

Oesophageal carcinoma

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Lancet 2013; 381: 400–12

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Oesophageal carcinoma affects more than 450 000 people worldwide and the incidence is rapidly increasing. Squamous-cell carcinoma is the predominant form of oesophageal carcinoma worldwide, but a shift in epidemiology has been seen in Australia, the UK, the USA, and some western European countries (eg, Finland, France, and the Netherlands), where the incidence of adenocarcinoma now exceeds that of squamous-cell types. The overall 5-year survival of patients with oesophageal carcinoma ranges from 15% to 25%. Diagnoses made at earlier stages are associated with better outcomes than those made at later stages. In this Seminar we discuss the epidemiology, pathophysiology, diagnosis and staging, management, prevention, and advances in the treatment of oesophageal carcinoma.

Introduction

Oesophageal carcinoma is the sixth leading cause of cancer-related mortality and the eighth most common cancer worldwide. It affects more than 450 000 people worldwide and the incidence is increasing rapidly.^{1–5} The overall 5-year survival ranges from 15% to 25%, and the best outcomes are associated with disease diagnosed in the early stages.^{3,6} Poor outcomes in patients with oesophageal cancer are related to diagnosis at advanced (metastatic) stages and the propensity for metastases, even when tumours are superficial.⁶ Although treatment of oesophageal carcinoma remains challenging, treatment is best approached by a multidisciplinary team and advances are resulting in progress.^{7,8} In this Seminar we review the epidemiology, pathophysiology, diagnosis and staging, management, and prevention of oesophageal carcinoma, and discuss advances in treatment.

Epidemiology

Squamous-cell carcinoma (SCC) is the predominant histological type of oesophageal carcinoma worldwide. In Australia, the UK, the USA, and some western European countries (eg, Finland, France, and the Netherlands), however, the incidence of oesophageal adenocarcinoma now exceeds that of SCC (appendix p 1–2).^{4,5} Other less common types of oesophageal carcinoma include melanoma, leiomyosarcoma, and small-cell carcinoma.³

The incidence of oesophageal carcinoma varies widely by region.⁹ The so-called Asian belt, which encompasses Turkey, northeastern Iran, Kazakhstan, and northern and

central China (appendix p 3), has a very high incidence of oesophageal SCC, with more than 100 cases per 100 000 population annually. Distribution is equal in men and women. Incidence of oesophageal SCC is also high in southern and eastern Africa.^{9–11} The prevalence of oesophageal adenocarcinoma is increasing in some Asian countries, such as Singapore. In the USA, 16 470 cases of oesophageal carcinoma were newly diagnosed in 2009, and 14 530 deaths were expected to occur in the same year.² From 1975 to 2004, age-adjusted incidence of oesophageal carcinoma in white men increased from 5.76 to 8.34 per 100 000 person-years, largely due to a 463% increase in oesophageal adenocarcinoma. In white women an increase, albeit less striking, was also seen in oesophageal adenocarcinoma.¹² In African American men, SCC is the predominant type of oesophageal carcinoma.¹¹ The rising incidence of oesophageal adenocarcinoma in the USA is not due to either overdiagnosis or reclassification of disease on the basis of histology or location.⁵ In the UK, the incidence of oesophageal adenocarcinoma has increased sharply. In a National Cancer Registry study of more than 40 000 patients, Lepage and colleagues⁴ reported a rise in incidence across all socioeconomic categories in England and Wales between 1971 and 2001 (appendix p 2). The age-adjusted incidence has risen by 39.6% for men and 37.5% for women every 5 years. A similar trend has been noted in other countries in western Europe, such as France, Finland, and the Netherlands.^{11,13} Similarly, in Australia an annual increase in incidence of more than 4.2% was seen.¹⁴

Pathophysiology and pathogenesis Squamous-cell carcinoma

Risk factors for SCC are shown in the panel.^{15–21} Tobacco use has been associated with increased risk of oesophageal SCC and adenocarcinoma related to nitrosamine exposure.^{22–24} Alcohol consumption is a risk factor for oesophageal SCC but not for adenocarcinoma.^{24,25} The pathophysiology in SCC probably involves the alcohol metabolite aldehyde, which is a recognised carcinogen. Mutations in enzymes that metabolise alcohol have been associated with increased risk of SCC.¹⁵ The combination of tobacco and alcohol consumption further increases the risk of SCC (panel).²⁵ Other important factors are low

See Online for appendix

Search strategy and selection criteria

We searched PubMed to identify papers that addressed the epidemiology, pathogenesis, prevention, selection of patients, staging strategies, surgical treatments, extent of resection, and the role of multimodal therapies for oesophageal cancer, published in any language from 1980 to 2010. We used the following search terms: “oesophageal cancer”, “epidemiology”, “pathophysiology”, “prevention”, “oesophagectomy”, “staging”, “mortality”, “surgical approach”, “endoscopic therapy”, “chemotherapy”, “radiation therapy”, “chemoradiation”, “multimodality therapy”, “neoadjuvant therapy”, and “adjuvant therapy”. We manually searched the reference lists of selected articles for additional articles. Additionally, we did focused searches for systematic reviews, Cochrane reviews, and meta-analyses, published from 2005 to 2010, in Embase and Cochrane Library. A few selected references from 2011 and 2012 were added during the article revision process.

