Diseases of the Esophagus (2004) **17**, 10–26

DISEASES OF THE ESOPHAGUS

Review article

Cancer of the esophagus and gastric cardia: recent advances*

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SUMMARY. **Esophageal cancer and cancer of the gastric cardia, in particular adenocarcinomas, have shown a rapid and largely unexplained increase in incidence in many developed countries around the world. These diseases have a poor prognosis and current therapies have a modest impact on survival. This review presents recent advances in the epidemiology, etiology, diagnosis, staging, prevention and treatment of resectable and advanced disease. Although significant progress has been made in these areas of research and patient management over the past years, prognosis for most patients diagnosed with esophageal cancer or cancer of the gastric cardia remains poor. New diagnostic procedures, improved surgical procedures, combined treatment modalities and new treatment modalities are being evaluated and may be expected to contribute to improved patient outcomes and better palliation of symptoms in the future.**

KEY WORDS: **carcinogenesis, diagnosis, epidemiology, esophageal cancer, gastric neoplasms, therapy.**

INTRODUCTION

Patients diagnosed with esophageal cancer have a poor prognosis with 5-year survival ranging between 5% and 20% in patients amenable to surgery. A recent Swedish study suggests that survival has improved between 1961 and 1996, in particular for patients with esophageal adenocarcinoma.[1] Further improvements in outcome are urgently needed however. In recent years, new insights into various aspects of esophageal cancer and cancer of the gastric cardia have been obtained, not in the least owing to improved imaging techniques, the elucidation of cellular and molecular characteristics of the disease, and advances in the fields of screening, preventive strategies and treatment.

The recent fourth meeting in the series of international 'From Gene to Cure' congresses was dedicated to cancer of the esophagus and gastric cardia. This congress served as the crystallization nucleus for the current review, which aims at providing an overview of the most important recent advances in our understanding of various aspects of these diseases. In the section titles below, reference is made to the relevant parts of the congress proceedings. In addition, reference is made to the most important original studies cited in the text.

The main conclusions and recommendations on diagnosing and staging of Barrett's esophagus (BE) and local therapy of BE are provided in detail by a separate working group report by Offerhaus *et al.*[2]

EPIDEMIOLOGY[1,3,4]

Cancer of the esophagus and the gastric cardia is one of a few malignancies showing a sharply increasing incidence in developed countries. The majority of esophageal and gastric cardia cancers are squamous cell carcinomas or adenocarcinomas. The relatively steep increase in the incidence of these cancers is predominantly due to the increased incidence of esophageal adenocarcinoma and gastric cardia adenocarcinoma, in particular in white males. The incidence of squamous cell carcinoma (SCC) of the esophagus has remained relatively stable in most regions. The incidence of both histological types is usually higher in men than in women and increases over the age of 35 years, although the rate of rise differs markedly between different regions,

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*All authors served on the Scientific Committee of the conference (Gene to Cure, 2002), on which the content of this paper is based, and actively participated in it as speaker, chairperson, or both. All authors contributed to the writing process by commenting on various draft manuscripts prepared and circulated by GNJT.

probably in association with differences in risk factor pattern.

Risk factors

Distinct sets of risk factors have been identified for esophageal adenocarcinoma and SCC. Long-standing gastroesophageal reflux disease, obesity, high age and male sex (white men) are the well-known risk factors for esophageal adenocarcinoma. Tobacco smoking may contribute to the risk of esophageal adenocarcinoma, but the results of epidemiological studies are inconsistent. Long-standing gastroesophageal reflux disease may induce BE, a premalignant condition characterized by columnar epithelial metaplasia of the distal part of the esophagus. Patients with BE have a highly increased risk of developing esophageal adenocarcinoma.

The main risk factors for esophageal SCC are tobacco smoking, alcohol consumption and high age. In addition, previously treated head-and-neck cancer (HNC), exposure to ionizing radiation, human papilloma virus infection, long-standing achalasia, prior esophageal lye damage and rare diseases, such as tylosis palmaris have been identified as risk factors for esophageal SCC. Exposure to heterocyclic amines is relatively weakly associated with an increased esophageal SCC risk.

There is evidence that a high dietary intake of fruit and vegetables may prevent the development of esophageal cancer of any histological type and that high intake of nutritional fibers may be negatively associated with the risk of esophageal adenocarcinoma and adenocarcinoma of the gastric cardia. There may be a protective effect by *H. pylori* infection against adenocarcinoma, but not SCC.

Patients with previous HNC have a high risk of developing a second primary malignancy of the upper aerodigestive tract, including esophageal SCC.[5] When esophageal SCC occurs as a second malignancy in (previous) HNC patients, prognosis is poor compared to patients who do not develop a second malignancy. Scherübl *et al.* have recently confirmed this observation in an endoscopic screening study in patients with previous HNC in Germany and have recommended screening for esophageal SCC in patients with HNC.[6]

Reasons for increased incidence of esophageal adenocarcinoma

The recently observed sharp increase in the incidence of adenocarcinoma of the esophagus and the gastric cardia remains largely unexplained. The pattern of increase seems to argue against genetic factors and no influence of heredity has been found in the etiology of these tumors. Therefore, acquired risk factors are more likely to be involved. In this respect, attention has focused on gastroesophageal reflux as an important and specific risk factor for esophageal adenocarcinoma. However, reliable data on a possible correlation between the incidence of gastroesophageal reflux disease and esophageal adenocarcinoma are lacking. It has been hypothesized that the increased use of lower esophageal sphincter (LES) relaxing medication (such as nitroglycerin, anticholinergics, beta-adrenergic agonists, aminophylline and benzodiazepines) might contribute to an increased incidence of reflux disease and thereby of esophageal adenocarcinoma. Although a large case-control study has demonstrated a positive association between previous use of LES-relaxing medication and the risk of esophageal adenocarcinoma,[7] this hypothesis remains speculative. It cannot explain the sex imbalance in the adenocarcinoma risk which is far more pronounced than that in use of LES-relaxing medication.

Since obesity is thought to increase the adenocarcinoma risk by increasing gastroesophageal reflux, it is tempting to attribute the increasing incidence of adenocarcinoma of the esophageal and the gastric cardia to the increase in average body mass observed in Western populations over the past decades. However, the pattern of deflection of the adenocarcinoma incidence curve, the rapidity of its increase, and the marked male predominance are inconsistent with this explanation. La Vecchia *et al.*[8] have recently postulated increased abdominal pressure, caused by central obesity, a sedentary position and wearing of tight belts, as a causal factor for increased gastroesophageal reflux.

Changes in smoking behavior do not provide an explanation for the increased incidence of adenocarcinoma: firstly, because the association between smoking and esophageal SCC is stronger than between smoking and adenocarcinoma, and secondly, because smoking has declined markedly among men over the past years in many developed countries, whereas the incidence of esophageal adenocarcinoma has increased in men in particular.

The decreasing prevalence of *H. pylori* infection, which has been reported in several populations, might contribute to an increased incidence of esophageal adenocarcinoma. However, the predominance of males among those affected by esophageal adenocarcinoma is not adequately explained by this hypothesis.

CARCINOGENESIS

Normal stratified squamous epithelium of the esophagus shows a gradient of proliferating, undifferentiated keratinocytes in the basal layer, differentiating cells in the suprabasal layer and a superficial layer of flat cells. Proliferating basal cells migrate

towards the lumen and undergo morphological changes from relatively round basal cells to the flat squamous epithelial cells with low nuclear content at the surface. These morphological changes are associated with a number of genetic and biochemical changes, such as keratin heterodimerization in basal cells. In the suprabasal layer, a different pattern of keratin dimerization is observed. Knockout studies have suggested that these keratins play key roles in the commitment to differentiation. The genetic machinery regulating keratin expression is targeted by human DNA viruses, such as human papilloma virus and Epstein–Barr virus (EBV). Recent research has identified a stem cell compartment among basal epithelial cells of the esophagus of mice.

