microarray) in biopsy specimens from 17 patients who had BE and EAC showed many genes and patterns not previously identified in addition to genes that were demonstrated to be overexpressed by other epithelial cancers, suggesting mutual mechanisms in pathogenesis. In addition, a similar stromal gene expression profile between BE and EAC was found, indicating that stromal and extracellular matrix genes associated with tumor growth are expressed long before pathologic evidence of dysplasia is present. Finally, no differences between short-segment BE (SSBE; BE length <2 cm) and long-segment BE (LSBE; BE length ≥ 2 cm) were found, which suggests that differences in
cell type or cell physiology are not responsible for the suggested higher risk of EAC in LSBE. These results provide important data for analysis of specific genes and pathways related to carcinogenesis of the esophagus. Thus, in combination with the previously mentioned exogenous risk factors, these types of genetic analyses improve our understanding of the main pathogenetic mechanisms of esophageal cancer.

**DIAGNOSIS**

Upper endoscopy is the preferred investigation for patients in whom there is a suspicion of esophageal cancer. Advances in endoscopic imaging such as narrow band imaging—and endocytoscopy and confocal endomicroscopy for even more detailed mucosal information—hold the promise that they may be able to better detect early malignant lesions of the esophagus. Further details on these new endoscopic imaging techniques are discussed in the article by Reddymasu and Sharma found elsewhere in this issue.

More advanced esophageal cancers can be exophytic, stenotic, or ulcerative or show a combination of these features (Fig. 1). Stenotic lesions are often circular and may prevent passage of a standard endoscope (diameter 9–11 mm). Because it is important to determine the upper and lower limit of the lesion and to visualize the stomach, which may be used for reconstructive purposes following esophagectomy, one should consider using a small-caliber endoscope (diameter 4.5–6 mm) in these cases. Another option is to dilate a stenotic tumor, which can safely be done by performing serial, progressive dilations over several days rather than by performing a single dilation.17 Following endoscopy of a dilated stenotic tumor, it is also advisable to perform endoscopic ultrasound (EUS) during the same session. Dilation of stenotic tumors significantly influences the accuracy of EUS staging in advanced tumors.18 Endoscopic biopsy completes an endoscopic examination of a suspected tumor. Without histologic proof, a strong suspicion may exist but the diagnosis cannot be established. At least six biopsy samples should be taken, preferably from the center and from the edges of the tumor.19

![Fig. 1](image_url)  
**Fig. 1.** Endoscopy in patients who have esophageal cancer. (A) Squamous cell carcinoma presenting as a combination of an exophytic, ulcerative, stenotic process. (B) Adenocarcinoma in BE presenting primarily as a stenotic process.
STAGING

To optimize the selection of patients who have esophageal cancer for curative or palliative treatment, it is important to determine the depth of infiltration of the tumor into the esophageal wall (T stage) and the presence of malignant regional lymph nodes (N stage) and distant metastases (M stage). An algorithm that can be used to stage esophageal cancer is summarized in Fig. 2.

EUS is nowadays used to determine the depth of tumor invasion and the presence of malignant regional and celiac lymph nodes in patients who have esophageal cancer. CT and fludeoxyglucose F18 positron emission tomography (FDG-PET) are commonly applied to determine whether malignant lymph nodes or distant metastases are present.

A recent meta-analysis evaluated the use of EUS for the detection of malignant regional and celiac lymph nodes, the use of CT for the detection of malignant regional and abdominal lymph nodes and distant metastases, and the use of FDG-PET for the detection of malignant regional lymph nodes and distant metastases. Random-effects pooled sensitivities of EUS, CT, and FDG-PET for regional lymph node metastases were 0.80 (95% CI, 0.75–0.84), 0.50 (95% CI, 0.41–0.60), and 0.57 (95% CI, 0.43–0.70), respectively; specificities were 0.70 (95% CI, 0.65–0.75), 0.83 (95% CI, 0.77–0.89), and 0.85 (95% CI, 0.76–0.95), respectively. Diagnostic performance was not different across these tests. For detection of celiac lymph node metastases by EUS (Fig. 3), sensitivity and specificity were 0.85 (95% CI, 0.72–0.99) and 0.96 (95% CI, 0.92–1.00), respectively. For abdominal lymph node metastases by CT, these values were 0.42 (95% CI, 0.29–0.54) and 0.93 (95% CI, 0.86–1.00), respectively. For distant metastases, sensitivity and specificity were 0.91 (95% CI, 0.86–0.96) and 0.52 (95% CI, 0.33–0.71) for CT, and 0.71 (95% CI, 0.62–0.79) and 0.93 (95% CI, 0.89–0.97) for FDG-PET, respectively. Compared with CT, diagnostic performance of FDG-PET for distant metastases was significantly higher and was not affected by study and patient characteristics.

