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1. Describe trends in esophageal adenocarcinoma (EAC) incidence and survival.
2. Discuss risk factors for EAC and interventions for prevention and early detection.
3. Outline the current treatment of patients with localized, regional, and distant stage EAC.

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Esophageal adenocarcinoma (EAC) is characterized by 6 striking features: increasing incidence, male predominance, lack of preventive measures, opportunities for early detection, demanding surgical therapy and care, and poor prognosis. Reasons for its rapidly increasing incidence include the rising prevalence of gastroesophageal reflux and obesity, combined with the decreasing prevalence of Helicobacter pylori infection. The strong male predominance remains unexplained, but hormonal influence might play an important role. Future prevention might include the treatment of reflux or obesity or chemoprevention with nonsteroidal antiinflammatory drugs or statins, but no evidence-based preventive measures are currently available. Likely future developments include endoscopic screening of better defined high-risk groups for EAC. Individuals with Barrett esophagus might benefit from surveillance, at least those with dysplasia, but screening and surveillance strategies need careful evaluation to be feasible and cost-effective. The surgery for EAC is more extensive than virtually any other standard procedure, and postoperative survival, health-related quality of life, and nutrition need to be improved (eg, by improved treatment, better decision-making, and more individually tailored follow-up). Promising clinical developments include increased survival after preoperative chemoradiotherapy, the potentially reduced impact on health-related quality of life after minimally invasive surgery, and the new endoscopic therapies for dysplastic Barrett esophagus or early EAC. The overall survival rates are improving slightly, but poor prognosis remains a challenge. CA Cancer J Clin 2013;63:232-248. ©2013 American Cancer Society.

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continuing at a seemingly similar rate, and the most recent update of its incidence in the United States, including the year 2009, reported a continued increase. Moreover, the increase is also seen within more recent birth cohorts, suggesting that the incidence of EAC will continue to rise over the coming decades.

**Reasons for the Increase**

**Multifactorial Etiology**

The etiology of EAC is multifactorial, and includes interactions between various environmental and genetic factors involving nucleotide polymorphisms of inflammatory and tumor growth-promoting pathways. A recent study found that up to 13% of EAC cases may have a genetic predisposition, and the genes involved may affect macrophage function and inflammatory pathways. There is limited knowledge of the interactions between molecular changes and environmental risk exposures, but recent studies have revealed that these interactions may be of relevance. Single-nucleotide polymorphisms in the matrix metalloproteinase gene family, in genes coding for insulin-like growth factor (IGF), epidermal growth factor, and vascular endothelial growth factor, may be markers of EAC risk. Furthermore, genes of the interleukin-18 pathway might indicate a susceptibility to EAC. Genetic changes are, however, very unlikely to explain or even contribute to the abrupt and rapid increase in the incidence of EAC. Environmental factors are more likely the key factors behind this prominent pattern. Several large-scale and well-designed epidemiologic studies have identified some previously unrecognized environmental etiologic factors. Of these, 3 exposures have the greatest potential to contribute to the increase: 1) gastroesophageal reflux disease; 2) obesity; and 3) *Helicobacter pylori* (*H. pylori*) infection (inverse association). These will be discussed in more detail below, while environmental risk factors that might not contribute as much to the increasing incidence are presented only briefly.

**Gastroesophageal Reflux**

Gastroesophageal reflux is a strong and clearly dose-dependent risk factor for EAC, which was established in the late 1990s, although 40% of the patients did not have symptomatic reflux. A recent meta-analysis based on 5 studies showed that compared with individuals without reflux symptoms, experiencing symptoms at least weekly increased the odds of developing EAC nearly 5-fold (odds ratio [OR], 4.9; 95% confidence interval [95% CI], 3.9-6.2), while daily symptoms increased the odds more than 7-fold (OR, 7.4; 95% CI, 4.9-11.1). The progression from reflux to EAC begins with the development of inflammation of the esophagus (esophagitis) followed by a long-term development of Barrett esophagus. Barrett esophagus presents as a metaplasia of the distal esophageal mucosa from the native squamous epithelium to a columnar-lined and intestinal-like epithelium, which is prone to becoming dysplastic and might progress to an invasive EAC. Interactions between functional polymorphisms in apoptotic genes and gene-environment interaction patterns seem to differ between patients with EAC with and without reflux. Single-nucleotide polymorphisms of the DNA repair protein O6-methylguanine-DNA methyltransferase, the major cellular defense against alkylating DNA damage, are associated with an increased risk of EAC, and exposure to reflux produces markedly higher risks among carriers of the homozygous variant genotype.

Few studies have assessed whether the population prevalence of reflux has increased over time, but some compelling evidence of an increasing prevalence comes from a recent population-based study from Norway with long-term follow-up of 29,610 individuals living in one of the Norwegian counties. The study indicated that the age-adjusted prevalence of at least weekly reflux symptoms increased by as much as 47% between the periods 1995 and 1997 and 2006 and 2009. This finding suggests an important role for reflux in the rising incidence of EAC. The reasons for this increase are uncertain, but obesity might play a part. Overall, reflux is likely to be an exposure that contributes to the increasing incidence of EAC.