Progression from BE to esophageal adenocarcinoma[9,10]

The evolution of BE involves a chronic inflammation process, following injury of the squamous esophagus by acid and/or bile reflux. Whether or not the chronic inflammation process causes Barrett's metaplasia seems to depend on genetic factors and possibly other, as yet unidentified, environmental factors. The transition from metaplasia to adenocarcinoma proceeds via low-grade and high-grade dysplasia with increasing aneuploidy.[10] Many cell signaling pathways have been implicated in carcinogenesis in other tissues and for a number of these there is now strong evidence that they are also involved in esophageal carcinogenesis, including several pathways involved in cell cycle/checkpoint control (p53 and p27), apoptosis/caspase control (FasL, TNF, c-myc), growth factor phosphorylation (PI3k), MAP kinase activation (in particular MEKK,/p38), cytokine signaling (NFκB, COX/prostaglandins), chromatin regulation and methylation, β-catenin and wnt signaling and gastrin. Genetic alterations generally occur during progression from metaplasia to malignancy. There is increasing evidence that genetic alterations are necessary but not sufficient for cancer formation, and that other factors, notably environmental factors, are required for carcinogenesis as well.

Cyclooxygenase (COX)-2 appears to be constitutively expressed in esophagus and duodenum and the level of COX-2 expression seems to increase with progression from BE to esophageal adenocarcinoma. Exposure of BE explants to acid or bile salt caused a significant increase in COX-2 expression and stimulated proliferation.[11,12]

Telomerase expression has been proposed as a possible biomarker for the prediction of cancer in BE on the basis of a small-scale study showing progression to cancer in patients with telomerase-positive nuclei in BE cells.[13]

Metaplasia of esophageal epithelium seems to differ from gastric epithelial metaplasia in several aspects. In both disorders, the original epithelium is replaced by intestinal-type epithelium, but major differences have been found in the progression to the malignant phenotype. Correa *et al.*[9] have evaluated biopsies from 104 patients undergoing endoscopy using a broad range of histologic techniques. They have shown a number of morphological differences that might be relevant to differences in natural history of these metaplasias arising in different microenvironments and having different prognostic implications. Esophageal metaplasia was predominantly incomplete, whereas gastric metaplasia was largely complete. Immunostaining showed more abundant expression of mucins MUC 2 and MUC 5AC in BE and in incomplete gastric metaplasia. Das-1 appeared to be a marker of BE and cytokeratin-7 was abundant in BE and forms the basis of the 'Barrett's pattern'. COX-2 was expressed in inflammatory cells and Barrett's epithelium.

Etiology of esophageal squamous cell carcinoma[14–21]

Genetic research in murine and human esophageal squamous epithelium has demonstrated that the transition from normal mucosa to the premalignant and malignant state involves over-expression of the epidermal growth factor receptor (EGFR) and cyclin D1 as early events. Inactivation of p53 seems to be a later event, at least in the mouse. Telomerase activation occurs not only during cancer development, but also as an early event. Although EGFR over-expression and activation seems to be an important, probably necessary, initiating event, it is not a sufficient event for cancer formation. Other events seem to be required for malignancy to occur. One of the candidate genes might be the GTP binding protein RAD, which appears to be activated by EGFR.

Chemical carcinogenesis[22]

New data supporting a role for N-nitroso compounds in the carcinogenesis of adenocarcinoma of the distal esophageal and the gastric cardia have been reported by McColl.[22] Key elements of this concept are that salivary nitrite, produced from dietary nitrate, is the major source of nitrite entering the acid secreting stomach, and that nitrosating species can be generated under the acidic conditions in the gastric lumen. Nitrite from saliva can rapidly be converted into nitrosating species such as N2O3, NO+ and NOSCN. These species are able to induce oncogenic mutations by reacting with secondary amines or amides. N-nitroso compounds can also be generated from nitric oxide at neutral pH. The gastric mucosa actively secretes ascorbic

acid, which neutralizes nitrosating compounds converting them into nitric oxide. Thus, the major determinant of N-nitrosation in the lumen of the acid secreting stomach is the relative availability of nitrite versus ascorbic acid.

Studies in human volunteers have shown that nitrite concentrations in the stomach are highest in the most proximal cardia and progressively fall going to the distal end. The converse pattern is seen for ascorbic acid. Consequently, the ratio of nitrite to ascorbic acid is highest in the cardia and lowest in the distal stomach, rendering the conditions for acid-mediated luminal nitrosation optimal in the cardia. Also, the concentration of nitric oxide in the cardia is high.[23] Concentrations of nitric oxide found in the cardia have been shown to be mutagenic in vitro. Thus, the capacity for mutagenic nitrosation reactions will be maximal around the gastroesophageal junction, in particular at the gastric cardia side of the junction in subjects without reflux, and in the distal esophagus in subjects with reflux.

Epstein-Barr virus in gastric carcinogenesis[24]

In addition to its role in other malignancies such as certain lymphomas and nasopharyngeal carcinoma, a role for EBV in gastric carcinogenesis has been proposed. About 10% of gastric adenocarcinomas contain EBV as demonstrated by EBER 1/2-RNA in situ hybridization. EBV infection seems to be a late event in gastric carcinogenesis, since metaplastic and dysplastic gastric epithelium was found to be EBV-negative. It is currently unknown how EBV reaches the gastric epithelium or how it enters epithelial cells, but the time of entering seems to be between the severely dysplastic and the early carcinoma stage.

Viral genomes in EBV-associated gastric carcinomas are monoclonal. The EBV gene expression pattern in gastric carcinomas is unique. Analysis by comparative genomic hybridization has shown that EBV-positive and EBV-negative gastric carcinomas have distinct chromosomal changes indicating the possibility of a role for EBV in different pathogenetic pathways.

EBV-positive gastric carcinomas differ from EBV-negative carcinomas not only in molecular terms but also clinically. According to the results of a large randomized trial involving surgical patients with D1 and D2 resection, EBV-positive gastric carcinomas were localized more to proximal parts of the stomach and occurred much more frequently in male patients.[25] Moreover, patients with EBV-positive tumors had a lower TNM stage, in particular less lymph node involvement, and longer disease-free survival after surgery than those with EBV-negative tumors. The less unfavorable behavior of EBV-positive gastric carcinomas may be the result of an immune response against an as yet unidentified EBV-induced antigen and supports the clinical relevance of detecting EBV in gastric carcinomas.

DIAGNOSIS AND STAGING

Tumor markers in esophageal cancer staging[26–29]

Much attention has recently been devoted to predicting progression from intestinal metaplasia to dysplasia and low-grade to high-grade dysplasia/adenocarcinoma on the basis of immunohistochemically detectable markers. Studies investigating tumor suppressor genes, cell adhesion molecules and apoptosis-related genes have yielded relatively disappointing results in terms of identifying useful markers for daily practice. Available data indicate that progression from BE to high-grade dysplasia and adenocarcinoma is a continuum rather than a distinct stepwise process and that no single marker reliably discriminates lesions that will progress from those that will not. Expression of p53 appears to increase with progression to high-grade dysplasia and adenocarcinoma. Thus, increased expression of p53 is indicative for dysplasia. In case of doubt, p53 expression may be helpful in diagnosing dysplasia. A similar role has been proposed for the Rb protein, the expression of which decreases with progression from low-grade to high-grade dysplasia and adenocarcinoma. Other markers that have been studied in this context are: p16 (loss of expression seems to be associated with progression), Ki-67 (increased staining in dysplasia, but also in non-dysplastic BE), β-catenin (translocation to the nucleus with progression from BE to high-grade dysplasia), and the mucins MUC1 and MUC4 (expression seems to be correlated with dysplasia).