socioeconomic status, poor oral hygiene, and nutritional deficiencies.^{3,17–20}

Oesophageal adenocarcinoma

The major risk factors for oesophageal adenocarcinoma are summarised in the panel. They include symptomatic gastro-oesophageal reflux disease (GORD), obesity, Barrett's oesophagus, tobacco use, and a diet that is low in vegetables and fruit.^{26–32} Risk might be decreased in patients with a history of *Helicobacter pylori* infection.²⁹

Symptomatic GORD is one of the strongest risk factors for oesophageal adenocarcinoma, although symptoms are infrequent or absent in more than 40% of patients.³¹ Obesity, which is increasing worldwide, is also an important risk factor for oesophageal adenocarcinoma and is associated with GORD; these disorders might interact to increase further the risk of oesophageal adenocarcinoma.^{33–36}

In Barrett's oesophagus the squamous mucosa is replaced by columnar epithelium, and upper-oesophageal endoscopy shows a cephalad displacement of salmon-coloured mucosa into the oesophagus (appendix p 4). These changes are strongly associated with oesophageal adenocarcinoma.^{32,37,38} The presence of goblet cells in the columnar epithelium is a diagnostic criterion for Barrett's oesophagus in the USA, but is not included in the British Society of Gastroenterology guideline (appendix p 7). The reported prevalence of Barrett's oesophagus is 1.6% in the general population and 10–15% in patients who undergo endoscopic assessment for reflux symptoms.^{39,40} GORD and bile reflux are risk factors for Barrett's oesophagus.^{41,42} Reflux injures the normal squamous mucosa, and Barrett's oesophagus is thought to be a protective adaptation.⁴³ Abdominal obesity might be a risk factor for Barrett's oesophagus.⁴⁴

The risk of oesophageal adenocarcinoma in patients with Barrett's oesophagus has been estimated to be 0.5% per year, but in one study was calculated to be as low as 0.12% per year (appendix p 7). The risk is highest in patients with high-grade dysplasia of the oesophagus,⁴⁵ which progresses to adenocarcinoma in 16–59% of patients.^{45–47} In a meta-analysis, the weighted incidence of oesophageal adenocarcinoma in patients with Barrett's oesophagus and high-grade dysplasia was 6.58 per 100 person-years.⁴⁸ Genetic abnormalities in Barrett's oesophagus (eg, chromosomal instability, cell-cycle abnormalities, and TP53 and KI67 staining) are potential biomarkers for progression to oesophageal adenocarcinoma.^{26,49–51}

Assessment

Clinical presentation

Dysphagia is the most common symptom of oesophageal carcinoma, although the number of asymptomatic patients in whom a diagnosis has been made by surveillance endoscopy has increased.^{52,53} In patients with SCC, the most common presentation is dysphagia, typically accompanied by weight loss and a history of smoking and

Panel: Risk factors for oesophageal cancer

Oesophageal SCC

- Tobacco use
- Alcohol consumption
- Mutations of enzymes that metabolise alcohol
- Achalasia
- Caustic injury
- History of thoracic radiation
- Low socioeconomic status
- Poor oral hygiene
- Nutritional deficiencies
- Non-epidermolytic palmoplantar keratoderma

Oesophageal adenocarcinoma

- Symptomatic gastro-oesophageal reflux disease
- Barrett's oesophagus
- Obesity
- Tobacco use
- History of thoracic radiation
- Diet low in vegetables and fruits
- Increased age
- Male sex
- Medications that relax the lower oesophageal sphincter
- Familial history (rare)

SCC=squamous-cell carcinoma.

alcohol intake.⁵⁴ By contrast, most patients with adenocarcinoma are white men with a history of GORD who have recently developed dysphagia. Weight loss is not a frequent finding. Endoscopy typically shows a tumour in the distal oesophagus or gastro-oesophageal junction.

Diagnosis

Barium oesophagography is widely used as the initial assessment in patients who present with symptoms of oesophageal carcinoma.⁵⁵ However, oesophagogastro-duodenoscopy is required to obtain biopsy samples to confirm the diagnosis of oesophageal carcinoma and, therefore, is preferentially used first in many patients. This approach also enables physicians to assess whether the cardia and stomach are involved in patients with adenocarcinoma of the distal oesophagus, and to see the proximal extent of the tumour and its relation to the cricopharyngeus in patients with SCC. In patients with severe stricture, careful dilatation might be required to assess the extent of the tumour. Bronchoscopy is recommended for mid-oesophageal tumours to exclude airway involvement. Biopsy of abnormalities in the oesophageal wall guided by endoscopic ultrasonography might also lead to diagnosis.⁵⁶

Staging

Once a diagnosis of oesophageal carcinoma is made, accurate staging must be done before treatment to ensure that the correct protocols are applied and that

results can be adequately assessed.^{7,57} The TNM (tumour, node, metastasis) staging system takes into account the depth of tumour invasion, the nodal status, and the presence or absence of metastatic disease. The system has changed over time, and the version used in studies must be known to compare data. The current staging system is shown in table 1. Notable changes in the latest version are the classification of T4 lesions as resectable (T4a) or unresectable (T4b), and stratification of N status on the basis of number of nodes involved (figure). M1 now refers to distant metastases, and the classifications M1a and M1b are no longer in use. Other changes include stratification of stage according to histology, degree of differentiation, and the location of the tumour.⁵⁹

The staging work-up should involve various approaches, including history, physical examination, upper-gastrointestinal endoscopy, CT of the chest and

abdomen (useful to assess local spread of disease and metastases), PET, endoscopic ultrasonography, and bronchoscopy (for midoesophageal or upper-oesophageal lesions).⁵⁴ Minimally invasive staging is also used selectively in some institutions (appendix p 7).⁵⁷ Molecular staging with analysis of gene expression profiles and to detect micrometastases in lymph nodes is currently under investigation.^{60,61} The most important techniques are endoscopic ultrasonography, PET, CT, and, at some institutions, minimally invasive staging.