**Obesity**

The association between increasing body mass index (BMI) and EAC is seemingly linear, and the association is stronger than that of any other obesity-related cancer. A recent meta-analysis based on 22 observational studies found that the risk ratio of EAC was 2.7 (95% CI, 2.2-3.5) among persons with a BMI of 30 or more compared with those with a normal BMI (25 or less), while a pooled
analysis of data from 12 studies comparing individuals with a BMI of 40 or higher with those with a BMI of less than 25 revealed a relative risk (RR) of 4.8 (95% CI, 3.0–7.7).21 Predominantly central and intraabdominal adiposity has a bigger influence than BMI alone.24,25 A recent cohort study of 218,854 individuals identified 253 with EAC during follow-up, and found abdominal adiposity to be associated with EAC, even in those with a normal BMI.26 Obesity is associated with an increased risk of several types of cancer; for this reason, various potential mechanisms have been proposed, including insulin resistance; increased levels of leptin, plasminogen activator inhibitor–1, and endogenous sex steroids; decreased levels of adiponectin; and chronic inflammation.27 The proinflammatory impact of adipocytokines associated with the metabolic syndrome of central obesity may be particularly relevant. A study of patients with Barrett esophagus who underwent anthropometry, bioimpedance tests (of body fat distribution), and blood pressure measurement and had their blood analyzed for lipids, insulin, glucose, C-reactive protein, and adipocytokines found that the metabolic syndrome was associated with the length of the Barrett mucosa.28 The IGF-1 axis might represent a plausible mechanism through which visceral obesity influences the development of EAC.29 One study highlighted the association between the IGF-1 and IGF-1 receptor expression and visceral obesity in patients with EAC.30 A more organ-specific mechanism that might explain the particularly strong link between obesity and EAC, however, is that adiposity causes increased intraabdominal pressure, facilitating reflux. This hypothesis is supported by the dose-dependent association between BMI and reflux.31,32

According to epidemiological studies, however, obesity is an equally strong risk factor for EAC irrespective of the presence of reflux symptoms, indicating another underlying mechanism.21 However, obese persons may more often have asymptomatic reflux. In fact, severe manifestations of reflux (ie, esophagitis and Barrett esophagus) are often asymptomatic.17 Endoscopic surveys in Western populations have reported an approximate 10% occurrence of reflux esophagitis among individuals without reflux symptoms.33 Although the rising incidence of EAC began earlier, and its relative increase is much greater than that of the “obesity epidemic,” it is likely that obesity to some extent contributes to the rising incidence of this tumor. This notion is corroborated by a recent assessment that showed that the rise in EAC incidence is likely to be only partly attributable to the secular trends in obesity.34

H. pylori Infection

Infection with the bacterium H. pylori, which commonly colonizes the gastric mucosa during childhood (and has infected greater than 50% of the world population),35 might evoke an approximately 50% decrease in the risk of EAC.36–38 This risk reduction is of similar strength across subgroups of patients with reflux frequency and current smoking status.36 A biological mechanism that might explain this inverse association is that the gastric atrophy often resulting from this infection reduces the acidity and volume of the gastric juices, and thereby lowers the risk of gastroesophageal reflux. This concept gained some support from a case-control study indicating that the gastric atrophy serum marker pepsinogen I was inversely associated with EAC,37 and also from a meta-analysis of 18 studies evaluating gastric atrophy in relation to EAC risk.39 The prevalence of H. pylori infection is decreasing in Western populations,40 mainly thanks to better hygiene and less overcrowded households. This drop is mirrored by a decreasing incidence of peptic ulcer disease and gastric cancer.35,41,42 The decreasing prevalence of H. pylori infection may, however, contribute to the rising incidence of EAC. The existing evidence suggests that although strategies for the broad eradication of H. pylori would reduce peptic ulcer disease and gastric cancer, they might not be beneficial with regard to the incidence of EAC.43

Other Etiologic Factors

The main risk factors for esophageal squamous cell carcinoma, tobacco smoking and alcohol overconsumption,44 should not contribute to the increasing incidence of EAC. Tobacco smoking raises the risk only moderately44,45 and smoking has become less popular over recent decades,46 facts that argue against their having any prominent role in the increasing incidence of EAC. The harmful effects of reflux might, however, be accentuated among tobacco smokers.47 Alcohol consumption is not associated with any increased risk of EAC,44,48 and some data even indicate a protective effect of a modest intake of wine.49,50 Among dietary factors, low intake of fruit and vegetables increases the risk of EAC,51 but the consumption of these has not decreased during the last decades, and should therefore not be responsible for the increase in EAC. Moreover, the consumption of red and processed meats might increase the risk, but the association is weak.52 The established risk factors seem to explain the majority of cases of EAC; combinations of gastroesophageal reflux, overweight, tobacco smoking, and low dietary intake of fruit and vegetables together accounted for 76% to 79% of EAC cases in studies from the United States and Australia.53,54 Other, more recently identified potential risk factors include diabetes and the acquired immunodeficiency syndrome. A meta-analysis indicated that men with diabetes may have a 2-fold increased RR of EAC (RR, 2.1; 95% CI, 1.0–4.5),55 but this remains controversial. Individuals with the acquired immunodeficiency syndrome might have a nearly 2-fold

Recent studies evaluating gastric atrophy in relation to EAC risk.39
increased risk of EAC compared with the US background population (standardized incidence ratio, 1.9; 95% CI, 1.3-2.7), but whether this is a causal association is uncertain.

Summary
Gastroesophageal reflux, either symptomatic or asymptomatic, seems to be the key factor behind the rising incidence of EAC, while the increasing prevalence of obesity and decreasing prevalence of H. pylori infection contribute to this pattern by increasing the population-based prevalence and severity of reflux. However, research addressing the interplay between obesity, gastroesophageal reflux, and H. pylori infection is needed to better understand the mechanisms behind the increasing incidence of EAC.