Immunohistochemical markers have also been studied in esophageal SCC. Frequently overexpression of p53 is observed, which seems to be associated with a poor prognosis. However, p53 overexpression has also been found in non-dysplastic mucosa, notably in relation to smoking and alcohol consumption. Nuclear staining of pTEN has been reported to be prognostically favorable. Cell proliferation and cell cycle regulating proteins such as cyclin D1, cyclin E, p21 and p27 have not been shown to be meaningful markers in this respect in esophageal SCC. Increased cathepsin D staining and increased thymidine phosphorylase expression seem to correlate with depth of invasion and a poor prognosis.

Retrospective studies conducted thus far suggest that immunohistochemical markers may provide useful information for guiding therapeutic decision making. Prospective studies are therefore needed to validate the practical importance of these markers.

Tumor gene expression profiling, rather than evaluations of a single tumor marker, seems to be a further worthwhile area for future study.

Morphological imaging techniques[30]

Recent technical improvements have rendered CT and MRI increasingly useful techniques in staging, assessing tumor resectability, radiotherapy planning and assessing treatment responses. The inherent multiplanar nature of MRI is no longer an advantage over CT. Modern multislice CT scanners can acquire a volume of data encompassing the esophagus and the stomach with a resolution of 1 mm.

The accuracy of CT in determining the depth of tumor penetration is 80–85%. CT is most accurate in advanced disease in detecting vascular and tracheobronchial involvement. The most reliable criterion for lymph node involvement remains '> 10mm'. Strong enhancement and heterogeneous enhancement patterns have been used as criteria but although they increase sensitivity, they do so at the expense of specificity. Lymph nodes are easy to detect with multislice CT but very difficult to characterize. Virtually all liver metastases greater than 10 mm diameter should now be detected by CT.

CT and MRI are largely comparable with respect to staging accuracy, but CT is significantly cheaper. Two interesting enhancements are under development: miniaturized MR receiver coils that can be mounted within an endoscope, giving a much higher resolution at the expense of a smaller field of view, and the design of novel contrast agents for use in MRI.

PET scanning[31,32]

Preoperative down-staging of locally advanced cancer of the esophagus or the gastroesophageal junction by neoadjuvant chemotherapy, radiotherapy or combined chemoradiotherapy (CRT) before esophagectomy has been shown to hold promise (see below). However, a relatively high percentage of patients do not respond and unnecessary treatment could be avoided if non-responding patients could be identified in advance or early on during CRT. Conventional imaging techniques, such as CT and endoscopic ultrasound, are generally considered inadequate for this purpose. Whole-body ^{18}F-deoxyglucose (FDG)-positron emission tomography (PET) scanning has been shown to be a useful tool in primary preoperative staging. PET has a higher sensitivity for the detection of distant lymph node metastases than CT or endoscopic ultrasound. Recent clinical studies support the usefulness of PET scanning in predicting tumor response to induction treatment in esophageal cancer. The presence and extent of lymph node involvement according to pre-treatment PET may have a predictive value for the response to CRT. Furthermore, serial PET scanning (before and during CRT) allows the assessment of tumor responses to CRT, although a complete pathological response cannot be accurately assessed by PET. However, Kroep *et al.* demonstrated that response determined with serial PET scanning accurately predicted a pathological response achieved with chemo-immunotherapy.[33]

Finally, a metabolic response to CRT as assessed by serial PET appears to provide a better prognosis of survival than the extent of lymph node involvement on a pre-CRT PET.

Diagnostic laparoscopy/thoracoscopy[34]

The increasing number of treatment options with a curative or a palliative intent has increased the importance of proper patient selection for a specific treatment. Diagnostic laparoscopy has been claimed to be superior to all non-invasive imaging modalities in the detection of liver metastases, intra-abdominal lymph node metastases and peritoneal tumor spread. Diagnostic gains in the range of 10–50% have been claimed by adding diagnostic laparoscopy to the staging of cancer of the gastroesophageal junction. The CALGB 9380 multicenter trial in patients with esophageal cancer has shown a limited diagnostic yield in terms of detecting lymph node metastases at various locations by combined thoracoscopy and laparoscopy.[35] In a recent series of patients, the diagnostic gain of applying laparoscopy with laparoscopic ultrasound, in addition to standard non-invasive imaging modalities, appeared to be greatest in patients with locally advanced (T3–4) esophageal adenocarcinoma, cancer of the cardia and gastric cancer. In patients with esophageal SCC or locoregional disease (T1–2), diagnostic gain was absent or minimal. Most of the diagnostic gain concerned the detection of otherwise unsuspected liver metastases, peritoneal tumor spread and cirrhosis. However, the potential diagnostic gain needs to be balanced against the fact that diagnostic laparoscopy is costly, time-consuming and associated with a risk of serious complications.

Diagnosis and staging of early disease[36–38]

In view of the poor prognosis of advanced esophageal cancer, several endoscopic techniques for the detection of early lesions in BE have been studied. Methylene blue staining is currently the only technique that has been shown to increase the detection rate of Barrett's dysplasia. However, this technique is cumbersome and the results are operator-dependent. Combining high-resolution endoscopy with contrast staining agents may further enhance mucosal contrast. Other optical techniques

antagonized by inhibiting either protein kinase C or COX-2, indicating a key role for these enzymes in the acid- or bile-induced proliferative response. A recent small-scale clinical study has demonstrated inhibition of BE proliferation in patients treated with the selective COX-2 inhibitor rofecoxib.[48] Further elucidation of the protective and/or harmful molecular mechanisms in BE mucosa may guide future preventive and therapeutic approaches to BE.

In view of the well-known relationship between gastroesophageal reflux and BE and between BE and esophageal adenocarcinoma, several clinical studies have addressed the efficacy of pharmacological and surgical acid suppression interventions.[46,49–53] The most-studied pharmacological intervention is treatment with a proton pump inhibitor (PPI). Surgical fundoplication is aimed at re-establishing the physical gastro–esophageal barrier to reflux.

A clinical study in patients with chronic reflux symptoms has shown that effective (in terms of symptom control and esophagitis) PPI acid suppression therapy may not completely eradicate the risk of development of BE, whereas successful surgical antireflux therapy (by complete or partial fundoplication) did. All patients undergoing surgical fundoplication were free of symptoms and of esophagitis, and had normal LES after surgery and before entering the study. Of the patients on PPI therapy, almost 15% still developed BE in 2 years. Of the patients undergoing surgery, none developed BE over 3.5 years of follow-up.[49] A retrospective observational study has demonstrated a lower risk of developing intestinal metaplasia of the esophageal epithelium after successful antireflux surgery compared with medical therapy with PPIs or H_2 receptor antagonists.[50]

The logical next question – whether effective antireflux therapy reduces the risk of esophageal adenocarcinoma developing from BE – has been addressed by several recently published and one unpublished study.[46,51–53] These studies have demonstrated that, even after prolonged follow-up, no esophageal high-grade dysplasia or adenocarcinoma developed in patients with BE who had had surgical antireflux therapy. The largest of these studies is an observational study in 140 patients with non-dysplastic BE at enrollment, who had had at least three surveillance endoscopies.[46] The relative risk of developing esophageal dysplasia was significantly lower in patients who had undergone successful antireflux surgery (success of the procedure was demonstrated by 6 months pH monitoring), compared to those receiving acid-suppressing drug therapy. Most importantly, the long-term risk of developing high-grade dysplasia or adenocarcinoma was significantly lower in the surgical group (Fig. 1).