Fig. 2. Diagnosis and staging of esophageal cancer.
EUS, CT, and FDG-PET each play a distinctive role in the detection of metastases in esophageal cancer patients. For the detection of regional and celiac lymph node metastases, EUS is most sensitive, whereas CT and FDG-PET are more specific tests. For the evaluation of distant metastases, FDG-PET may have a higher sensitivity than CT. The combined use of FDG-PET and CT, which is increasingly being applied, could be of clinical value, with FDG-PET detecting possible metastases and CT confirming or excluding their presence and precisely determining their location.

Fludeoxyglucose F18 Positron Emission Tomography

The role of FDG-PET in a state-of-the-art preoperative staging protocol including CT of the chest and upper abdomen, EUS, and ultrasonography of the neck, combined with selective fine-needle aspiration if indicated, is questioned by some investigators. To determine the role of FDG-PET in staging of esophageal cancer, 199 patients considered eligible for curative surgery after CT, EUS, and ultrasonography of the neck underwent FDG-PET in a prospective cohort study.21 FDG-PET revealed suspicious hot spots in 30 of 199 (15%) patients. Metastases were confirmed in 8 (4%). In 6 of these, distant metastases were confirmed before surgery, but exploratory surgery was necessary for histologic confirmation in the other 2. All 8 upstaged patients already had clinical stage III to IV disease before FDG-PET (7% of 122 with stage III–IV disease). In another 7 (4%) patients, hot spots appeared to be synchronous neoplasms (mainly colonic polyps). Those in the remaining 15 (8%), however, were false positive, leading to unnecessary additional investigations.

FDG-PET may thus improve the selection of patients who have esophageal cancer for potentially curative surgery, especially when in stages III to IV. The diagnostic benefit, however, seems limited to after state-of-the-art staging procedures.

CT

Recently, it was suggested that metastases in patients who have esophageal cancer were more frequently detected on CT examinations in a high-volume referral center for esophageal cancer.22 Thus, two radiologists from referral centers (“expert radiologists”) and six radiologists from nonreferral centers (“nonexpert radiologists”) evaluated 72 hard-copy CT examinations of patients diagnosed with esophageal or cardia cancer between 1994 and 2003.23 Compared with nonexpert radiologists, expert radiologists almost three times more frequently (OR, 2.9; 95% CI, 1.4–6.3) made
a correct diagnosis of the presence or absence of distant metastases. For the subgroup of CT examinations showing distant metastases, a statistically significant correlation (OR, 3.5; 95% CI, 1.4–9.1) was found between CT quality and a correct diagnosis. It therefore appears that radiologist experience and quality of the CT examination play a role in the detection of distant metastases in esophageal or gastric cardia cancer. This finding could lead to the suggestion that staging procedures for esophageal and gastric cardia cancer should preferably be performed in centers with state-of-the-art equipment and experienced radiologists.

### Endoscopic Ultrasonography

Is the same also true of EUS? It is known that a learning curve exists for the quality of performing EUS.24,25 After having performed 75 to 100 examinations, acceptable results can be obtained; however, it is not known whether the number of EUS investigations in subsequent years affects the results of esophageal cancer staging over time. Van Vliet and colleagues26 compared the results of EUS in the evaluation of T stage and the presence of regional and celiac lymph nodes in (1) a low-volume center where fewer than 50 EUS procedures per endoscopist per year were performed with (2) seven high-volume EUS centers for esophageal cancer (≥50 EUS/endoscopist/y). From 1994 to 2003, 244 patients underwent EUS in the low-volume center. In this center, no specific measures to pass a stenotic tumor or to perform fine-needle aspiration were taken. The criterion standard in the low-volume EUS center was postoperative TNM stage. In the high-volume centers, 670 EUS investigations for esophageal cancer were performed (with dilation if needed), with postoperative TNM stage with or without fine-needle aspiration as the criterion standard. In the low-volume center, results of EUS for T3 staging in patients in whom passage of the EUS probe was possible were almost comparable to those of the high-volume centers for sensitivity (85% versus 88%–94%) but were lower for specificity (57% versus 75%–90%). Results for T1 and T2 stages were lower in the low-volume center than in the high-volume centers for sensitivity (58% versus 75%–90%) and specificity (87% versus 94%–97%). In the low-volume center, sensitivities of EUS for regional (45% versus 63%–89%) and celiac (19% versus 72%–83%) lymph nodes were lower than those from high-volume centers, whereas specificities (75% versus 63%–82% and 99% versus 85%–100%, respectively) were comparable. Results in the low-volume EUS center were worse when the EUS probe could not pass the stricture, which occurred in almost 30% of patients. It was concluded that EUS performed in a low-volume EUS center compared unfavorably with that performed in high-volume EUS centers. This study suggests that preoperative staging by EUS, like the evaluation of CT examinations, should be performed by experienced and dedicated physicians to optimize the selection of patients who could undergo esophageal resection.