Strong Male Predominance
Sex Ratio
The striking male predominance of EAC, with a male:female ratio of 3 to 9:1, is a global phenomenon. The male predominance is, for reasons yet unknown, stronger in the United States (9:1) than in any other country (Fig. 2). Although the baseline incidence is much lower in women, the increase in the incidence of EAC is occurring at a similar rate in both sexes, and the incidence ratios between the sexes are stable over time.

Reasons for the Sex Distribution
Known Risk Factors
The distribution prevalence of the main etiologic factors is virtually the same between sexes. However, reflux is on average more severe in men than in women, as indicated by a higher ratio of erosive esophagitis to nonerosive gastroesophageal reflux noted among men. This erosive reflux disease is a notably stronger risk factor for EAC compared with nonerosive reflux disease. Regarding obesity, the strong association between EAC and a typical male fat distribution (predominantly central and intraabdominal adiposity), which is larger than that of BMI, might also contribute to the sex difference. There was, however, no support for this hypothesis in a study that did not find any increase in sex ratios with increasing levels of BMI in patients with EAC. The etiologic factors of tobacco smoking, consumption of fruit and vegetables, and H. pylori infection are equally distributed between the sexes, and their associations with EAC are no stronger in men than in women.

Hormonal and Reproductive Influence
The hypothesis that sex hormones and reproductive factors have an influence on the sex distribution is supported by the delayed development of EAC of on average 20 years in females compared with males. Moreover, recent data have indicated a decrease in cell growth and apoptosis in EAC cells after treatment with selective estrogen receptor ligands. However, most epidemiological studies have not provided conclusive results in favor of the involvement of estrogens or reproductive factors in the etiology of EAC, and clearly more evidence is needed. Identified associations between the reproductive factors of parity and age at first birth and the risk of EAC might not be explained by sex hormone influence, since these associations are at least as robust in men as in women. An interesting finding is a strongly protective effect of breastfeeding. A pooled study of 218 female cases and 862 controls showed a gradually reduced risk of EAC with an increased duration of breastfeeding (OR, 0.4 [95% CI, 0.2-0.8] for breastfeeding for 12 months or longer). The hormone-related factors of parity, menstruation, history of pregnancy, and use of oral contraceptives or hormone replacement therapy were not associated with EAC. The finding of a protective role of breastfeeding encourages further research (eg, regarding hormonal factors involved in breastfeeding).

Summary
The striking male predominance in EAC remains a mystery, although more severe gastroesophageal reflux occurring among men is probably a contributing factor. Further research is needed to reveal how various hormones contribute to the pattern of the substantial delay in the average onset of EAC in women compared with men.

Need for Preventive Strategies
Opportunities for Prevention
When EAC is detected after the presentation of symptoms (typically progressive dysphagia and weight loss), the prognosis is poor, stressing the importance of identifying preventive strategies to decrease the mortality from this cancer. An understanding of strong and easily identifiable
risk factors (ie, reflux, obesity, male sex, and age) might help to identify evidence-based targets for primary preventive strategies. The presence of the premalignant condition Barrett esophagus should offer excellent opportunities for secondary prevention in a limited group of patients at high risk of developing EAC (Fig. 3). Moreover, observational research has consistently suggested that long-term use of nonsteroidal antiinflammatory drugs (NSAIDs) and statins strongly decreases the risk of developing EAC. Antireflux therapy, weight loss, and chemoprevention with NSAIDs and statins should be of key interest in both the primary and secondary prevention of EAC. These exposures are discussed here.

Antireflux Therapy

The hypothesis that antireflux medication and antireflux surgery reduce the incidence of EAC among individuals with gastroesophageal reflux has been addressed mainly in uncontrolled studies. Valid data supporting any cancer preventive effect of antireflux medication are limited, and the results of randomized clinical trials (RCTs) have provided no strong evidence that surgical or pharmacological antireflux therapies eradicate Barrett dysplasia. However, a recent cohort study of 540 patients with Barrett esophagus who were followed for a median of 5.2 years found that the use of proton pump inhibitors (PPIs) strongly decreased the risk of developing high-grade dysplasia or EAC (hazard ratio [HR], 0.2; 95% CI, 0.1-0.7). Some basic research also suggests that PPIs have antioxidative properties and immune-modulatory effects, and an ability to prevent adhesion molecule binding in cancer cells.

The potentially beneficial influence of antireflux surgery on EAC is probably limited or even absent. The risk of EAC did not decrease with time after surgery in a population-based cohort study from Sweden including 14,102 individuals who had undergone antireflux surgery. These results were supported by a Finnish study where the incidence of EAC in patients undergoing antireflux surgery was compared with that of the general population. An explanation for the lack of preventive effects of antireflux surgery might be that many patients experience recurrent reflux after surgery, which was highlighted in a RCT comparing antireflux surgery with medical therapy.
recently gained further support from a population-based study from Finland that found that only one-third of those who developed EAC had a functioning fundoplication,\textsuperscript{77} and a nested case-control study showing that recurrent reflux was the main risk factor for developing EAC after antireflux surgery.\textsuperscript{78}

**Weight Loss**

The potentially preventive role of weight loss on the risk of developing EAC is unknown. This is due to the fact that exposure to weight loss in terms of timing and extent is difficult to assess or define. Obesity surgery would provide an ideal human model for studies of weight loss, as it results in a substantial weight loss initiated at a defined time point, occurring within a limited time frame. However, a long follow-up period of large cohorts of patients who underwent obesity surgery is needed before any potential effects on EAC can be addressed. Currently, there are insufficient data with which to assess this interesting topic,\textsuperscript{79} but the rapidly increasing use of obesity surgery will enable the examination of cohorts that could be used to answer this question in the future. If research would reveal that obesity surgery strongly reduces the risk of EAC, it would indicate a possible role for weight loss in the primary, and potentially even secondary, prevention of EAC.