Endoscopic ultrasonography

Endoscopic ultrasonography provides detailed information on the oesophageal wall and is important in the assessment of tumour status (T descriptor). The accuracy of tumour staging by this method varies according to the stage and ranges from 73% to 89%.⁶² Endoscopic ultrasonography can be used to assess nodal status in node-positive patients with an accuracy of up to 84%, but accuracy falls to around 69% when patients with N0 status are taken into account.^{54,62} The obtaining of biopsy samples by fine-needle aspiration during endoscopic ultrasonography can improve the accuracy of nodal staging, although the endoscope might be unable to advance through tight strictures and cannot traverse the tumour to sample the node. In a study of endoscopic fine-needle aspiration, accuracy was 72% for overall staging and 90% for nodal staging.⁶³

PET

¹⁸F-fluorodeoxyglucose PET (FDG-PET) is increasingly being used to stage oesophageal cancer, but it is not useful to establish tumour status (T descriptor), and accuracy in the assessment of nodal status varies widely (27–90%).⁵⁴ The primary usefulness of FDG-PET is the detection of distant metastatic disease.⁶⁴ Promising findings have also been reported for the assessment of response to induction chemotherapy. In a prospective study, PET was used to assess response early after neoadjuvant chemotherapy.⁶⁵ Patients who responded early completed chemotherapy treatment before they underwent oesophagectomy, whereas non-responders underwent surgery immediately. Survival differed significantly between patients who responded to treatment and those who did not (median event-free survival 29.7 months [95% CI 23.6–35.7] vs 14.1 months [7.5–20.6]; hazard ratio 2.18 [1.32–3.62], *p*=0.002). FDG-PET might be less accurate in the early assessment of response to induction chemoradiation than to neoadjuvant chemotherapy (appendix p 7).

Minimally invasive staging

Minimally invasive staging with laparoscopy or thoracoscopy is not widely practised, but can be very useful in selected patients.^{7,57} We have reported better accuracy with minimally invasive staging than with PET in the diagnosis of distant metastases, especially for lesions

| | Tumour status | Nodal status | Metastatic status | Grade | Tumour location |
|--------------------------------|---------------|--------------|-------------------|--------|-----------------|
| Squamous-cell carcinoma | | | | | |
| 0 | Tis (HGD) | N0 | M0 | 1, X | Any |
| IA | T1 | N0 | M0 | 1, X | Any |
| IB | T1 | N0 | M0 | 2–3 | Any |
| | T2–3 | N0 | M0 | 1, X | Lower, X |
| IIA | T2–3 | N0 | M0 | 1, X | Upper, middle |
| | T2–3 | N0 | M0 | 2–3 | Lower, X |
| IIB | T2–3 | N0 | M0 | 2–3 | Upper, middle |
| | T1–2 | N1 | M0 | Any | Any |
| IIIA | T1–2 | N2 | M0 | Any | Any |
| | T3 | N1 | M0 | Any | Any |
| | T4a | N0 | M0 | Any | Any |
| IIB | T3 | N2 | M0 | Any | Any |
| IIIC | T4a | N1–2 | M0 | Any | Any |
| | T4b | Any | M0 | Any | Any |
| | Any | N3 | M0 | Any | Any |
| IV | Any | Any | M1 | Any | Any |
| Adenocarcinoma | | | | | |
| 0 | Tis (HGD) | N0 | M0 | 1, X | NA |
| IA | T1 | N0 | M0 | 1–2, X | NA |
| IB | T1 | N0 | M0 | 3 | NA |
| | T2 | N0 | M0 | 1–2, X | NA |
| IIA | T2 | N0 | M0 | 3 | NA |
| IIB | T3 | N0 | M0 | Any | NA |
| | T1–2 | N1 | M0 | Any | NA |
| IIIA | T1–2 | N2 | M0 | Any | NA |
| | T3 | N1 | M0 | Any | NA |
| | T4a | N0 | M0 | Any | NA |
| IIB | T3 | N2 | M0 | Any | NA |
| IIIC | T4a | N1–2 | M0 | Any | NA |
| | T4b | Any | M0 | Any | NA |
| | Any | N3 | M0 | Any | NA |
| IV | Any | Any | M1 | Any | NA |

Tis=intraepithelial neoplasia. HGD=high-grade dysplasia. NA=not applicable.
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Table 1: Stage classification for oesophageal carcinoma in the 2010 TNM staging system

with diameter smaller than 1 cm (appendix p 5),⁶⁶ and than with endoscopic ultrasonography for the diagnosis of lymph-node metastasis.⁶⁷ Minimally invasive staging, however, has potential disadvantages: general anaesthesia is required and the procedure is expensive. Since minimally invasive staging with laparoscopy is particularly useful in the detection of occult distant metastases and the exclusion of patients from definitive surgical resection, it can be used before laparotomy, at the time of planned resection.