### CURATIVE TREATMENT OPTIONS

#### Early Esophageal Neoplasia

For many years, surgery was considered the treatment of choice for all patients who had esophageal cancer, including high-grade intraepithelial neoplasia (HGIN) and esophageal cancer confined to the mucosa. Histologic examination of surgical specimens showed, however, that there was no or only a minimal risk of metastases in mucosal esophageal cancer.27 Moreover, surgery is associated with a mortality of 3% to 5% and a morbidity of 30% to 40% in high-volume centers (>20 procedures/y) or with experienced surgeons. In low-volume centers (≤20 procedures/y) or with
less experienced surgeons, the mortality rate of esophageal resection may increase to above 20%.\textsuperscript{28,29}

The endoscopic treatment options for HGIN or early esophageal cancer include ablative therapies and endoscopic mucosal resection (EMR). Ablative therapies are based on the premise that injury to the metaplastic and dysplastic Barrett’s epithelium will lead to the restoration of the normal squamous epithelium in an anacid environment. EMR involves local snare excision of the lesion. It has also been used to resect the entire at-risk BE segment to reduce the risk of recurrence. The advantage of EMR compared with ablative techniques is that complete histopathologic assessment of the resected specimen is possible.

**Ablative Therapy**

The most commonly used ablative techniques in BE in the last 5 years have been photochemical destruction by photodynamic therapy and thermal destruction by argon plasma coagulation. Other techniques include multipolar electrocoagulation and destruction of BE by liquid nitrogen or ultrasonic energy. These techniques are associated with local complications (such as strictures) due to the deep thermal injury (mainly photodynamic therapy) and the possibility of buried glandular mucosa (all methods).\textsuperscript{30}

Recently, a balloon-based circumferential endoscopic radiofrequency device (HALO360) was introduced (BARRX Medical, Sunnyvale, California) (Fig. 4).\textsuperscript{31} It consists of a high-power radiofrequency energy generator, sizing balloon catheters, and ablation catheters. Sharma and colleagues\textsuperscript{32} were the first to report 1-year findings of a study that assessed dose response, safety, and efficacy of circumferential endoscopic radiofrequency ablation (RFA) of metaplastic BE without dysplasia using the HALO360 system. In the first phase of the study, the dosimetry phase, an energy level of 10 J/cm\textsuperscript{2} was found to be optimal, and this level was used for the effectiveness phase. A second RFA procedure was performed when BE was still present at 1 or 3 months. In the effectiveness phase, 70 patients were enrolled. At 12 months’ follow-up, complete BE eradication was achieved in 70% of patients. There were no strictures and no buried glandular mucosa. In a follow-up study, with the help of a more focal RFA device (HALO90), a 98% eradication rate of BE was achieved.\textsuperscript{33} Another large United States series that included cases of HGIN achieved an eradication rate of HGIN of 90%, with only moderate results for eradicating all BE (54%). These rates were achieved using only the circumferential RFA device.\textsuperscript{31}

The best clinical results with RFA can probably be achieved with the combination of a circumferential (HALO360) and a focal (HALO90) device. The number of published

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**Fig. 4.** The ablation balloon (length 4 cm) of the endoscopic radiofrequency ablation system (HALO360; BARRX Medical). (Courtesy of BARRX Medical, Sunnyvale, CA; with permission.)
reports of this technique, however, is still limited, so the conclusions should be viewed with caution. More studies and long-term follow-up are needed.

**Endoscopic Mucosal Resection**

EMR serves diagnostic and therapeutic roles. EMR resects a lesion entirely for histopathologic assessment and, when the resection margins are clear, it is curative. EMR involves local snare excision of the target lesion, for which a variety of techniques have been reported. These EMR techniques include (1) the “inject and cut” technique, (2) the “simple snare” resection technique, (3) the cap technique (Fig. 5), and (4) the ligation technique.34,35 Of these techniques, the latter two are the most frequently used.

The question of whether the cap technique or the ligation technique is superior was answered in a randomized trial.36 A total of 100 consecutive EMR procedures were performed in 70 patients who had early esophageal cancer, of which 50 were performed with the reusable ligation device without previous injection and 50 were performed with the cap technique with previous submucosal injection of a saline-epinephrine solution. Apart from a slight advantage for the ligation device in patients who had had previous treatment, no significant differences between the

![Fig. 5](image)

**Fig. 5.** (A) EMR of an early squamous cell carcinoma of the midesophagus as seen through a cap. (B) A mucosal defect after resection of the lesion. (C) After resection, the lesion is stretched for reliable pathologic diagnosis.
two groups were observed. No severe complications were seen. The mean diameter of the resected specimen was 16.4 × 11 mm with the ligation device compared with 15.5 × 10.7 mm with the cap technique.

A drawback of EMR is that only lesions with a diameter 20 mm or less can be resected en bloc. In addition, ulcerated lesions often have fibrosis, resulting in failure of the lesion to lift. In these cases, EMR is not advisable. Larger lesions can usually be resected completely using a piecemeal technique, but this method is associated with more recurrences because of small neoplastic residues resulting from insufficient overlapping of the resection areas. In addition, en bloc resection allows more accurate histologic evaluation of the neoplastic lesion, especially of the lateral and basal margins.