**Nonsteroidal Antiinflammatory Drugs**

NSAIDs may reduce the level of cyclooxygenase-2, which might play an important role in cell proliferation and the inhibition of apoptosis, and the increased expression of cyclooxygenase-2 has been shown to be associated with a progressive escalation in the esophageal metaplasia-dysplasia-adenocarcinoma sequence.\textsuperscript{80} Two recent meta-analyses and one pooled analysis of 6 population-based studies, all mainly based on case-control studies, revealed very similar results: a 32% to 36% decrease in the risk of EAC among users of aspirin and among users of non-aspirin NSAIDs compared with nonusers.\textsuperscript{81-83} However, factors influencing the use of NSAIDs constitute a threat to the validity of observational studies, as highlighted in some previous investigations.\textsuperscript{81,82,84,85} For example, individuals with the known risk factor of gastroesophageal reflux might be more likely to be advised to avoid NSAIDs, since these drugs are known to be associated with upper gastrointestinal disorders. RCTs would avoid such confounding by indication. One published RCT compared nearly one year's daily use of the NSAID celecoxib with a placebo in 100 patients with Barrett esophagus with low-grade or high-grade dysplasia, but found no decreased rate of progression of the dysplasia in the celecoxib group.\textsuperscript{86} In a multicenter RCT of 122 patients with Barrett esophagus who were separated into 3 treatment arms, prostaglandin concentrations in biopsy samples were compared in patients given the PPI esomeprazole at a dose of 40 mg twice per day combined with placebo (n = 30 patients), 81 mg of aspirin (n = 47 patients), or 325 mg of aspirin (n = 45 patients) for 28 days. A statistically significantly reduced prostaglandin concentration was revealed in patients receiving esomeprazole plus 325 mg of aspirin compared with the placebo group (P = .02), indicating that higher doses of aspirin combined with esomeprazole might prevent EAC.\textsuperscript{87} However, pending the results of further and larger RCTs (eg, the AspECT trial in the United Kingdom, which is evaluating the use of aspirin and PPIs in patients with Barrett esophagus), there is currently insufficient evidence to recommend NSAIDs for the prevention of EAC.

**Statins**

The data supporting a protective effect of statins in the etiology of EAC are more limited compared with those for NSAIDs. In a Dutch cohort study of 570 patients with Barrett esophagus, at least 1 month's use of NSAIDs (HR, 0.47; 95% CI, 0.24-0.93) or statins (HR, 0.46; 95% CI, 0.21-0.99) was associated with a reduced risk of progression to high-grade dysplasia or EAC, and the use of a combination of NSAIDs and statins further seemed to reduce this risk (HR, 0.22; 95% CI, 0.06-0.85).\textsuperscript{88} In a US cohort of 11,823 patients with Barrett esophagus, 116 cases of EAC and 696 matched controls were compared, and statin use was found to be associated with a 45% reduction in the risk of EAC (HR, 0.55; 95% CI, 0.36-0.86), with a significant trend toward a greater risk reduction with a longer duration of use.\textsuperscript{73} A recent case-control study from the United Kingdom of 112 cases of EAC and 448 controls reported a dose-dependent decreased risk of EAC among users of statins (mainly simvastatin), with an overall OR of 0.52 (95% CI, 0.27-0.92), and the use of statins combined with aspirin rendered a further reduction in the odds of developing EAC (OR, 0.27; 95% CI, 0.05-0.67).\textsuperscript{89} There are no interventional studies that have evaluated whether statins actually prevent EAC, but the above studies suggest that RCTs are indeed indicated. To answer the question of whether statins might be used in the future prevention of EAC, large RCTs with long follow-up are required.

**Summary**

It remains uncertain whether antireflux therapy reduces the risk of EAC, but recent indications of a preventive effect of PPIs emphasize the need for more research. The role of weight loss will be possible to assess in future epidemiologic studies using obesity surgery as the exposure. NSAIDs have consistently been found to considerably reduce the risk of EAC, and RCTs of patients with Barrett esophagus will clarify if such medication can be used for prevention in
high-risk individuals. The recent results indicating strongly preventive effects of statins give grounds for future RCTs in obese individuals with Barrett esophagus.

**Opportunities for Early Detection**

**Endoscopic Screening**

Endoscopic screening based on risk factors would be useful and cost-effective only if it would lead to the detection of a high rate of Barrett esophagus with dysplasia or EAC at an early and curable stage. The high prevalence of gastroesophageal reflux (noted to occur in 10%-20% of adults) combined with the low incidence of EAC (1-5/100,000 person-years) make endoscopic screening programs of unselected populations not feasible. Endoscopic surveys of unselected populations have shown that Barrett esophagus affects approximately 1.3% to 1.6% of adults in Western populations. A precise selection of a limited and easily identifiable high-risk group would be necessary (eg, based on age, sex, reflux symptoms, and obesity). Before considering screening of relative high-risk groups, it is important to stress that RR estimates evaluate only the strength of the association between an exposure and a disease, but screening must be based on the individual's absolute risk, which takes the incidence of the target disease into account. Moreover, the test (endoscopy) must have a high specificity and sensitivity to detect the outcome conditions (dysplastic Barrett esophagus and EAC). Endoscopic screening carries a risk of complications, is costly, and is associated with errors in the detection of the target conditions as a result of selective sampling and subjective pathological evaluation. A longer endoscopy time, for example, improves the detection of dysplasia or early EAC in patients with Barrett esophagus. In the future, screening with a cytosponge device may be a cost-effective alternative to conventional endoscopy for screening purposes since it circumvents the invasiveness of the endoscopy, but this method is currently restricted by a limited sensitivity in the assessment of dysplasia. Moreover, there are no data showing a significant reduction in the number of deaths from EAC as a result of endoscopic screening.