Thus, there is mounting evidence supporting the hypothesis that cessation of reflux, in particular by successful antireflux surgery, will alter the progression from reflux esophagitis to BE as well as the progression from BE to esophageal malignancy. Possible explanations for the relative inefficacy of pharmacological acid-suppressant therapy compared to antireflux surgery may be the occurrence of break-through periods of acid production on PPI therapy.[54–56] Moreover, bile reflux may be completely inhibited by successful antireflux surgery.[55]

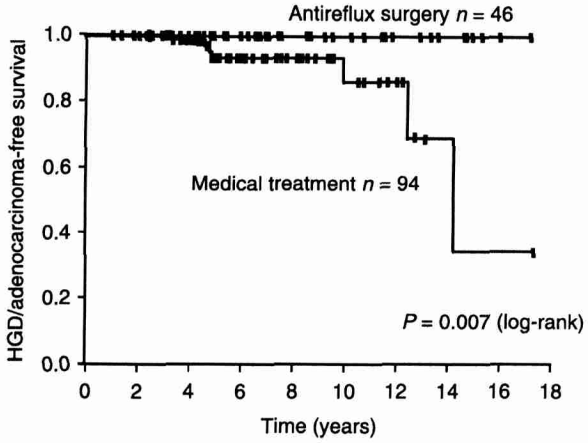

Fig. 1 High-grade dysplasia- (HGD) and adenocarcinoma-free survival in patients with Barrett's esophagus. Medical treatment consisted of acid suppression with proton pump inhibitors or H2 receptor antagonists. Antireflux surgery included open Nissen fundoplications, laparoscopic Nissen fundoplications, Hill and posterior hemifundoplication. (Reproduced with the kind permission of T. R. DeMeester).[46]

RECENT ADVANCES IN SURGERY

For decades, the procedure of choice for esophageal cancer resection has been the Lewis-Tanner operation in which the tumor and periesophageal tissue with its adjacent lymph nodes are resected through thoracotomy in combination with laparotomy. One of the major disadvantages of radical esophagectomy with extensive lymphadenectomy is its high rate of morbidity and mortality. Mortality rates in association with this procedure are in the range of 1–12% and morbidity rates are often in the range of 50–60%, whereas long-term survival of patients after surgery is usually disappointingly low. Novel strategies have emerged aimed at decreasing or postponing locoregional tumor recurrence and prolonging long-term survival or decreasing early postoperative morbidity and mortality by limiting the extent of the surgical procedure. On the other hand, novel surgical strategies combining more radical local tumor resection with extended lymphadenectomy have also been studied in recent years, as well as ablative procedures and limited surgery in early esophageal malignancy.

Table 1 Grading of early esophageal tumors by depth of submucosal invasion[37,38]

Grading	Submucosal invasion
m1	Only epithelial tumor
m2	Tumor invading the lamina propria
m3	Tumor attached to the muscularis mucosae
Mm	Tumor invading the muscularis mucosae
sm1–sm3	Increasing extent of submucosal invasion (from sm1 to sm3)

such as fluorescence endoscopy, optical coherence tomography and narrow-band imaging are under investigation.

Recently, a classification system for mucosal patterns obtained by high-resolution endoscopy has been proposed by Japanese researchers, mainly based on their experience in esophageal SCC (Table 1).[38] A positive association between increasing relative depth of tumor invasion and the presence of lymphatic or venous permeation, on the one hand, and an increased risk of lymph node metastases on the other hand has been demonstrated. Within the group of sm1–sm2 tumors, cytological grade (low-grade versus high-grade) appeared to be a significant factor in predicting the risk of nodal involvement, the risk being significantly higher in patients with high-grade esophageal SCC. In order to improve the usefulness of the sm1–sm3 grading, Watanabe *et al.* have proposed the use of the absolute depth (measured in mm from the lower edge of the muscularis mucosae) of submucosal invasion, as this would give a more objective and generally useful measure of the need of additional surgery (Table 1).

Detection of micrometastases in bone marrow[39]

The majority of patients diagnosed with esophageal cancer will eventually die of metastatic disease even if tumor dissemination is not evident at the time of diagnosis. It has therefore been hypothesized that most patients will have minimal residual disease after complete ablation of locoregional disease by surgery. Cytokeratin 18-positive micrometastases have been found in the bone marrow in 80–90% of patients undergoing resection of esophageal cancer, node-positive or node-negative esophageal adenocarcinoma or SCC, with a curative intent. These results suggest that hematogenous dissemination occurs independently of lymphatic spread and that a node-negative status does not preclude metastatic spread. Metastatic cells isolated from bone marrow were viable on culture and were sometimes tumorigenic in athymic mice. In patients receiving neoadjuvant chemoradiotherapy, the detection rate of bone marrow metastatic cells was less than 40%, but after marrow culture, viable cytokeratin-positive cells were detectable in a further 30% of patients. Despite pathological complete responses of the primary tumor occurring in some patients after neoadjuvant therapy, micrometastases were found in the bone marrow of the same patients, implying resistance of metastatic cells to the chemotherapeutic agents used. Thus, bone marrow culture after chemotherapy seems to increase diagnostic yield. New drugs or treatment strategies are required to improve overall outcome.

SCEENING AND PREVENTION

Chemopreventive strategies[40,41]

Chemoprevention trials have been and continue to be conducted in various types of upper aerodigestive tract cancer, but not in esophageal cancer. Most studies have evaluated interventions based on β-carotene, vitamin A, retinoids and antioxidants (in particular N-acetylcysteine) and have generally yielded disappointing results. The results of ongoing chemoprevention trials as well as the emergence of more powerful chemopreventive agents are therefore awaited.

The COX-2 cyclooxygenase isoenzyme seems to be an emerging target for chemoprevention of esophageal adenocarcinoma. The original hypothesis of COX-2 as a target for preventive strategies in gastrointestinal cancer stems from nonclinical, clinical and epidemiological observations in colon cancer.[42,43] Many studies of preinvasive tumors and almost all studies of invasive tumors in various other parts of the gastrointestinal tract, including the esophagus and the stomach, have yielded evidence of increased COX-2 expression.[44] Moreover, it has been known for about a decade that regular aspirin use reduces the risk of death from esophageal cancer and that occasional use of aspirin reduces the risk of developing esophageal cancer.

Acid suppression therapy and antireflux surgery[45–47]

The notion that the evolution of dysplastic esophageal mucosa and esophageal adenocarcinoma depends on the interplay between components of the refluxate (i.e. acid and bile) and the mucosa is increasingly supported by experimental and clinical data. The probability of mucosal injury increases as exposure to acid or bile or both increases. It has been demonstrated in BE tissue explants that exposure to acid pulses can induce histological and molecular changes such as increased proliferation, activation of the Na/H-exchange pump, activation of protein kinase C, increased COX-2 expression and MAPK activation. Similar to acid, exposure to bile can also induce proliferation in BE explants in vitro. It has recently been demonstrated that both acid- and bile-induced proliferation can be

Limited-extent surgery[57,58]

A systematic review of 50 studies published in the English literature between 1990 and 1999 revealed that transthoracic esophagectomy (TTE) was associated with significantly higher (pulmonary) morbidity and mortality than transhiatal esophagectomy (THE), while 5-year survival rates were comparable at 21–22%.[59] This meta-analysis could be criticized for comparing types of surgical access without taking into account the extent of oncological resection.

A minimally invasive esophagectomy (MIE) procedure pursued at the University of Pittsburgh Medical Centre involves video-assisted thoracic surgery, mobilization of the intrathoracic esophagus with laparoscopic THE and neck anastomosis.[58,60,61] Pyloroplasty and needle jejunostomy are performed in most cases (Fig. 2). Patients are selected for MIE using CT scan, endoscopic ultrasound and laparoscopic staging to confirm tumor resectability and to exclude the presence of metastases. MIE has now been performed in over 200 patients and initial results in a series of 77 patients have confirmed the feasibility and safety of this procedure with low mortality, low anastomotic leak rate and satisfactory 2–3 years survival rate.[60] A recent update on 222 cases from the same centre has confirmed and extended these results and has shown a median intensive care unit (ICU) stay of 1 day, a median length of hospital stay of 7 days and an overall mortality of 1.4%.[61] A multicenter feasibility study of MIE is currently being prepared by the Eastern Co-operative Oncology Group (Fig. 2).