A new technique, endoscopic submucosal dissection (ESD), was therefore developed, which was initially described for early neoplastic lesions in the stomach. ESD is a method in which the submucosal layer underneath the carcinoma is dissected to obtain a larger mucosal specimen, with the neoplasm resected en bloc. Published data on ESD procedures in early esophageal cancer, however, are limited.

Indications and contraindications of EMR for early esophageal neoplasia were recently summarized by Pech and colleagues (Box 1). The main indications include HGIN and mucosal esophageal cancer. For risk stratification, it is important to consider grade of differentiation, lymph vessel or venous infiltration, and infiltration depth of the carcinoma. Whether cancers limited to the upper submucosal layer (sm1) are also eligible for EMR is not clear. Surgical series have shown that patients

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<td><strong>Indications and contraindications of endoscopic mucosal resection for early esophageal neoplasia</strong></td>
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**Absolute indication**
- HGIN (BE)
- T₁ m1–m3

**No risk factors**
- Lymphatic invasion (L1)
- Venous infiltration (V1)
- Poorly differentiated
- Carcinoma (G3)
- Macroscopic elevated or flat

**Intermediate indication**
- Tumor size >20 mm
- Multifocal cancer
- T₁ sm1 infiltration

**No risk factors**

**Contraindication**
- T₁ sm2 infiltration or deeper
- T₁ sm1 cancer with one risk factor
- Ulcerative lesion

who have sm1 cancer in BE have a very low risk of metastatic lymph nodes, but larger series reporting results on the endoscopic treatment of these cancers are lacking. The results of EMR for early squamous cell neoplasia and early Barrett’s neoplasia of the esophagus were summarized by Ono and colleagues. EMR of early squamous cell neoplasia has been proved safe and effective in several studies. Complete response in 10 reported series varied between 92% and 100%. Recurrent/metachronous lesions were seen in 0% to 26%. Risk factors for these lesions included piecemeal resection and multifocal lesions. Minor bleeding was seen in up to 23% of patients, stricture formation in up to 24%, and perforation in up to 7%. Perforations could be managed by endoscopic means.

EMR of early Barrett’s neoplasia has also been shown to be a safe and effective procedure. For early Barrett’s neoplasia, however, three types of treatment series have been reported: localized EMR of the neoplastic lesion only; circumferential EMR of BE, including the neoplastic lesion; and EMR with or without ablative therapy for the neoplastic lesion and BE.

Localized endoscopic mucosal resection of the neoplastic lesion only
The largest series on the use of localized EMR has been reported by Ell and colleagues who evaluated this technique in 100 patients who had mucosal EAC (≤20 mm) without invasion into lymph vessels and veins that was moderately to well differentiated (G1 and G2). Complete local remission was achieved in 99% of patients after 2 months and a maximum of three resections. During a mean follow-up period of more than 3 years, recurrent/metachronous carcinomas were found in 11% of patients, but successful repeat treatment with EMR was possible in all cases. The calculated 5-year survival rate was 98%. No major complications were observed, but minor bleeding occurred in 10% of patients.

Although localized EMR has favorable outcomes in patients who have early EAC, the remaining BE is still at risk of developing recurrent/metachronous lesions due to persistent multifocal (pre-) malignant areas in BE and the metachronous development of new foci of dysplasia in BE.

Circumferential endoscopic mucosal resection of Barrett’s esophagus, including the neoplastic lesion
The concept of circumferential EMR is interesting because it should be able to remove all BE on detection of HGIN or of early EAC. Circumferential EMR can be achieved in one or two sessions (half of the BE segment in each session). Two sessions (each session 1 month apart) may be most attractive to prevent the formation of esophageal strictures. In a case series of 37 patients, complete eradication of early neoplasia was achieved in all cases and complete resection of BE was achieved in 33 (89%) patients. Twenty-six percent of patients developed a stricture following treatment. Recurrent neoplasia or Barrett’s mucosa was not seen; however, the median follow-up time after treatment was only 11 months. In another study by Lopes and colleagues, BE patients who had HGIN or early EAC underwent circumferential EMR. During a mean follow-up of 32 months, BE was completely removed in 31 (76%) cases. There were 10 complications, of which all were managed endoscopically: 8 bleedings and 2 perforations occurred in 9 (14%) patients. One patient developed a stricture. Barrett’s epithelium recurred in 10 (24%) patients, and recurrent or metachronous early cancer was detected in 5 (12%), of which 4 were treated again by EMR and 1 patient was referred to surgery.
The problem of recurrent disease despite complete circumferential EMR is due to the fact that EMR is not an en bloc resection technique. Incomplete resection of BE is therefore inevitable because the resected specimens do not always completely overlap. The risk can be minimized by overlapping margins of resection or by using the ESD technique. Another problem with circumferential EMR is that of esophageal stricture formation. These strictures can be treated with endoscopic dilatation; however, they are sometimes difficult to manage by endoscopic means.