The Clinical Guidelines Committee of the American College of Physicians has recently published guidelines for upper endoscopy in which men aged at least 50 years with long-standing reflux symptoms (over 5 years), combined with other known risk factors, are advised to undergo screening endoscopy for the detection of dysplastic Barrett esophagus or EAC. This seems like a reasonable recommendation, but it will probably need to be revised and more precisely defined after proper scientific evaluation. Estimation models that consider a combination of known risk factors have recently been found to identify individuals with a high enough absolute risk of developing EAC that warrants screening, but more studies are needed to assess the potential gain of such targeted screening. Future screening programs may be facilitated by the assessment of genetic markers of an increased susceptibility to developing Barrett esophagus in individuals exposed to the main risk factors. As noted in a recent Cochrane report, RCTs are required to determine the efficacy of screening for EAC.

**Endoscopic Surveillance**

Barrett esophagus provides opportunities for the detection of premalignant dysplasia and early EAC on the basis of endoscopic surveillance, but the risk of developing EAC in patients with known Barrett esophagus seems to have been overestimated in the past. Recent large-scale studies have reported lower incidence rates of EAC compared with the past literature. A Danish population-based cohort of 11,028 patients with Barrett esophagus was followed for a median of 5.2 years, and 1.2 cases of EAC (95% CI, 0.9-1.5) per 1000 person-years of surveillance were identified, for an annual risk of 0.12% (95% CI, 0.09%-0.15%). However, low-grade dysplasia was associated with a higher incidence of EAC (5.1 cases per 1000 person-years; 95% CI, 3.0-8.6). Another cohort study of 8522 patients from Northern Ireland with a diagnosis of Barrett esophagus with a mean follow-up of 7.0 years found 0.22% EAC cases per year (95% CI, 0.19%-0.26%), while the risk was higher (1.40% per year) in patients with low-grade dysplasia. This new information has to be taken into consideration when evaluating the potential benefit of endoscopic surveillance intervals. Updated current clinical guidelines from the United States recommend endoscopic surveillance every 3 to 5 years in patients with Barrett esophagus without dysplasia, while more frequent intervals (not defined) are indicated in those with dysplasia.

Future surveillance strategies to facilitate the detection of dysplasia in patients with Barrett esophagus might include new molecular imaging methods. Biomarkers such as aneuploidy and loss of heterozygosity of p53 seem to be associated with an increased risk of malignant progression of Barrett esophagus. Cell surface glycans change during the progression from Barrett esophagus to EAC and lead to specific alterations in lectin binding patterns, and germline mutations might also be used in the future, as a more sophisticated assessment of EAC risk in patients with Barrett esophagus. The presence of a combination of biomarkers, including low-grade dysplasia, abnormal DNA ploidy, and lectin binding patterns might help to identify patients with Barrett esophagus who are more prone to developing EAC. Moreover, DNA methylation changes and expression of microRNAs, as well as overexpression or loss of expression of p53, might predict tumor progression.

**Summary**

Barrett esophagus constitutes a unique possibility for the early detection of EAC, although the risk has been exaggerated in the past and robust recommendations for...
screening and surveillance are presently difficult to provide. Endoscopic screening and surveillance might rapidly become unfeasible for health care providers if such strategies are not based on strict scientific evidence. Current guidelines will probably need to be continuously updated after careful evaluation of the benefits versus the costs and risks associated with the guidelines.

**Demanding (Surgical) Therapy**

**Preoperative Therapy**

Improvements to tumor staging by means of, for example, better imaging techniques, have resulted in the more accurate selection of patients who are suitable for curatively intended therapy. The increased use of positron emission tomography scanning has resulted in better detection of metastatic disease. A more stringent patient selection mirrors the decreased rate of curatively intended surgery, which is approaching 20% to 25% according to recent population-based studies. With early detection (stage I disease [determined according to the TNM staging system, 7th edition]), treatment with surgery alone has a high cure rate. The value of administering chemotherapy or chemoradiotherapy prior to surgery in patients with more advanced tumors has been a topic of much controversy, resulting from underpowered trials providing contradictory results. The majority of studies have not shown any statistically significant benefit for this strategy, but this seems to be due to the limited statistical power of the individual trials. Data from more recent large RCTs, as well as meta-analyses of RCTs, provide valid evidence in favor of a survival benefit from preoperative chemoradiotherapy followed by surgery compared with surgery alone. A recent Dutch RCT including a total of 366 patients with esophageal cancer, mainly EACs (75%), compared preoperative chemoradiotherapy followed by surgery with surgery alone and found a substantial survival benefit for chemoradiotherapy (HR, 0.66; 95% CI, 0.50-0.87). A recent meta-analysis based on 4188 patients included in RCTs found that compared with surgery alone, neoadjuvant chemoradiotherapy was followed by a decrease in all-cause mortality in patients with EAC (HR, 0.75; 95% CI, 0.59-0.95), while neoadjuvant chemotherapy also reduced this risk (HR, 0.83; 95% CI, 0.71-0.95). Therefore, the use of preoperative chemoradiotherapy or chemotherapy followed by surgery is currently the prevailing treatment for most patients selected for curatively intended treatment (ie, those with locally advanced but resectable tumors). More large and well-designed RCTs are required to define an optimal preoperative oncological strategy that can be generally recommended, and more data are required to ascertain whether preoperative chemoradiotherapy is superior to chemotherapy. Moreover, the preoperative treatment needs to be better customized, assessing whether patients are benefitting from it (pathological response).