Treatment of oesophageal carcinoma

Locally advanced disease, defined by the extent of the primary tumour and involvement of locoregional lymph nodes (higher than stage T2, node positive without distant metastases, or both), is generally treated with curative intent with a multimodal approach that includes surgery. Advanced (metastatic or disseminated) and recurrent disease are treated with palliative intent with chemotherapy to extend survival and local therapies, such as radiotherapy, or endoscopic therapies, such as stents, to treat dysphagia. Tumour histology and location affect the choice of chemotherapeutics and approach to surgery, but are seldom used as stratification factors for treatment. Generally, the surgical members of the multidisciplinary team determine resectability for patients with locally advanced oesophageal carcinoma, after which the specifics of neoadjuvant treatment, timing of surgery, and adjuvant therapies are discussed. Non-surgical palliative measures for patients with tumours that are deemed inoperable because of coexisting comorbidities or advanced cancer are decided by the multidisciplinary team.

Surgical treatment

Resection

Surgical options for resection of oesophageal carcinoma include transhiatal oesophagectomy and transthoracic approaches, such as Ivor Lewis oesophagectomy (abdominal and right thoracic approach; also called Lewis-Tanner oesophagectomy), the three-incision modified McKeown oesophagectomy that involves laparotomy, right thoracotomy, and neck anastomosis, and left thoracotomy or a left thoracoabdominal approach.^{7,68-74} The choice of surgical approach depends on the location of the tumour and the preference of the surgeon. All the procedures are complex and, therefore, treatment in high-volume centres with experienced surgeons and the availability of critical-care support is associated with improved outcomes.^{75,76}

Meta-analyses and randomised trials that have assessed open oesophagectomy have shown no significant differences in long-term survival between techniques.⁷⁷⁻⁸⁰ In one large randomised study that compared transthoracic oesophagectomy and transhiatal oesophagectomy, mortality was similar in the two groups, although morbidity was decreased with transhiatal oesophagectomy.

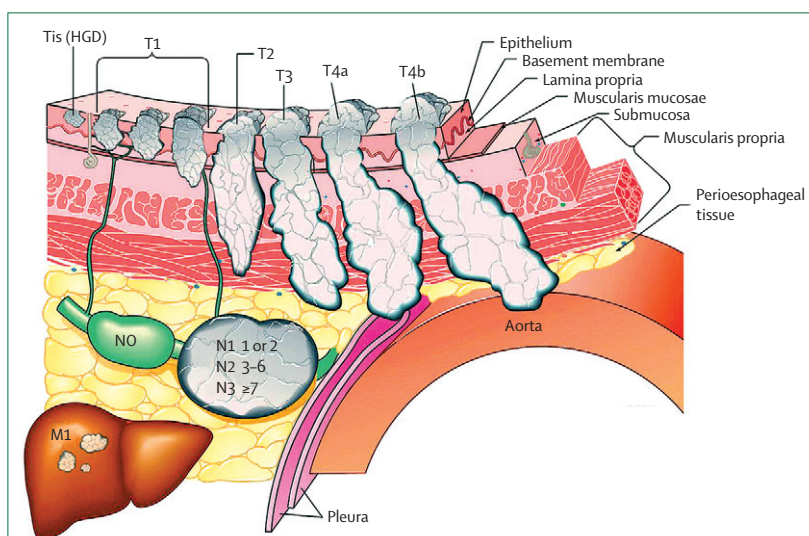


Figure: Features used to stage oesophageal carcinoma according to the latest version of the TNM classification system

Notable updates are the classification of T4 lesions as resectable (T4a) or unresectable (T4b), and the stratification of N status on the basis of number of nodes involved. Tis=intraepithelial neoplasia. HGD=high-grade dysplasia. Reproduced by permission of Cleveland Clinic Center for Medical Art and Photography, Cleveland, OH, USA.

Non-significant associations with disease-free and overall survival were seen in the transthoracic oesophagectomy group. A subgroup analysis of patients without extensive nodal involvement revealed improved locoregional disease-free survival with a transthoracic approach.⁸¹

Lymph-node dissection

The extent of lymph-node dissection required in patients with oesophageal carcinoma is controversial. Proponents of transhiatal oesophagectomy typically dissect the abdominal lymph nodes and limit dissection of thoracic lymph nodes. Three-field lymphadenectomy in the abdomen, chest, and neck (with dissection of nodes along the recurrent nerves) is mainly practised in Japan where SCC predominates.⁸² In Europe and the USA, this approach has few proponents^{71,83} and two-field lymphadenectomy in the abdomen and chest is more commonly used. In a randomised study of two-field versus three-field lymphadenectomy, the complication rate was significantly higher with three-field lymphadenectomy and no significant differences were seen in recurrence or survival.⁸² The survival advantage with three-field dissection reported in some non-randomised trials might be attributable at least partly to stage migration due to improved staging rather than any therapeutic benefit of the dissection itself.⁸³ The need for adequate lymph-node sampling to ensure accurate staging is, however, becoming evident.⁸⁴