**Endoscopic mucosal resection with or without ablative therapy for the neoplastic lesion and Barrett's esophagus**

The concept of a more individualized treatment using EMR with or without ablative therapy is interesting. For example, in the context of LSBE, localized EMR is not an option because premalignant and malignant areas in BE still may be present and new foci of dysplasia may develop over time. In addition, following circumferential EMR of LSBE, strictures may be long and difficult to treat. For such patients who have LSBE and early malignant changes, the combination of localized EMR and endoscopic ablation might be promising. So far, experience with this approach is limited.

The Wiesbaden group from Germany has extensive experience with different types of endoscopic treatment of HGIN and mucosal EAC. Recently, 5-year follow-up data of 349 patients—61 patients who had HGIN and 288 who had mucosal EAC (173 SSBE and 176 LSBE) from a total of 486 patients presenting with Barrett’s neoplasia—were reported. Patients who had submucosal or more advanced EAC were excluded. EMR was performed in 279 patients, photodynamic therapy in 55, and both procedures in 13; 2 patients received argon plasma coagulation. The mean follow-up period was 64 ± 23 months. Complete response was achieved in 337 patients (97%); surgery was necessary in 13 (4%) after endoscopic therapy had failed. Recurrent/metachronous lesions developed during follow-up in 74 patients (22%); 56 died of concomitant disease, but none died of Barrett’s carcinoma. The calculated 5-year survival rate was 84%. The risk factors most frequently associated with recurrence were piecemeal resection, LSBE, no further ablative therapy for BE after complete response, time until complete response greater than 10 months, and multifocal neoplasia.

Endoscopic therapy for early esophageal neoplasia is effective and safe. It appears that the best results can be obtained by an individualized approach, using EMR with or without ablative therapy. Particular risk factors may help to stratify patients who are at risk for recurrence and require more intensified follow-up. Further long-term data from a larger number of treated patients are needed to establish the role of an endoscopic approach as standard alternative treatment to surgery in early esophageal neoplasia.

**Advanced Esophageal Cancer**

Surgery is still considered the treatment of choice for advanced esophageal cancer. In the last few years, studies on the surgical treatment of esophageal cancer have focused on further optimizing the surgical approach of esophageal cancer. Several studies have added evidence to the importance of various technical issues related to esophageal cancer surgery, such as resection margins, lymph node characteristics, T4 status, and advanced age. Further details on the surgical treatment of esophageal cancer are discussed in the article by Dubecz and colleagues found elsewhere in this issue.

**Neoadjuvant Therapy**

Because the recurrence rate of esophageal cancer after surgical treatment is still high, studies have used combinations of surgery and chemotherapy with or without radiation therapy. In a recent systematic review and decision analysis, surgery alone,
chemoradiation (CRT) followed by surgery (CRT-S), chemotherapy followed by surgery (C-S), and surgery with adjuvant CRT (S-CRT) for advanced esophageal cancer were compared. The relative risk of death for treatments compared with surgery alone was 0.87 (CI, 0.75–1.02) for CRT-S, 0.94 (CI, 0.82–1.08) for C-S, and 1.33 (CI, 0.93–1.93) for S-CRT. The quality-adjusted live-years (QALYs) gained for surgery alone, CRT-S, C-S, and S-CRT were 2.07, 2.18, 2.14, and 1.99, respectively. When the reduction in utility for multimodality treatment was increased to 21%, the QALYs gained for surgery alone, CRT-S, C-S, and S-CRT were 2.07, 2.03, 1.99, and 1.85, respectively.

Because the effect of multimodal treatment of esophageal cancer on survival and QALY seems modest, it is important to identify prognostic factors for tumor recurrence and long-term survival to select patients who will most likely benefit from neoadjuvant therapy. Kim and colleagues analyzed the clinical outcome of 269 patients who had ESCC (70% stage IIb or III disease) and were enrolled in three clinical trials assessing neoadjuvant CRT. These investigators performed recursive partitioning analysis to create a decision tree, which showed that female patients who achieved a clinical response and underwent esophagectomy had the most favorable prognosis. Among patients who underwent esophagectomy, the group that had good performance status, clinical stage II, and a major pathologic response to CRT had the most favorable prognosis. Matsuyama and colleagues studied the effect of neoadjuvant chemotherapy on lymph node micrometastases in 107 patients who had lymph node–positive advanced esophageal cancer. The presence of micrometastases (defined as eradicated, persistent, no effect, or not informative) in the postoperative pathology report correlated well with survival (3-year survival rates of 78%, 18%, 0%, and 38%, respectively). In multivariate analysis, the presence of micrometastases was found to be an independent prognostic factor together with the number of pathologic metastases.