**Esophagectomy**

**Surgical Approach**

Surgery for EAC is an extraordinarily extensive procedure (Fig. 4), entailing a 30% to 50% risk of significant postoperative complications, and more than a 5% risk of inhospital mortality. The 2 dominant surgical approaches for EAC resections are transthoracic and transhiatal surgery. The transthoracic approach allows for better clearance of local and regional lymph nodes, while the transhiatal approach avoids opening the chest. Issues of relevance in selecting the surgical approach include the location of the esophageal tumor, gross total resection, access to lymph nodes, and the experience of surgical team. There are limited data addressing which approach is better, but a large RCT demonstrated a lower pulmonary morbidity in the patients undergoing the transhiatal approach and, while no statistically significant differences in survival were found, a tendency toward better 5-year survival was reported in the patients treated with the transthoracic approach. Thus, existing evidence does not provide any clear clinical recommendations for which approach should be used, but an individualized strategy depending on the patient’s fitness level and the tumor location has been suggested. There is a need to improve the surgical procedure to reduce the negative impact of the surgery on health-related quality of life (HRQL) by, for example, better tailoring of the surgery and the development of less invasive techniques (eg, using minimally invasive surgery, including robotic surgery). Some studies have suggested that minimally invasive surgery might reduce the negative impact of surgery on HRQL and recent nonrandomized comparisons of large series of minimally invasive surgery indicate a substantially reduced risk of pulmonary complications compared with open surgery. The existing data were put together in a meta-analysis based on 16 studies and 1212 patients, which showed no difference in overall survival. In a recent RCT conducted at 5 centers in the Netherlands, Spain, and Italy, 56 patients were randomized to open surgery and 59 to minimally invasive surgery. A reduced risk of early pulmonary infection was noted in the group undergoing the minimally invasive surgery, indicating a benefit for this approach in the short term. More and larger RCTs with longer follow-up that mainly assess HRQL outcomes are necessary.

**Annual Surgery Volume**

The short-term outcomes after esophagectomy are more strongly dependent on annual surgeon volume and hospital volume compared with virtually any other
standard surgical procedure. Since the short-term mortality after esophagectomy is considerably lower in high-volume centers and among high-volume esophageal surgeons, an increased centralization to fewer hospitals has taken place in recent years. Much of the lower risk of short-term mortality observed at high-volume centers seems to be explained by better handling of severe complications. The risk of complications, however, appears to be related more to the skills of the individual esophageal surgeon than to volume alone. Long-term prognosis is an even more important outcome than short-term postoperative results due to the large number of patients dying of tumor recurrence after surgery. However, the influence of surgery volume on long-term survival has been less consistent in the previous literature. Two recent large and population-based studies with long-term follow-up have shown that a higher annual hospital volume and higher annual surgeon volume substantially improve the chance of long-term survival. A study from the United Kingdom demonstrated that even after the exclusion of short-term mortality, survival was statistically significantly better at high-volume centers. A study from Sweden, which adjusted the results for all relevant clinical prognostic factors including tumor stage and comorbidity, as well as mutual adjustment for annual hospital volume and annual surgeon volume, found that annual surgeon volume, but not hospital volume, was an independent predictor of a better 5-year prognosis after the exclusion of short-term mortality. Thus, further centralization to fewer surgeons working at high-volume centers would substantially improve the long-term prognosis after surgery in patients with EAC. This gains further support from research showing that centralization yields better long-term, population-based overall survival.

**Postoperative HRQL**

A main concern after esophagectomy is the severe and often long-lasting deterioration of many aspects of HRQL, particularly regarding physical function, general and esophageal cancer-specific symptoms, and malnutrition. Among long-term survivors (at least 5 years), HRQL levels deteriorate significantly over time after surgery in a subgroup of patients (15%), while in the majority of patients HRQL returns to the level of the corresponding background population. There is a need to identify patients at risk of HRQL deterioration, and pay greater attention to these individuals in the clinical setting. The occurrence of acute postoperative complications, comorbidity, and advanced tumor stage are predictors of poor HRQL, particularly in terms of dyspnea, fatigue, and eating restrictions. Malnutrition is a threat to the main outcomes of esophageal cancer surgery (ie, survival, complications, and HRQL). Preoperative weight loss is mainly due to the obstructing tumor and preoperative oncological therapy, and the esophagectomy is typically followed by further weight loss. Intensified preoperative nutrition might improve recovery after surgery. A population-based cohort study found that nearly two-thirds of patients who underwent surgery had lost at least 10% of their preoperative BMI within 6 months of surgery. The weight loss continued for at least 3 years, and was more pronounced in overweight patients and in patients treated with preoperative oncological therapy, which indicates a need for enhanced nutritional support in these patients. The very commonly encountered problems with postoperative malnutrition indicate a general need for close follow-up by trained dieticians after esophagectomy. Observational research indicates that prolonged...
postoperative feeding through catheter jejunostomy could be considered, but these observations need support from valid RCTs. Use of HRQL measures in the clinical routine follow-up after EAC surgery may help to identify those patients in need of interventions or who are at risk of poor recovery and facilitate tailored follow-up.