Minimally invasive oesophagectomy

The risks associated with oesophagectomy, including mortality of 1-23%, are of concern.⁷⁵ In an effort to

| | Number of patients | Study treatments | Chemotherapy regimen | Histology | Median survival (months) | Overall survival (%) |
|--|--------------------|-------------------------------------|---|--|--------------------------|----------------------|
| Kelsen et al, 1998 ⁹¹ | 440 | Surgery vs surgery and chemotherapy | Cisplatin+fluorouracil for three cycles before surgery | 204 (46%) SCC, 236 (54%) adenocarcinoma | 14.9 vs 16.1 | (3-year) 26% vs 23% |
| MRC, 2002 ⁹² and Allum et al, 2009* | 802 | Surgery vs surgery and chemotherapy | Cisplatin+fluorouracil for two cycles before surgery | 247 (31%) SCC, 533 (66%) adenocarcinoma, 24 (3%) undifferentiated or unknown | 13.3 vs 16.8 | (5-year) 17% vs 23%† |
| Cunningham et al, 2006 ⁹³ | 503 | Surgery vs surgery and chemotherapy | Epirubicin+cisplatin+fluorouracil for three cycles before and after surgery | 503 (100%) adenocarcinoma (372 [74%] gastric, 131 [26%] oesophageal) | NR | (5-year) 23% vs 36%† |

SCC=squamous-cell carcinoma. MRC=Medical Research Council Oesophageal Cancer Working Group. NR=not reported. *Appendix p 7. †Significant difference in favour of the neoadjuvant chemotherapy group.

Table 2: Results of randomised trials of neoadjuvant chemotherapy

decrease the morbidity and mortality of open oesophagectomy, we and others have adopted minimally invasive approaches (appendix p 6). In a large series of 1011 consecutive minimally invasive oesophagectomies done with a combined laparoscopic and thoracoscopic approach, the median stay in intensive care after surgery was 2 days (IQR 1–3), and in hospital was 8 days (6–14), and the 30-day operative mortality was 1.7%.⁸⁵ The oncological results per stage were similar to those of historical series of open oesophagectomy.

The preliminary results of the Eastern Cooperative Oncology Group (ECOG), phase 2, prospective, multi-institutional study (ECOG 2202) of minimally invasive oesophagectomy showed low mortality (2%).⁸⁶ The estimated 3-year overall survival was 50% and stage-specific survival was similar to that in open series. Longer follow-up is required to fully assess the oncological outcomes of minimally invasive oesophagectomy.

A randomised trial of minimally invasive oesophagectomy compared with open oesophagectomy showed a decrease in the frequency of pulmonary complications in the minimally invasive group.⁸⁷ Retrospective comparison has shown improvements in perioperative morbidity with minimally invasive oesophagectomy.^{7,68,88} In a systematic review of studies that in total involved more than 1100 patients, minimally invasive oesophagectomy was associated with decreased morbidity compared with open oesophagectomy,⁸⁹ although all the studies assessed were retrospective. This study design has inherent limitations and selection bias, and the results should be interpreted with caution.

Quality of life after oesophagectomy is an important consideration.⁶⁸ An early study showed that quality-of-life scores after oesophagectomy initially worsened, with reduced scores being reported at 6 weeks, but had returned to baseline values by 9 months in patients who survived longer than 2 years (appendix p 7). In another study, quality of life declined after surgery, but was restored within 1 year (appendix p 7). Minimally invasive oesophagectomy seems to preserve quality of life (appendix p 7).

Neoadjuvant chemotherapy with surgical resection

The combination of chemotherapy with surgery can be used to control the early spread of systemic disease.⁹⁰ Large, randomised trials of chemotherapy before and after surgery in patients with oesophageal SCC or adenocarcinoma have shown conflicting results (table 2). In a US study of patients randomly assigned to neoadjuvant chemotherapy followed by surgery or surgery alone, 3-year overall survival did not differ between groups.⁹¹ By contrast, one of the largest randomised studies to date, the UK Medical Research Council Oesophageal Cancer Working Group study, found that the use of chemotherapy before surgery significantly improved 3-year survival compared with surgery alone (appendix p 7).⁹² On the basis of these results, neoadjuvant chemotherapy followed by resection has become a common approach in the UK for locally advanced disease. In the MAGIC trial,⁹³ chemotherapy given before and after surgery significantly improved 5-year overall survival compared with surgery alone. Whether these results are generalisable to all oesophageal adenocarcinoma, however, is unclear because gastro-oesophageal-junction tumours and oesophageal adenocarcinoma accounted for only 26% of the tumours in the trial.

Neoadjuvant chemoradiotherapy and surgery

In the USA, neoadjuvant chemoradiotherapy is commonly used for locally advanced oesophageal carcinoma. Many randomised trials have assessed chemoradiotherapy followed by surgery compared with surgery alone in patients with potentially resectable oesophageal carcinoma (table 3).^{94–100} Most studies have shown non-significant results. Two showed significant survival benefit with concurrent chemoradiotherapy.^{98,99} One of these studies, however, had several notable limitations, including short follow-up, the absence of CT staging (which could have led to imbalances between the treatment groups), and 3-year survival with surgery alone of 6%,⁹⁸ which is lower than expected.⁹⁰ The other study closed prematurely because of poor accrual.⁹⁹ Survival seemed to favour the chemoradiotherapy group,