A recent randomized trial has compared early morbidity,[62] early mortality and long-term survival after THE and TTE with extended two-field lymphadenectomy. Early morbidity was higher after TTE, mainly due to pulmonary complications, leading to prolonged ventilation times, longer ICU/medium care unit stay and longer hospital stay. Hospital mortality was comparable (2% and 4%, respectively). Also radicality of surgery and TNM stages were comparable. There was a non-significant trend towards higher 5-year survival benefit after TTE (29% versus 39%). Therefore, THE seems to carry a lower risk of early morbidity while TTE might be more advantageous in terms of overall survival. For the time being, the authors recommend THE for patients with gastroesophageal junction tumors, unless an endoscopic ultrasound fine needle aspirate has shown positive lymph nodes at or above the carina, and TTE for mid or distal esophageal tumors, unless the patient is unfit for an extensive surgical procedure.[57]

Cervical esophagogastric anastomosis[63]

Cervical esophagogastric anastomosis after esophagectomy is becoming an increasingly popular procedure in patients requiring esophageal replacement. However, TTE with intrathoracic esophagogastric anastomosis is associated with major disadvantages including the risks involved in a thoraco-abdominal operation, the hazards of anastomotic disruption and cervical anastomotic leak. Orringer *et al.* have developed a revised procedure for cervical esophagogastric anastomosis using THE without thoracotomy and a stapler for the construction of a side-to-side cervical esophagogastric anastomosis (Fig. 3). Preferably, the stomach is positioned in the posterior mediastinum, the original esophageal bed, which provides the most reliable approach with the least immediate and long-term morbidity. Based on experience in hundreds of patients with esophageal

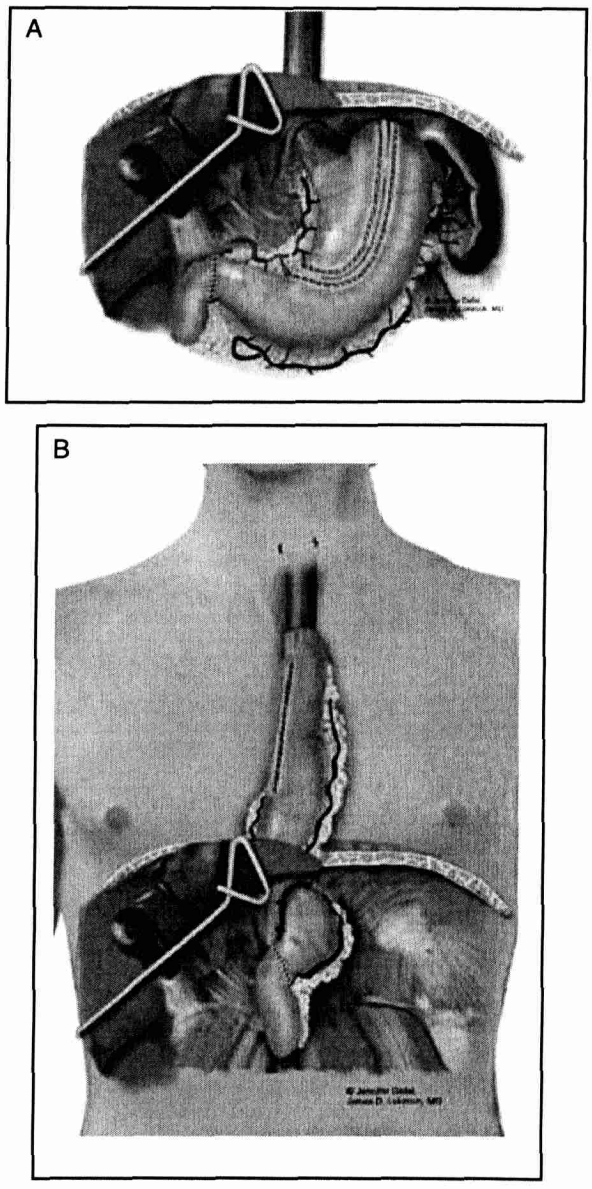

Fig. 2 Laparoscopic gastric tubularization (panel A) and completed laparoscopic and thorascopic esophagectomy (panel B).[58] (Reproduced with the kind permission of JD Luketich.)

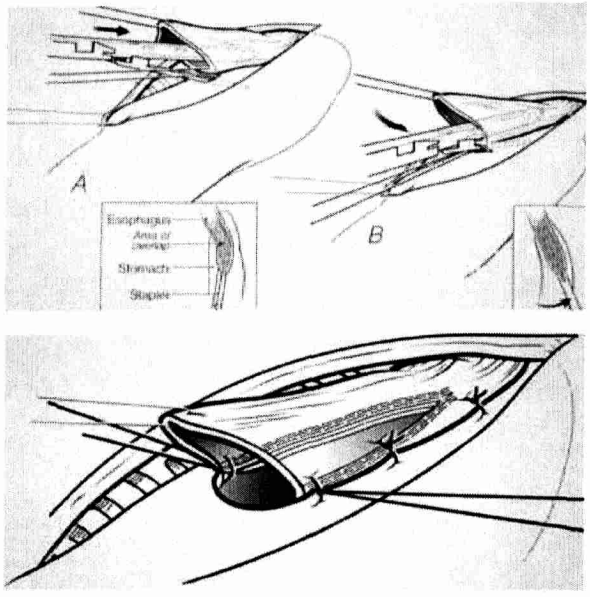

Fig. 3 Esophagogastric anastomosis using a stapler to reduce the risk of anastomotic leak.[63] (Reproduced with the kind permission of Elsevier Health Sciences from MB Orringer, J Thorac Cardiovasc Surg 2000; 119: 277–88).

malignancy, it can be considered successful in the vast majority of cases, although it is not totally free of complications. The risk of anastomotic leakage is in the range of only 5–15% and anastomotic leaks, when they occur, are more easily managed than with other techniques. The risk of recurrent laryngeal nerve injury, causing hoarseness and possibly impaired swallowing, has been reduced to a level of about 2%. Other serious complications occur even less frequently (< 1%) and may include gastric tip necrosis, anastomotic stricture resulting from fibrosis after healing of an anastomotic leak, and tracheo-esophagogastric anastomotic fistula (Fig. 3).

Extensive lymph node dissection in the neck[64]

Several older studies, mainly from Japan, have found a high incidence of cervical lymph node metastases after esophagectomy with 3-field lymphadenectomy and have claimed a long-term survival benefit from this procedure, in particular in patients with esophageal SCC. Preliminary data from an ongoing study in Belgium seem to confirm the feasibility and success of this procedure.[64] In a group of 192 patients undergoing esophagectomy with 3-field lymphadenectomy as primary surgery for cancer of the gastroesophageal junction, overall hospital mortality was 1.1% and morbidity 58%. Morbidity consisted predominantly of pulmonary and cardiac events as would be expected. R_0 resection was achieved in 174 patients and positive cervical nodes were found in 25% of these patients, mostly unforeseen positive nodes which led to a change of TNM stage in 15% of cases. Five-year overall survival in the group with R_0 resection was 41.9%. In the subgroup of patients with positive cervical nodes and R_0 resection, 5-year survival was still 12.8%. From this and other experience reported in the literature, it seems that adding the third field of lymphadenectomy may offer patients with positive cervical lymph nodes a better chance of obtaining a complete R_0 resection although no randomized studies have been conducted yet. Classifying non-cervical tumors with positive cervical nodes as stage IV (i.e. incurable) disease does not seem valid any longer. The debate on the value of extensive lymphadenectomy in general and 3-field lymphadenectomy is likely to continue.

Prognosis of resected adenocarcinoma[65]

A recent prospective study has demonstrated the prognostic significance of p53 mutations for survival of patients with esophageal adenocarcinoma.[66] The presence of p53 mutations had a significant negative impact on survival after curative (R_0) resection with an almost 3-fold higher cumulative 5-year survival probability for patients with mutation-negative tumors (68.8% versus 24.3%). Thus, p53 mutational status may be a valuable parameter in defining the risk of treatment failure after curative resection.

In another series of patients with type II cardia or type III subcardia carcinoma, the same group found that among a range of markers the absence of matrix metalloproteinase 2 expression was a favorable prognostic factor for 3-year survival.[67] Langley *et al.*[68] have recently identified extensive blood transfusion as being negatively associated with survival in a series of 234 patients undergoing esophagectomy for carcinoma.