**Definite Chemoradiotherapy**

There is limited evidence addressing whether surgery should be avoided in some patients with locally advanced disease who might instead undergo definite chemoradiotherapy. Chemoradiation alone is typically used for patients with advanced stages of disease, those in whom surgery is not deemed to be feasible, or in patients who are not candidates for surgery (eg, the elderly or unfit). Moreover, some studies have indicated it is feasible to avoid surgery in patients with clinical complete responses, and this is a consideration in patients who may not be surgical candidates. The development of metastatic disease in the majority of patients and the poor survival even after combined modality therapy indicate that chemoradiotherapy without surgery could be considered in highly selected patients. However, there is uncertainty about the optimal chemotherapy in chemoradiation for patients with locally advanced disease, and the selection of drugs may often be based on toxicities as comparative data about survival are limited.

**Endoscopic Therapies**

Various endoscopic therapies are emerging as potential alternatives to surgical therapy in the limited group of patients with Barrett esophagus with high-grade dysplasia (not all patients with Barrett esophagus), or even those with intramucosal EAC. Such local procedures do not allow for the excision of larger tumors (which are dominant) or lymph node metastases, but are much better tolerated than standard surgery from the perspective of HRQL, and might be justified given the low likelihood of lymph node metastases in patients with very early tumors. However, in patients with T1 tumors, a submucosal invasion appears to be present in 40% of individuals, in whom the presence of lymph node metastases has recently been assessed to be as high as 22% to 23%. In patients with high-grade dysplasia, however, endoscopic therapy is currently increasingly recommended rather than esophagectomy or endoscopic surveillance. Although far from perfect, endoscopic ultrasound might help to improve the selection of patients who are not suitable for endoscopic therapy (those with tumors that are too advanced) if the endoscopy is not conclusive enough, while endoscopic mucosal resection gives a more definite assessment of the invasion of superficial tumors. Endoscopic mucosal resection, photodynamic therapy, argon plasma coagulation, and radiofrequency ablation can all induce regression of Barrett esophagus and dysplasia. In a large RCT, the eradication rates for patients with Barrett esophagus with dysplasia were 82% and 94%, respectively, with radiofrequency ablation or a placebo treatment. However, until longer term RCTs are available, radiofrequency ablation should be used only in expert centers. A combination of endoscopic resection with radiofrequency ablation might offer an even better outcome. Endoscopic treatment might be cost-effective for patients with Barrett esophagus compared with esophagectomy as well as endoscopic surveillance. However, the recurrence of metaplasia after ablation therapies is a recently acknowledged concern that requires attention and indicates a possible need for further surveillance, even after the treatment.

**Noncurable Disease**

There is currently no generally agreed upon second-line chemotherapy for EAC whenever tumor recurrence occurs after curatively intended therapy. A meta-analysis of 24 trials of chemotherapy as second-line therapy in patients with esophageal cancer, 19 of which included EAC, showed a limited response rate (0%-39%), a short time to tumor progression (1.4 months-6.2 months), and a poor overall survival (4.0 months-11.4 months). A survival benefit for docetaxel combined with irinotecan as second-line chemotherapy has recently been identified. Population-based studies have shown that approximately 75% of patients with EAC are not eligible for curatively intended surgery at diagnosis. There are several alternative palliative therapies that can improve HRQL in the majority of patients with EAC in whom curatively intended therapy is not possible. Palliative chemotherapy and radiotherapy are valuable treatment options in this respect. Palliative chemotherapy typically combines a fluorinated pyrimidine with a platinum agent. Moreover, human epithelial growth
factor receptor 2 (HER2)-targeted therapy (trastuzumab) has recently been approved in the treatment of patients with HER2-positive metastatic EAC. A main HRQL concern is to relieve dysphagia, for which self-expanding metallic stent insertion and intraluminal brachytherapy (local radiotherapy) seem to offer the best palliation. A meta-analysis of 16 RCTs found that esophageal stenting required fewer reinterventions compared with other locoregional modality treatments (brachytherapy, laser, radiotherapy), although the survival was shorter among patients treated with stenting. In patients receiving palliative treatment, the limited number of studies addressing HRQL as the endpoint suggest that brachytherapy, external beam radiotherapy, and combination chemotherapy improve HRQL and dysphagia after a longer period of time, while stent treatment offers a more prompt effect. A combination of stenting and brachytherapy may further improve HRQL and dysphagia, but RCTs are needed to confirm these findings. Antireflux stents have not been found to show any better control of gastroesophageal reflux compared with conventional open stents.

The Care of the Patients Throughout the Clinical Pathway

The treatment of patients with EAC requires good resources, special skills, and a well-coordinated multidisciplinary team that regularly meets to discuss the best possible treatment options for each individual patient, and ascertains that the patients are considered for inclusion into RCTs and prospective cohort studies whenever suitable. Moreover, the increased centralization of EAC surgery to fewer centers puts further strain on the care pathway, since there are more patients requiring various types of attention from fewer staff members. Patients with EAC have a great need for supportive care due to the many HRQL issues associated with the disease and its treatment. These circumstances emphasize the need for good coordination and continuity of the care pathway. The key role of specialized contact nurses, with oncological training and experience in the management of these patients, in maintaining this care pathway has been highlighted in an RCT. Dedicated specialized contact nurses might be the ideal primary contact for patients with EAC and their families. This primary contact would facilitate a continuity of care, simplify individualized follow-up, and improve the possibility of administering interventions in a timely way, all of which may improve survivorship. Significant issues in the care pathway to improve recovery and outcomes for patients with EAC include preoperative and postoperative nutritional support, psychological support, postoperative care and tailored follow-up, and specialized and tailored rehabilitation after treatment.