| | Number of patients | Study treatments | Regimen | Histology | Median survival (months) | Overall survival (%) |
|---------------------------------------|--------------------|----------------------------|--|---|--------------------------|----------------------|
| Le Prise et al, 1994 ⁹⁴ | 86 | Surgery vs surgery and CRT | Sequential cisplatin+fluorouracil and RT to 20.0 Gy | 86 (100%) SCC | 10.0 vs 10.0 | (1-year) 47% vs 47% |
| Walsh et al, 1996 ⁹⁸ | 103 | Surgery vs surgery and CRT | Concurrent cisplatin+fluorouracil and RT to 40.0 Gy | 103 (100%) adenocarcinoma | 11.0 vs 16.0 | (3-year) 6% vs 32%* |
| Bosset et al, 1997 ⁹⁵ | 282 | Surgery vs surgery and CRT | Sequential interrupted cisplatin and RT to 37.0 Gy | 282 (100%) SCC | 18.6 vs 18.6 | (3-year) 34% vs 36% |
| Urba et al, 2001 ⁹⁶ | 100 | Surgery vs surgery and CRT | Concurrent cisplatin+fluorouracil +vinblastine and RT to 45.0 Gy | 25 (25%) SCC, 75 (75%) adenocarcinoma | 17.6 vs 16.9 | (3-year) 16% vs 30% |
| Burmeister et al, 2005 ¹⁰⁰ | 256 | Surgery vs surgery and CRT | Concurrent cisplatin+fluorouracil and RT to 35.0 Gy | 95 (37%) SCC, 158 (62%) adenocarcinoma, 3 (1%) mixed or other | 22.2 vs 19.3 | NR |
| Tepper et al, 2008 ⁹⁹ | 56 | Surgery vs surgery and CRT | Concurrent cisplatin+fluorouracil and RT to 50.4 Gy | 14 (25%) SCC, 42 (75%) adenocarcinoma | 21.5 vs 53.8 | (5-year) 16% vs 39%* |

CRT=chemoradiotherapy. RT=radiotherapy. SCC=squamous-cell carcinoma. NR=not reported. *Significant difference in favour of neoadjuvant chemoradiotherapy.

Table 3: Results of randomised trials of neoadjuvant chemoradiotherapy

| | Number of patients | Study treatments | Regimen | Histology | Median survival (months) | Overall survival (%) |
|---------------------------------------|--------------------|--|---|--|--------------------------|-------------------------|
| Macdonald et al, 2001 ¹⁰⁶ | 556 | Surgery vs surgery and adjuvant CRT | Sequential and concurrent CRT with fluorouracil | 556 (100%) adenocarcinoma (445 [80%] stomach, 111 [20%] gastro-oesophageal junction) | 27 vs 36 | (3-year) 41% vs 50%* |
| Ando et al, 2003 ¹⁰⁵ | 242 | Surgery vs surgery and adjuvant chemotherapy | Fluorouracil+ cisplatin | 242 (100%) SCC | NR | (5-year) 52% vs 61%† |
| Armanios et al, 2004 ^{103,‡} | 55 | Surgery and adjuvant chemotherapy | Cisplatin+ paclitaxel | 55 (100%) adenocarcinoma | 31.2 | (3-year) 42% |
| Xiao et al, 2003§ | 495 | Surgery vs surgery and adjuvant RT | 50.0–60.0 Gy in 25–30 fractions | 495 (100%) SCC | NR | (5-year) 31.7% vs 41.3% |
| Ténière et al, 1991§ | 221 | Surgery vs surgery and adjuvant RT | 45.0–55.0 Gy | 221 (100%) SCC | 18 vs 18 | (5-year) 17.6% vs 18.6% |
| Fok et al, 1993§ | 130 | Surgery vs surgery and adjuvant RT | 49.0–52.5 Gy in 14 fractions | 104 (80%) SCC, 26 (20%) adenocarcinoma | 15.2 vs 8.7¶ | NR |
| Zieren et al, 1995§ | 68 | Surgery vs surgery and adjuvant RT | Up to 30.6 Gy | 68 (100%) SCC | NR | (3-year) 20% vs 22% |

CRT=chemoradiotherapy. RT=radiotherapy. SCC=squamous-cell carcinoma. NR=not reported. *Difference significant for overall survival. †Although overall survival did not differ (p=0.13), disease-free survival was improved with adjuvant chemotherapy (45% vs 55%, p=0.037). ‡Phase 2 non-randomised, non-controlled trial. §Appendix pp 7–8. ¶Difference significant for median survival.

Table 4: Results of trials of adjuvant chemotherapy, radiotherapy, and chemoradiotherapy

but this finding must be interpreted with caution. A multicentre study reported in 2012 (CROSS), showed a benefit with chemoradiotherapy, particularly in patients with SCC (appendix p 7). A meta-analysis has also shown a benefit for neoadjuvant chemoradiotherapy.¹⁰¹ Studies have started to assess preoperative chemoradiotherapy that uses next-generation platinum, such as oxaliplatin, and biologically targeted agents.¹⁰²

Surgery with adjuvant chemotherapy, radiation, or chemoradiation

Adjuvant chemotherapy for oesophageal carcinoma treated with primary resection might be beneficial, especially in patients with node-positive disease (table 4, appendix pp 7–8).^{7,103–106} In a phase 2 trial (ECOG E8296)

of adjuvant cisplatin and paclitaxel in patients with completely resected oesophageal adenocarcinoma, 49 (89%) of 55 patients had node-positive disease.¹⁰³ Despite N1 disease, 2-year survival was 60%, which compares well with the findings of other studies of neoadjuvant chemotherapy (table 2) and suggests that this approach is beneficial in oesophageal adenocarcinoma. Several randomised trials by the Japan Clinical Oncology Group assessed surgery with or without chemotherapy in patients with SCC.^{104,105} In one study of adjuvant chemotherapy, 5-year disease-free survival favoured the combined therapy group.¹⁰⁵ In a randomised study of observation alone or adjuvant chemoradiotherapy after resection, survival was significantly better with adjuvant chemoradiotherapy.¹⁰⁶

Randomised trials of adjuvant radiation without chemotherapy have not consistently shown benefits (table 4), and its indication is for positive margins or residual tumour (appendix pp 7–8).