Endoscopic ablation and surgery of early malignancy[58,69–71]

Improved detection and staging techniques, such as high-resolution video-endoscopy, chromoendoscopy and endosonography, have fueled research of endoscopic mucosal resection in early esophageal malignancy. If early, locally resectable malignancy could be identified, it may be removed by endoscopic mucosal resection, photodynamic therapy or thermal ablation. Studies on endoscopic mucosal resection in patients with superficial esophageal SCC, mainly from Japan, suggest that this procedure equals surgery in terms of efficacy but has a lower risk of complication. A recent series of 115 patients with early adenocarcinoma or high-grade intraepithelial neoplasia has generated similar results in a Western population.[71] The complete local remission rate was 98% with an overall rate of (minor) complications

of 9.5%. After a median follow-up of almost 4 years, 95 out of 110 evaluable patients were alive. Although the long-term results of this study are being awaited, early and intermediate results suggest that organ-preserving local endoscopic resection may become an alternative to radical esophageal resection also in Western populations.

A group at the Technical University of Munich is applying a limited surgical resection procedure in selected patients with high-grade neoplasia or T1 Barrett's adenocarcinoma of the distal esophagus. This procedure consists of transabdominal limited resection of the distal esophagus (entire segment with intestinal metaplasia), limited regional lymphadenectomy with preservation of the vagus nerve and interposition of an isoperistaltic jejunal segment for the prevention of reflux in a modified Merendino procedure (Fig. 4).[69,70]

Current experience in 49 patients indicates that this procedure is oncologically adequate and safer than radical esophagectomy. With a median follow-up of 41 months, there have been no recurrences, while the rate of postoperative mortality (0% versus 3.7%) and morbidity (14% versus 40%) seemed lower than those in a historical series of 80 patients undergoing radical esophagectomy at the same institute. Reconstruction with an interposed jejunal loop prevented postoperative gastroesophageal reflux in over 80% of patients and was associated with recovery of quality of life into the normal range.[69]

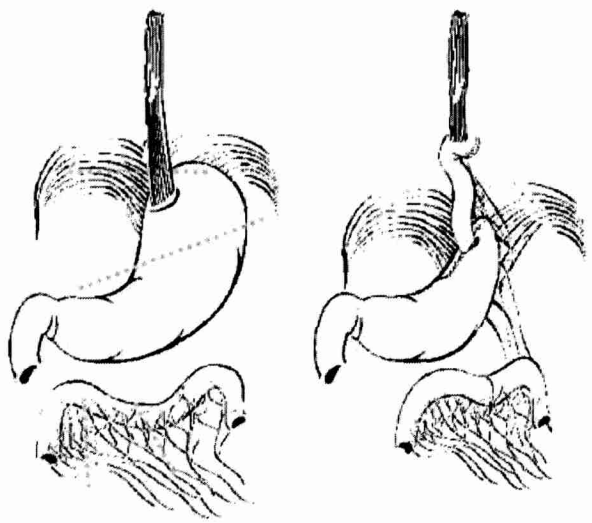

Fig. 4 Limited esophageal resection and jejunum interposition in patients with early Barrett's malignancy.[70] (Reproduced with the kind permission of Lippincott Williams & Wilkins from H. J. Stein, Ann Surgery 2000; 232: 733–42).

RECENT ADVANCES IN CHEMOTHERAPY AND CHEMORADIOTHERAPY

Much research on the role of chemotherapy and chemoradiotherapy (CRT) over the past years has focused on neoadjuvant treatment of resectable esophageal cancer. The chemotherapeutic agents mostly used in these trials have been conventional cytotoxic agents, such as cisplatin and 5-fluorouracil (5-FU) (Table 2).[72–75] Other trials have investigated the efficacy of chemotherapy in advanced esophageal cancer with a palliative intent, again mostly using established chemotherapeutic agents. Some of the newer chemotherapeutic agents are also being evaluated in the neoadjuvant and palliative setting (Table 2).

Neoadjuvant chemotherapy[76]

Previous randomized trials have failed to demonstrate a survival benefit for neoadjuvant chemotherapy in patients with resectable esophageal cancer. However, the recently completed large MRC OE02 trial has demonstrated a survival advantage for preoperative chemotherapy (two cycles of 3-weekly cisplatin 80 mg/m^2 and 5-FU 1 g/m^2/day by continuous infusion for 4 days) compared to surgery alone.[77] The hazard ratio for overall survival was 0.79 ($P = 0.004$) in favor of neoadjuvant chemotherapy. Resection was microscopically complete in 54% of assessable surgery-only patients and in 60% of patients receiving neoadjuvant chemotherapy plus surgery ($P < 0.0001$). Post-operative complications were similar in both arms. The MRC OE02 study is the only trial to date that has shown a modest but significant survival advantage for a short course of neoadjuvant chemotherapy in esophageal cancer without increasing postoperative morbidity.

Table 2 Results of phase III trials of neoadjuvant chemotherapy in locally advanced esophageal cancer

Neoadjuvant treatment		Median survival (months)	
Chemotherapy	Radiotherapy	Neoadjuvant therapy	Surgery
Cisplatin, vindesine, bleomycin[72]	ND	9	9
Cisplatin, 5-FU[73]	–	10	10
Cisplatin, 5-FU[74]	–	17	13
Cisplatin, vinblastin, 5-FU[75]	+	17	17.5

ND, no data.

Neoadjuvant chemoradiotherapy[78–81]

In phase II studies of neoadjuvant cisplatin- or mitomycin C-based chemoradiotherapy (CRT), pathological complete response rates of about 30% have been observed, offering the prospect of improved survival. Six randomized phase III studies have therefore compared the efficacy of preoperative CRT. Of the four studies conducted in patients with esophageal SCC, three were negative.[82–84] The fourth and largest study (FFCD 8805 – EORTC 40881), which investigated cisplatin-based preoperative CRT in 297 patients, has shown a significantly higher rate of curative resection, a longer local disease-free interval, a lower rate of cancer-related death and longer disease-free survival in patients receiving neoadjuvant CRT compared with surgery alone.[78] However, the incidence of distant metastases and overall survival were not significantly altered. Postoperative mortality was significantly higher in the neoadjuvant group and was mainly associated with acute respiratory distress syndrome and infection. With 5-year survival approaching 60%, overall survival in patients with a pathological complete response was significantly better than in all other patients.

The efficacy of preoperative CRT in resectable esophageal adenocarcinoma has been investigated in two phase III trials.[75,85] One study, employing radiotherapy at a total dose of 45 Gy over 3 weeks and concurrent cisplatin, vinblastin and 5-FU, has failed to demonstrate a survival advantage.[75] In the other study, a significant 3-year survival advantage for neoadjuvant CRT (36% versus 6%; $P = 0.01$) has been demonstrated, but 3-year survival in the surgery-only arm was unusually low in this study.[85]

Despite its clear-cut local efficacy, neoadjuvant CRT remains an experimental treatment that can be relatively toxic. The ongoing FFCD–EORTC trial is comparing optimized treatment (45 Gy over 5 weeks with concurrent 5-FU-cisplatin) with surgery in patients with stage II_{A-B} esophageal adenocarcinoma and SCC.[86] To decrease postoperative morbidity and mortality, the use of fractionated radiotherapy and sophisticated techniques such as conformal radiotherapy to spare normal tissues, in particular the lungs, may be considered.