Neoadjuvant CRT is associated with a better survival and a larger expected gain in QALYs. This improvement in quality-adjusted life expectancy, however, is only modest at 40 days. The hope for the future is the development of more specific, targeted therapies that will also treat micrometastatic disease. Moreover, individual patient, treatment, and tumor characteristics may aid in identifying patients who have the highest likelihood to respond to neoadjuvant therapy.

Chemoradiation T4 Esophageal Cancer

It is generally believed that the role of surgery in T4 esophageal cancer is limited. De Manzoni and colleagues therefore used preoperative CRT in 51 patients who had nonmetastatic T4 ESCC. The most frequently involved structures were the trachea (43%), left bronchus (18%), and aorta (16%). After preoperative CRT, 49 (96%) patients underwent resection, which was ultimately possible in 40 (78%) patients. An R0 resection was obtained in 20 (39%) patients, whereas a complete pathologic response (pT0N0) was found in 7 (14%) patients. Survival was better after R0 resection ($P < .001$) and in responders to CRT ($P = .019$).

Multimodal therapy with CRT followed by surgery in patients who have stage T4 esophageal cancer is feasible. Surgery, however, should be limited to patients who have a significant response to CRT and a high probability of an R0 resection.

Definitive Chemoradiation

Until now, surgery with or without neoadjuvant therapy has been the mainstay of curative treatment in patients who have esophageal cancer; however, a 5-year survival rate of 27% has been reported with CRT alone in a previous randomized study.
This rate is not largely different from the reported 5-year survival rates after surgery.\textsuperscript{2,3} Bedenne and colleagues\textsuperscript{50} randomized 259 patients who had T$_3$N$_{0,1}$M$_0$ esophageal cancer (89\% ESCC) and who had responded to two courses of CRT to surgery alone (arm A) or to another three cycles of CRT (arm B). The 2-year survival rates were not different (arm A: 34\% versus arm B: 40\%), nor were the 2-year local control rates (arm A: 66\% versus arm B: 57\%). Three-month mortality, however, was higher in the surgery arm (9.3\% versus 0.8\%, $P = .002$), which also translated in a longer cumulative hospital stay in the surgery arm (68 days versus 52 days, $P = .02$). It should be noted that patients undergoing surgery had a lower rate of local tumor recurrence compared with the nonsurgical group (34\% versus 43\%) and were less likely to undergo a palliative intervention to relieve dysphagia (24\% versus 46\%). It is also important to consider that patients who were randomized accounted for only 57\% of all patients, which may have led to a bias toward a benefit for CRT alone.

What to do when definitive CRT fails to achieve local control? In these situations, salvage esophagectomy is the only treatment available. In a recent review, nine series with a total of 105 patients who had undergone salvage esophagectomy were included.\textsuperscript{51} Each center performed one to three salvage resections per year, accounting for 1.7\% to 4.1\% of the esophagectomy workload. The anastomotic leak rate was 17\% and the in-hospital mortality rate was 11\%. The 5-year survival rate was within the expected rates of 25\% to 35\%. Prognostic factors for survival were an R$_0$ resection and a longer interval between CRT and recurrence.

In patients who have locally advanced esophageal cancer, particularly with ESCC, it is questionable whether performing surgery in patients who responded to definitive CRT is of benefit. Esophagectomy should be considered, however, in patients who have insufficient local control after CRT. If done, operability should be determined and distant metastases ruled out. In addition, esophagectomy should be attempted only when an R$_0$ resection is likely.

PALLIATIVE TREATMENT OPTIONS

Options to palliate dysphagia from esophageal cancer can be divided into endoscopic and nonendoscopic procedures and are equally effective for ESCC and EAC. It is generally accepted that surgery should no longer be performed when metastases or local/regional irresectability is demonstrated by preoperative staging investigations.

An exciting development is the use of new chemotherapeutic regimens alone or in combination with radiation therapy, not only for palliation of dysphagia but also in an effort to prolong survival of patients who have an otherwise poor prognosis. Clinical experience is limited and trials are needed to elucidate which patients are candidates for this treatment.

The most frequently used method to palliate dysphagia from esophageal cancer is stent placement. Single-dose brachytherapy (intraluminal radiation therapy), however, is increasingly being performed.