Neoadjuvant chemoradiation is commonly used in the USA for locally advanced oesophageal carcinoma, whereas in Europe neoadjuvant chemotherapy is a common approach.^{91–101} In patients with gastro-oesophageal-junction or gastric adenocarcinoma, adjuvant chemoradiotherapy after resection is an acceptable approach, but the findings of studies are not generalisable to all patients with oesophageal carcinoma.¹⁰⁶ Adjuvant chemotherapy is typically used for node-positive disease in Asia, where SCC predominates, and also seems to show some benefit in oesophageal adenocarcinoma.^{103–105}

Non-surgical treatment

Radiotherapy

Historically, external beam radiotherapy has played an important part in the management of unresectable oesophageal carcinoma. Although this approach alone can be a useful palliative treatment for dysphagia, sustained remission and long-term survival are rarely achieved. Chemoradiotherapy is the preferred approach for patients who are suitably fit for combined therapy because it provides better palliation than radiotherapy alone and improves the likelihood of long-term progression-free survival.¹⁰⁷

Concurrent definitive chemoradiation

The RTOG 85-01 trial,^{108,109} assessed radiotherapy versus chemoradiotherapy with cisplatin and fluorouracil, mainly in patients with SCC (90%). The estimated 5-year survival was 27% in the chemoradiotherapy group, but no 5-year survival was seen in the radiotherapy group. This study, however, was done in the 1980s when staging did not require CT scanning, which might have led to imbalance between study groups. A follow-up trial (RTOG 94-05) compared chemoradiotherapy regimens with radiation doses of 64·8 Gy or 50·4 Gy (appendix p 8). The study was closed prematurely because of a lack of improved locoregional control and increased mortality in the high-dose radiotherapy group. On the basis of these results, 50·4 Gy is the standard dose used in the USA.

Although concurrent chemoradiotherapy without surgery is accepted as a treatment for SCC, local control is significantly improved with surgery (appendix p 8).¹¹⁰ In randomised trials of chemoradiotherapy followed by surgery versus chemoradiotherapy alone for SCC, local progression-free survival was significantly improved in the surgery groups (appendix p 8),¹¹⁰ and surgery has been associated with improvement in dysphagia (appendix p 8).

Salvage oesophagectomy after definitive chemoradiation

The rate of locoregional recurrence after definitive chemoradiation is high (40–60%, appendix p 8), and

some patients are referred for salvage oesophagectomy. Typically, patients have received high-dose radiation and are referred for surgery several months after undergoing chemoradiotherapy. The morbidity and mortality of salvage oesophagectomy is higher than that of oesophagectomy done in the neoadjuvant setting (appendix p 8). Despite the increase in perioperative risks, estimated 5-year survival of 25% has been reported in selected patients (appendix p 8). Salvage oesophagectomy should be considered for highly selected patients in specialised centres (appendix p 8) and is not a routine option in all patients who do not respond to definitive chemoradiotherapy. Due consideration should therefore be given to planned oesophagectomy with neoadjuvant or adjuvant therapy, which has a lower morbidity.

Advanced, metastatic, or recurrent disease

Many patients with oesophageal carcinoma have metastases at diagnosis,⁸ and in these patients the goal is to prolong and maximise quality of life. Chemotherapy or chemoradiation is effective in around 50% of patients, but management of pain and nutrition is effective in almost all. Pain is treated with combined short-acting and long-acting narcotics and local radiotherapy (eg, for bone metastases). Dysphagia may be improved with endoscopic therapies or brachytherapy (appendix p 9).

Palliative chemotherapy is chosen on the basis of projected efficacy, the patient's performance status and comorbidities and on the side-effect profiles of relevant agents.^{111–118} Few regimens have been validated in phase 3 trials. Combinations of cisplatin and fluorouracil are better than the best supportive care, particularly for SCC.¹¹¹ Regimens for oesophageal adenocarcinoma now frequently use three drugs and some incorporate biological or targeted therapies. A widely used regimen for patients with advanced gastro-oesophageal carcinoma is irinotecan and cisplatin.^{112–114} Van Cutsem and colleagues¹¹⁵ did a randomised trial of cisplatin and fluorouracil versus docetaxel plus cisplatin and fluorouracil in 445 patients with advanced gastro-oesophageal-junction and gastric cancers. The addition of docetaxel significantly lengthened the time to progression and overall survival.