Further improvements in outcome might be achieved if systemically more effective agents or longer lasting systemic therapy could be incorporated in preoperative CRT regimens. A recent phase II study conducted by the Rotterdam Esophageal Tumor Study Group has investigated carboplatin and paclitaxel with concomitant radiation in patients with surgically resectable esophageal SCC, esophageal adenocarcinoma or undifferentiated carcinoma of the lower esophagus. Preliminary results indicate good tolerability and modest toxicity, and a high rate of R_0 resection and N_0 lymph node status at surgery. Survival data have not yet been reported.[81]

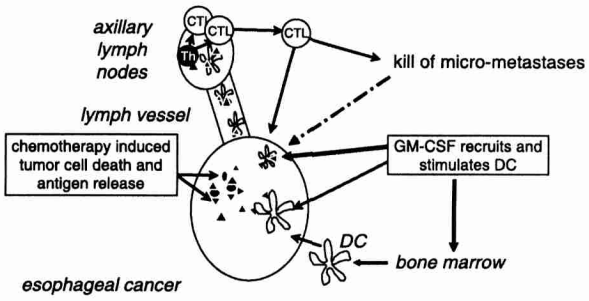

Fig. 5 Tentative mechanism of immunotherapeutic effects of granulocyte macrophage colony stimulating growth factor (GM-CSF), involving T-helper cell (Th), cytotoxic T lymphocytes (CTL) and dendritic cells (DC). (Reproduced with the kind permission of the J Buter from the Cancer Information Group from *Immune Enhancing Cytokines* August 2001; 3(1): 2–4.)

Neoadjuvant chemotherapy in combination with GM-SCF[87]

An ongoing clinical trial in the Netherlands is investigating the novel combination of cisplatin, gemcitabine and granulocyte macrophage colony stimulating growth factor (GM-CSF) in a 3-weekly schedule for up to six cycles in the neoadjuvant setting in esophageal cancer. Previous studies have shown a positive interaction between cisplatin and gemcitabine. In a trial by the same group in locally advanced breast cancer, recruitment and activation of dendritic cells have been observed, potentially enhancing the host immune response against tumor cells (Fig. 5).[88] It was therefore hypothesized that combined modality cisplatin-gemcitabine-GM-CSF neoadjuvant treatment might be able to down-stage locally advanced tumors and eliminate micrometastases in patients with resectable esophageal cancer. Interim results after recruitment of 31 of the planned 40 patients with locally advanced esophageal SCC or esophageal adenocarcinoma indicate reasonable tolerability. Grade 3/4 hematological toxicity without sequelae has been observed. Most patients have been able to receive the planned number of cycles of therapy and have undergone surgery after completion of chemotherapy plus GM-CSF. Tumor down-staging has been achieved in about 50% of patients thus far, particularly by an improvement in nodal status. No pathological complete responses have been observed (Fig. 5).

Chemotherapy in advanced esophageal cancer[87,89,90]

The main purposes of chemotherapy in patients with advanced esophageal cancer are palliation of disease symptoms, notably dysphagia, and prolongation of survival. Most available chemotherapeutic

agents, including 5-FU, cisplatin, mitomycin C, methotrexate, docetaxel, paclitaxel, irinotecan, vinorelbine and gemcitabine have shown limited single-agent activity with tumor response rates often in the range of only 0–20%. Combinations of cytotoxic agents, such as 5-FU plus cisplatin, cisplatin plus paclitaxel or the triple combination of epirubicin, 5-FU and cisplatin, have shown higher response rates in the range of 30–50%, but their impact on survival remains limited.

A recent phase II study in the Netherlands has investigated chemotherapy with cisplatin (50 mg/m^2; days 1 and 8) followed by gemcitabine (800 mg/m^2; days 2, 9 and 16) every 28 days in patients with advanced esophageal cancer (12 esophageal SCC and 24 esophageal adenocarcinoma).[90] The sequence, cisplatin followed by gemcitabine, is not commonly used, but was selected based on a pharmacokinetic study, which showed that giving cisplatin before gemcitabine was associated with an increase in the levels of the active metabolite of gemcitabine, dFdCTP, and total platinum.[91] Moreover, three out of five patients with esophageal cancer responded,[92] which prompted the phase II study with this schedule. Toxicity was substantial but manageable with grade 3/4 hematological toxicity being observed in the majority of patients. Myelotoxicity was cumulative and required skipping the planned day-16 gemcitabine administration in 63% of cycles. Objective tumor responses were observed in 14 out of 34 evaluable patients (41%) and included two complete remissions. Disease stabilization was observed in 17 patients and median survival was 9.8 months. The further exploration of the combination of cisplatin and gemcitabine in this setting seems warranted.

Several older studies in advanced gastric cancer, mostly adenocarcinomas of the gastroesophageal junction, have demonstrated a modest but significant 4–6 months survival benefit for conventional chemotherapy regimens over best supportive care. On the basis of their clinical benefit, 5-FU/cisplatin-based regimens (e.g. 5-FU/leucovorin/cisplatin and epirubicin/cisplatin/5-FU [ECF]) have obtained standard chemotherapy status for patients with advanced gastric cancer. However, in search of more effective options, new cytotoxic agents, such as docetaxel, paclitaxel and irinotecan, have been tested in gastric cancer, where they have shown clinical activity, either as a single agent or in combination with conventional agents. Two such combinations are currently being evaluated in large-scale phase II/III studies: docetaxel/cisplatin/5-FU and irinotecan/5-FU/leucovorin.

Another noteworthy development is the incorporation of the oral fluoropyrimidine capecitabine and the less toxic third-generation platinum compound oxaliplatin in chemotherapy regimens for gastric cancer. An ongoing phase II/III study in gastro-esophageal cancer in the United Kingdom (REAL-2) is investigating variations on the current ECF standard therapy in which 5-FU is replaced by capecitabine and cisplatin by oxaliplatin. Results of a planned interim analysis of the phase II part indicated that neither replacement caused a loss of antitumor activity compared to the standard ECF regimen, while symptom resolution and adverse event profiles seemed to be improved.[93]

OTHER TYPES OF THERAPY

Experience with novel targeted agents and other highly innovative therapies in patients with esophageal cancer remains limited, despite the fact that such therapies have sometimes been used successfully in other malignancies.

Targeted therapy[94]

Novel molecularly targeted agents, currently applied routinely or still under investigation in a range of other malignancies, include antiproliferative agents, apoptosis-inducing agents, antiangiogenic approaches and anti-invasive agents. Although relatively few targets have been or are being pursued clinically in esophageal cancer, there is a good rationale to do so based on current knowledge of the molecular abnormalities in this disease. Among the genes that could be considered candidates for targeted therapy in esophageal cancer are oncogenes, such as EGFR, c-erbB2 and cyclin D, as well as tumor suppressor genes, such as Rb, p53 and p16.

An ongoing phase II study is investigating the EGFR tyrosine kinase inhibitor gefitinib in second-line therapy of esophageal cancer. Remarkably, one partial remission and one minimal response have been observed after 21 patients have been entered. The most typical toxicity of gefitinib and other EGFR tyrosine kinase inhibitors as well as anti-EGFR antibodies is a form of manageable skin toxicity. No unexpected side-effects have been encountered thus far in the phase II study.[94]

Another targeted agent undergoing clinical evaluation in esophageal cancer is the anti-HER2 antibody trastuzumab. In a phase I study of trastuzumab in combination with CRT in patients with esophageal adenocarcinoma, endoscopic complete remissions have been reported to occur at comparable rates in HER2-positive and HER2-negative patients.[95]

Gene therapy[94,96,97]

One of the most advanced developments in gene therapy of cancer concerns the use of the E1B 55K-deleted replicative adenovirus ONYX-015, which

was designed to replicate selectively in tumor cells lacking wild-type p53 and tumor cells harboring p53 or p14ARF mutations. Despite a number of obstacles encountered along the way, ONYX-015 has advanced through preclinical and early clinical development and is now being investigated in a phase III trial for recurrent HNC and in phase I and II trials in several other malignancies. Clinical trials thus far have demonstrated replication of viral DNA in tumor cells and a tolerable side-effect profile, consisting mainly of flu-like symptoms, fatigue and fever, without signs of hepatic toxicity. Clinical efficacy has been documented in a phase II study in head and neck cancer.[98] No clinical evaluation of this agent in esophageal cancer has been undertaken yet.