Stents for Mid- and Distal Esophageal Cancer

It has now convincingly been shown that partially or fully covered metal stents give better long-term palliation of malignant dysphagia than uncovered stents.\textsuperscript{52} The technical success rate for placement of partially or fully covered metal stents is close to 100\%. Almost all patients experience rapid improvement of dysphagia within a few days. The dysphagia grade usually improves from a median of 3 (able to eat liquids only) to a median of 1 (able to eat most solid foods). Procedure-related complications after stent placement occur in 5\% to 10\% of patients and mainly consist of
perforation, aspiration pneumonia, fever, hemorrhage, and severe pain. Minor complications, which are reported by 10% to 20% of patients, include mild retrosternal pain and GE reflux symptoms. Delayed complications and recurrent dysphagia following stent placement are important problems and have been reported to occur in 30% to 40% of patients. Delayed complications include hemorrhage, fistula formation, stent migration, tissue ingrowth or overgrowth, and food-bolus obstruction.\(^{53}\)

There is a need to improve the results of stent placement by introducing new stent designs. These new devices should overcome the problems encountered with the older-generation metal stents, particularly the relatively high rate of recurrent dysphagia due to migration or tumoral and nontumoral ingrowth and overgrowth. Two new stent designs, the fully covered Polyflex stent (Boston Scientific, Natick, Massachusetts) and the fully covered Niti-S double stent (Taewoong Medical, Seoul, Korea), were recently introduced with the specific objective to overcome the problem of recurrent dysphagia (Fig. 6). The completely covered Polyflex stent is a silicone device with an encapsulated monofilament braid made of polyester. The nonmetal material of this device has been suggested to reduce nontumoral tissue overgrowth, which is commonly seen with metal stents, particularly in patients surviving 20 weeks or longer. The Niti-S double stent combines two specific characteristics to reduce stent migration. First, the Niti-S stent flares to 26 mm at both ends. Second, it has a double-layer configuration, consisting of an inner polyurethane layer over its entire length and an outer uncovered nitinol wire tube to allow the mesh of the stent to embed itself in the esophageal wall. These two new types and the most commonly used stent type worldwide, the Ultraflex stent (Boston Scientific), were recently compared in a randomized trial in patients who had dysphagia from esophageal or gastric cardia cancer. In total, 125 patients were randomized to placement of the Ultraflex stent, the Polyflex stent, or the Niti-S double stent.\(^{54}\) Dysphagia scores and complications were similar.

Fig. 6. Two new stents designed to overcome the problem of recurrent dysphagia: the fully covered Niti-S double stent (Taewoong Medical) (left) and the fully covered Polyflex stent (Boston Scientific) (right).
among the three groups, but recurrent dysphagia occurred more frequently with Ultraflex stents. Of the main causes of recurrent dysphagia, stent migration was most commonly seen with Polyflex stents, whereas tissue (mainly nontumoral) ingrowth and overgrowth was more frequent with Ultraflex stents and, to a lesser degree, Niti-S stents. The higher rate of stent migrations with Polyflex stents was confirmed in another randomized trial comparing Ultraflex and Polyflex stents. Another drawback of Polyflex stents is the large size and nonflexibility of the delivery system, which increases the risk of stent-related complications such as perforation and bleeding.

The new fully covered stents, particularly the Niti-S stents, are appropriate for palliation of dysphagia from esophageal cancer. An alternative stent choice in this position remains the Ultraflex stent, although recurrent dysphagia caused by tissue ingrowth and overgrowth occurs more frequently with this stent. Polyflex stents seem less preferable in malignant dysphagia.

**Stents for Proximal Esophageal Cancer**

Tumors close to the upper esophageal sphincter (UES; 7%–10% of all esophageal carcinomas) are traditionally regarded as more difficult to manage. Stents at this location are associated with an increased risk of complications such as perforation, aspiration pneumonia, proximal migration, and patient intolerance caused by pain and globus sensation; therefore, palliative radiation therapy is often offered to these patients. Recently, a large study with 104 patients reported the insertion of stents at this location. Of these, 44 patients had a stricture within 4 cm of the UES. Dysphagia improved significantly in most patients, and complications and recurrent dysphagia were comparable to those of stent placement in the mid- or distal esophagus. Five percent to 15% of patients experienced globus sensation; however, in none of the patients was stent removal indicated. In the authors’ experience, Ultraflex stents, with their relatively low radial force and flexible mesh compared with other stent designs, are currently the preferred stent type in patients who have a malignant stricture in the proximal esophagus (Fig. 7). Another new stent for this indication has a shorter length of the upper flange (7 mm) and was specifically designed to reduce foreign-body sensation (M.I. Tech Co., Ltd., Pyongtack, South Korea). The authors successfully inserted this stent in three patients, with rapid improvement of dysphagia and no complications or foreign-body sensation; however, further experience with this type of stent is necessary. Esophageal cancer near the UES should no longer be considered

![Fig. 7. Malignant stricture in the proximal esophagus close to the UES (A), for which an Ultraflex stent (Boston Scientific) was placed (B).](image)

Siersema
a contraindication for stent placement; however, stent choice and expertise are important for optimal results.