Summary

Preoperative chemotherapy or chemoradiotherapy has become standard treatment in most cases of advanced but resectable EAC. Some surgical approaches might provide better postoperative HRQL than others, but there is a need for large RCTs before any recommendations can be given. Further centralization to fewer surgeons working at dedicated centers is recommended to optimize all aspects of the care of these patients, as well as research. The complex care pathway is probably best coordinated by specially trained contact nurses. Endoscopic therapies are replacing esophagogastrectomy in patients with Barrett esophagus with high-grade dysplasia, and evaluation of these techniques among individuals with early EAC is eagerly foreseen.

Poor Prognosis

Survival Trends

Despite all efforts to improve the surveillance, diagnostic procedures, and therapy, the overall 5-year survival in patients with EAC remains lower than 15% in Western societies. Recent population-based data indicate moderate improvements in survival, even after adjustment for expected death (Fig. 6). The population-based 5-year survival rate after curatively intended surgery in patients with EAC is 30% to 55%, a figure that has improved in the past few years. These better postoperative results might partly be explained by a better selection of patients who are suitable for surgery, as reflected by the decreasing rate of surgery for EAC. It is also likely that the increased use of effective neoadjuvant therapies contributes to the improved survival rates. Further improvements to tumor staging also are a key factor in patient selection in the future, since early recurrence after the completion of treatment is still common. Unfortunately, patients who develop disease recurrence after surgery are usually not able to be cured, due to the lack of effective second-line treatment.
Clinical Prognostic Factors

The strongest clinical prognostic factor in patients with EAC is tumor stage, while tumor location, presence of Barrett mucosa, comorbidity, weight loss, dysphagia at presentation, and surgical approach are other known, but more moderate, prognostic variables. Moreover, another US study of 778 patients with EAC who were undergoing surgery found that BMI and tobacco smoking status interacted in the prognosis; among never-smokers, obesity was associated with a 2-fold increased adjusted risk of overall mortality (HR, 1.97; 95% CI, 1.24-3.14), while obesity had no prognostic influence among current smokers. Acute surgical complications after esophagectomy might also be independent predictors of poorer long-term survival in patients undergoing surgical resection. Interestingly, recent research has demonstrated that HRQL assessments can be a clinically useful and readily available tool with which to predict survival after surgery for EAC. HRQL as assessed before surgery and changes in HRQL between surgery and the 6-month follow-up, as well as HRQL at 6 months after esophagectomy, are all predictive of long-term survival. HRQL assessments already seem to influence treatment recommendations at some centers.

Molecular Prognostic Factors

The search for clinically relevant molecular factors and biomarkers that can predict prognosis in patients with EAC has escalated. Such markers might also allow for better customized multimodality therapy in the future. Some studies have indicated that genetic polymorphisms might play a role in the prognosis of EAC, but this research is currently at an early stage and chance findings due to multiple testing (the risk of false-positive findings increases with the number of tests conducted) are a threat to the validity of the results. A recent study assessed the impact of heterogeneous HER2 gene amplification and polysomy 17 on survival in 675 patients with EAC; for the 20 individuals (3%) with HER2 heterogeneity with amplification, the disease-specific mortality was increased (adjusted HR, 2.04; 95% CI, 1.09-3.79), while polysomy 17 also indicated a worse prognosis among patients with non–HER2-amplified EAC. If proven true in further research, HER2-targeted therapy (trastuzumab) might become useful in this limited number of patients, but currently there is no evidence that HER2 overexpression is a prognostic marker in patients with EAC. A study from the United Kingdom identified that expression levels of 4 genes together predicted the prognosis in patients with EAC independent of tumor stage. Moreover, expression of proteases and their inhibitors have recently been suggested to be potential prognostic markers in patients with EAC. Studies of interactions between genetic and clinical prognostic factors might provide important clues regarding an improved future prediction of survival.

Predictive Markers to Direct Therapy

Equally important in identifying prognostic markers is the identification of predictive markers that can help direct therapy. Recent advances made in imaging, including positron emission tomography scanning, to assess response to neoadjuvant therapy can potentially direct and select further therapy, and are the subject of ongoing trials.

Summary

The overall prognosis in patients with EAC has improved during the last decades, but the 5-year survival is still poor. An improved selection of patients for tailored treatment is warranted, and modern imaging techniques might provide a better prediction strategy to direct further therapy. Earlier tumor detection, new therapeutic agents, and an increased centralization of the treatment would improve the prognosis in patients diagnosed with EAC.

Future Perspectives

There is a great need to reduce the mortality and suffering caused by EAC. The reasons behind the increasing incidence of the disease and its male predominance need to be clarified; such knowledge might help to identify preventive and new therapeutic strategies. Primary prevention through avoidance of risk exposures and the use of new secondary preventive factors in certain high-risk patients might also contribute to this goal in the future. It should be possible to identify a feasible strategy to detect EAC at an earlier and more curable stage, for example by the better targeting of certain high-risk individuals in whom screening and surveillance are warranted, possibly by using new biomarkers and other new diagnostic tools together with etiologic and clinical predictors. Future screening or surveillance would ideally be less invasive (ie, not require endoscopy). The selection of patients for surgery must be further improved and the future treatment should be better tailored to allow better survival and an improved HRQL. The inclusion of specialized primary contact nurses throughout the care pathway and individualized follow-up care based on the reported HRQL may improve survivorship. Among new treatment strategies, algorithms of clinicopathologic characteristics might be useful to aid decision-making and predict prognosis. Lastly, new molecularly targeted therapies might improve the prognosis for appropriately selected patients (eg, through pharmacologic inhibition of cyclooxygenase-2 or vascular endothelial growth factor).
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