A gene-based approached that is being investigated in esophageal cancer involves the agent TNFerade, a second-generation replication-defective adenoviral vector carrying the transgene encoding human TNFα and a radiation-inducible promoter.[94] Preclinical experiments have demonstrated that TNFerade gene therapy plus radiation can induce tumor regression in models of esophageal cancer and other solid tumors. A completed phase I study has shown the absence of dose-limiting toxicities of TNFerade plus radiation, no drug-related serious adverse events and a remarkably high tumor response rate in patients with advanced solid tumors.[99] The agent is currently being investigated in a phase II study in patients with advanced esophageal cancer in combination with conventional chemotherapy and radiation.

Photodynamic therapy[100]

Photodynamic therapy is a minimally invasive, organ-preserving therapeutic modality showing promise in the treatment of high-grade esophageal dysplasia and early carcinoma in BE. The ideal photosensitizing agent has not yet been identified however. Current laser probes allow the homogeneous and circumferential irradiation of a segment of up to 8 cm in a single session. This represents a clear advantage over other local ablative techniques, in particular thermoablation.

Although data are still limited, they seem to indicate a slightly better efficacy for photodynamic therapy than thermoablation in the treatment of Barrett's epithelium. There is also increasing evidence that photodynamic therapy may be suitable in the ablation of high-grade intraepithelial neoplasia or early mucosal cancer. In particular when a biopsy has demonstrated malignancy or severe dysplasia while macroscopic identification is unclear, and in cases of long Barrett's segments with advanced histological changes, photodynamic therapy may become the preferred form of local treatment. There have been very few reports thus far on the use of photodynamic therapy in the treatment of early esophageal SCC.

A significant disadvantage of the usual form of photodynamic therapy using photofrin as the photosensitizer is the development of strictures, which may occur in up to half of the patients. This problem appears to be less prominent with 5-aminolevulinic acid, a 'milder', mucosa-specific photosensitizer. With this agent, the depth of tissue destruction remains limited to 2 mm, which seems to be adequate for superficial high-grade dysplasia, but may not be adequate for early carcinoma. When mucosa and/or tumor tissue thicker than 2 mm needs to be removed, the more 'aggressive' photosensitizer mTHPC might be an option.

Palliative modalities[101,102]

More than 50% of patients with esophageal cancer present at an advanced stage of disease or with severe comorbidity and are not amenable to surgery. In these patients, the main aim of initial treatment is to relieve their disease symptoms as rapidly, effectively and simply as possible, with minimal toxicity. Palliative treatment is often necessary to relieve dysphagia. This may require recanalization of the esophageal lumen and/or reduction of tumor bulk also outside the lumen. A number of different techniques can be applied to induce relief of dysphagia, such as external beam radiation therapy, intraluminal radiation therapy (brachytherapy), dilation, insertion of a self-expanding metal stent, thermal laser treatment, photodynamic therapy or local injections of absolute alcohol into tumor nodules. Patients with advanced esophageal cancer are probably best treated in centers that have the full range of treatment options available.[102]

The role of palliative systemic chemotherapy has been discussed above. A recent pilot study has demonstrated the feasibility of endoscopic injections of a cisplatin/epinephrine gel into tumor nodules.[103] This combination retains the active drug at the site of injection, which eliminates most of the systemic side-effects of cisplatin. Subjective and objective improvement was achieved in several patients with this procedure.

A multicenter study has shown that fewer treatment sessions were required with photodynamic therapy in comparison with Nd:YAG laser therapy in the palliative setting.[104] It is debatable, however, whether photodynamic therapy is an attractive option in this setting in view of its complexity, side-effects and costs.

Several studies have suggested longer lasting relief of dysphagia after combined treatment by laser therapy plus external beam radiation therapy or laser therapy plus brachytherapy. However, the

key to optimizing palliation of malignant dysphagia seems to be to match treatment to the individual patient and to look for the best combination of options. It has also been advocated to restore the esophageal lumen by one of the endoscopic ablative techniques before more radical treatments such as chemoradiation are commenced.

A broad variety of self-expanding metal stents are currently available for palliation of dysphagia. Their main advantages over the previously used conventional prosthetic tubes include the requirement of minimal dilation before placement, the small diameter of delivery catheters, the greater lumen diameter achieved and the better quality of swallowing owing to greater stent flexibility. The technical success rate for placement of metal stents is close to 100%. Nowadays, covered stents are most commonly used to avoid tumor ingrowth. Three types of stent have been compared in the CEPEC 3 randomized study.[105] All three were equally effective in improving the dysphagia score. Complication rate was greatest with the Z-stent (33% of patients) but without statistically significant differences between stents. Procedure-related complications following metal stent placement included aspiration pneumonia, chest pain, perforation and bleeding. Also, the rate of post-placement pain (9–12%) and recurrent dysphagia (24–33%) were not significantly different between stents.[105] Possible delayed complications of stenting included bleeding, fistula formation, gastroesophageal reflux, stent migration, food bolus obstruction and tumor overgrowth at either end of the stent. These occurred in 35–45% of patients.

For patients with irresectable esophageal cancer due to tumor ingrowth into adjacent organs, the combination of external beam radiation therapy and brachytherapy may be an option. However, due to their general poor condition, most patients do not tolerate 5–7 weeks of radiation therapy and can only be treated with brachytherapy. Brachytherapy offers the advantage of a high dose of radiation that can be given in a relatively short period of time without damage to surrounding organs. A disadvantage is that an improvement of dysphagia often becomes apparent only after a week. Brachytherapy has been demonstrated to reduce dysphagia in 70–80% of patients with esophageal cancer. A large international study has compared two fractionation schedules and found no difference in efficacy between both schedules: improvement in dysphagia in about 80% of patients with a median duration of dysphagia-free survival of 7 months.[106]

A retrospective analysis of 149 patients treated with brachytherapy showed an improvement in the ability to swallow in 51% of the patients. Complications occurred in 12% of patients and included severe chest pain, fistula formation and esophageal hemorrhage. Thirty-seven per cent of patients required additional treatment for the recurrence of dysphagia.[107] Data from a small-scale study seem to indicate that palliative brachytherapy and laser therapy may have comparable efficacy. A randomized study, comparing laser therapy with or without brachytherapy, has demonstrated a significant prolongation of palliation by the addition of brachytherapy.[108]

The use of brachytherapy after chemoradiotherapy has been associated with a high rate of tracheobronchial fistulas and strictures. These toxicities were partly due to disease progression but may also have been caused by the brachytherapy.

The randomized multicenter Stent or Intraluminal Radiotherapy for inoperable Esophageal Carcinoma (SIREC) study has recently compared stenting and a single session of high-dose brachytherapy for the palliation of dysphagia in 209 patients with inoperable esophageal cancer or cancer of the gastric cardia.[101,109] Dysphagia improved more rapidly after stenting than after brachytherapy. Brachytherapy initially failed in 18% of patients, who then received a stent. After 4 weeks, the degree of improvement was similar in both groups. Major complications, notably bleeding, perforation and fistulas, and recurrence of dysphagia were observed more frequently in the stent group. Median survival and quality of life scores were similar in both treatment groups. Thus, brachytherapy might be an attractive alternative for stenting in the palliation of malignant dysphagia.

Acknowledgments

The content of this review paper is partly based on presentations made by an international group of experts during the Fourth International From Gene to Cure Congress: Cancer of the Esophagus and Gastric Cardia, Amsterdam, The Netherlands, December 13–15, 2002. Meeting abstracts can be found at http://www.EurCanCen.org/genetocure.

The authors wish to thank all speakers for their stimulating lectures which have greatly facilitated the preparation of this paper. We also thank M. W. Lobbezoo, medical writer, for his efforts in the realization of this review; the staff of the European Cancer Centre, the Scientific Committee and V. W. T. Ruiz van Haperen, I. Husmann and A. E. van Leeuwen-Stok from the Local Organizing Committee for making the congress a very informative and stimulating event.

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