**Single-Dose Brachytherapy**

A few years ago, the authors retrospectively evaluated the outcome of single-dose brachytherapy in 149 patients, which was administered in one or two sessions at a median dose of 15 Gy (Fig. 8). At 6 weeks after brachytherapy, dysphagia scores had improved slightly from a median of 3 (liquids only) to 2 (some difficulty with solid food; \( n = 104, P < .001 \)); however, dysphagia had not improved in 51 (49%) patients. Procedure-related complications occurred in 7 (5%) patients. Late complications, including fistula formation and bleeding, occurred in 11 (7%) patients. Twelve (8%) patients experienced minor retrosternal pain. Median survival was 160 days. At follow-up, 55 (37%) patients experienced recurrent dysphagia. In 34 (23%) patients, a metal stent was placed to relieve persistent or recurrent dysphagia. Thus, high dose rate brachytherapy seemed moderately effective but was associated with a low rate of procedure-related complications. Recurrent dysphagia occurred frequently, requiring additional treatment in a substantial number of patients.

**Single-Dose Brachytherapy Versus Stent Placement**

Because the complication rate of single-dose brachytherapy was low, with acceptable results for palliation of malignant dysphagia, the authors decided to compare

![Fig. 8. Esophageal applicator for brachytherapy (arrows) positioned in the esophagus.](image-url)
single-dose brachytherapy with metal stent placement for the palliation of dysphagia from inoperable esophageal cancer. A total of 209 patients, recruited in nine hospitals in the Netherlands, were randomized to single-dose (12 Gy) brachytherapy or stent placement (Ultraflex stent). Of these 209 patients, 144 (69%) had an adenocarcinoma, 58 (28%) had a squamous cell carcinoma, and 7 (3%) had another malignant tumor in the esophagus. Dysphagia improved more rapidly after stent placement than after brachytherapy, but long-term relief of dysphagia was better after brachytherapy. Stent placement had more complications than brachytherapy (36/108 [33%] versus 21/101 [21%]; P = .02), which was mainly due to an increased incidence of late bleeding (14 [13%] versus 5 [5%]; P = .05). Groups did not differ in persistent or recurrent dysphagia (P = .81) or in median survival (P = .23). Quality-of-life scores were in favor of brachytherapy compared with stent placement. Total medical costs were also much the same for stent placement ($10,348) and brachytherapy ($10,247). It was concluded that despite slow improvement, single-dose brachytherapy gave better long-term relief of dysphagia with fewer complications than metal stent placement.

A prognostic model was then developed that could help guide treatment (ie, stent placement or single-dose brachytherapy) in individual patients who had dysphagia from incurable esophageal cancer. Significant prognostic factors for survival included tumor length, World Health Organization (WHO) performance score, and the presence of metastases. A simple score was developed, which included age (increasing age has a worse prognosis), sex (men have a worse prognosis), tumor length (increasing length has a worse prognosis), WHO performance score, and the presence of metastases. A total score based on these factors was able to separate patients who had a poor, intermediate, and relatively good prognosis. It was found that in the intermediate and relatively good prognostic groups, the use of brachytherapy resulted in a better dysphagia-adjusted survival. Alternatively, in the poor prognosis group, the difference in dysphagia-adjusted survival was 23 days in favor of stent placement compared with brachytherapy (77 days versus 54 days). Based on this model, it is recommended to use stents in patients who have dysphagia from esophageal cancer and have a calculated life expectancy of 3 months or less, and to reserve single-dose brachytherapy for patients who have a life expectancy longer than 3 months. Stent placement may also be reserved for patients who have persistent or recurrent tumor growth after brachytherapy.

FUTURE DEVELOPMENTS

Over the past 10 to 20 years, an alarming increase in the incidence of EAC has been noticed. This increase mainly reflects changes in the prevalence of risk factors. Of these, GERD and BE, and their common risk factor abdominal obesity, are most important. As long as the increase in obesity in Western countries cannot be halted, it is likely that the incidence of EAC will increase further.

Staging is of utmost importance to select patients who will most likely benefit from esophageal cancer resection. An optimal staging procedure should include CT, EUS, and ultrasonography of the neck. These investigations should be performed by experienced physicians with state-of-the-art equipment. It remains to be established what the role of FDG-PET is; however, with the increasing introduction of machines that combine FDG-PET and CT, it is likely that FDG-PET will also be part of the staging procedure, particularly in stage III to IV esophageal cancer.

Although surgical results have slowly improved, particularly when performed in high-volume centers by experienced surgeons, local recurrent cancer and metastatic disease remains a problem after esophageal resection. It can be expected that
survival after esophageal cancer surgery can further be improved when combined with specific combinations of chemotherapy and radiation therapy.

Another way to improve survival in esophageal cancer is to detect this malignancy at a stage when it is still likely to be curable. It is currently not clear what the role of screening for early-stage esophageal cancer is. For HGIN and esophageal cancer confined to the mucosa, endoscopic treatment with EMR with or without ablative therapy is the preferred treatment option.

Finally, dysphagia due to incurable esophageal cancer can be palliated with local treatment (eg, stent placement or single-dose brachytherapy). In an effort to prolong survival of these patients, a role for the new chemotherapeutic regimens, alone or in combination with radiation therapy, can be expected.

REFERENCES