The REAL-2 study of 1002 patients with oesophago-gastric cancers assessed three-drug regimens that included epirubicin plus oxaliplatin or cisplatin and fluorouracil or capecitabine.¹¹⁶ The primary outcome of non-inferiority in overall survival was reached and favoured better survival in the group that received epirubicin, oxaliplatin, and capecitabine (table 5). Studies of metastatic disease, however, have mainly involved gastric cancers, and the results are not generalisable to all oesophageal carcinoma. The preliminary results of the REAL-3 trial of epirubicin, oxaliplatin, and capecitabine with or without panitumumab in patients with advanced oesophago-gastric cancer have been reported and suggest decreased survival in the panitumumab group (appendix p 9).

| | Number of patients | Histology | Regimen | Outcomes |
|--|--------------------|--|---|---|
| van Cutsem et al, 2006 ^{115*} | 221 | 198 (89.6%) adenocarcinoma (42 [21.2%] gastro-oesophageal junction, 156 [78.8%] gastric, 21 [9.5%] linitis plastica, 2 [0.9%] other) | Docetaxel 75 mg/m ² plus cisplatin 75 mg/m ² on day 1, followed by fluorouracil 750 mg/m ² daily by continuous intravenous infusion for 5 days, repeated every 3 weeks | Response rate 37%, median survival 9.2 months |
| van Meerten et al, 2007 ¹¹⁷ | 51 | 4 (8%) SCC, 45 (88%) adenocarcinoma, 2 (4%) undifferentiated | Oxaliplatin 130 mg/m ² on day 1 and capecitabine 1000 mg/m ² twice daily on days 1-14, repeated every 3 weeks | Response rate 39%, median survival 8 months |
| Lee et al, 2008 [†] | 45 | 45 (100%) SCC | Cisplatin 60 mg/m ² on day 1 and capecitabine 1250 mg/m ² per dose, twice daily on days 1-14 | Response rate 58%, median survival 11.2 months |
| Cunningham et al, 2008 ^{116*} | 239 | 29 (12.1%) SCC, 209 (87.4%) adenocarcinoma, 1 (0.5%) undifferentiated | Epirubicin 50 mg/m ² on day 1, oxaliplatin 130 mg/m ² on day 1, and capecitabine 625 mg/m ² twice daily on days 1-21, repeated every 3 weeks | Response rate 48%, median survival, 11.2 months |
| Bang et al, 2009 ^{*†} | 294 | 294 (100%) adenocarcinoma‡ (58 [20%] gastro-oesophageal junction, 236 [80%] gastric) | 800 mg/m ² fluorouracil daily by IV infusion on days 1-5, or 1000 mg/m ² capecitabine twice daily on days 1-14, plus 80 mg/m ² cisplatin on day 1 by IV infusion, repeated every 3 weeks, and 8 mg/kg trastuzumab by IV infusion on day 1 of first cycle followed by 6 mg/kg every 3 weeks until disease progression | Response rate 47%, median survival 13.8 months |
| Ajani et al, 2010 ^{*†} | 521 | 521 (100%) adenocarcinoma (82 [15.7%] gastro-oesophageal junction, 438 [84.1%] gastric, 1 [0.2%] both) | Cisplatin 75 mg/m ² on day 1 and S-1 (fluoropyrimidine) 50 mg/m ² divided across twice daily doses on days 1-21, repeated every 28 days | Response rate 29%, median survival 8.6 months |

SCC=squamous-cell carcinoma. IV=intravenous. *Results given for treatment with the best survival outcome in a comparison of two or more treatments. †Appendix pp 8-9. ‡Restricted to patients with HER2 (also known as ERBB2)-positive tumours.

Table 5: Studies of first-line chemotherapy for metastatic oesophageal cancer

Biological and targeted therapies

Agents containing small molecules and antibodies that have been created on the basis of tumour biology are being incorporated into multimodal therapies.¹¹⁸ The most commonly used agents include the angiogenesis inhibitor bevacizumab and the inhibitors of epidermal-growth-factor receptors, panitumumab, cetuximab, and erlotinib. Further studies are underway to assess these drugs.

Endoscopic treatment

Although endoscopic therapies are widely used to treat advanced or inoperable cancers, they have gained interest as potential curative approaches for early-stage oesophageal carcinoma. Barrett's oesophagus and early-stage cancer might be treatable endoscopically with resection or ablation. Resection techniques have the advantage of enabling sample collection for histological assessment and T-staging, and include mucosal resection and submucosal dissection for large lesions. Endoscopic ablation therapies include photodynamic therapy, argon plasma coagulation, and radiofrequency ablation, which enable treatment of large areas but cannot be used to collect samples.^{119,120} In Europe and Japan, endoscopic resection is used mainly, and endoscopic ablation is used as an adjunct. In the USA, ablative therapy is the first-line approach with resection as an adjunctive approach.

Staging (TNM) must be confirmed before endoscopic therapy is started. Depth of invasion and other tumour characteristics, such as length, differentiation, and

angiolympathic invasion, should be assessed in addition to nodal (N) and metastatic (M) status. Ell and colleagues¹²¹ used endoscopic mucosal resection and photodynamic therapy to treat 100 highly selected patients who had T1 intramucosal cancer and reported an estimated 3-year survival of 98%. These results are encouraging, but the resection margins were positive in around a third of patients, and recurrent or metachronous lesions were detected in 11% of patients during a median follow-up of 33 months. In a study of resection of T1 tumours, multifocal neoplasia, angiolympathic invasion, or nodal metastases were frequently noted irrespective of tumour depth, which led the authors to conclude that endoscopic therapies should be reserved for high-risk patients.¹²² In our experience, the risk of N1 disease in patients with T1 intramucosal lesions is 7%.⁶ Further work is required to define the role of endoscopic therapies with curative intent for oesophageal carcinoma.^{6,122,123}

Endoscopic palliative treatments for dysphagia in patients with oesophageal carcinoma include oesophageal dilatation, esophageal stents, photodynamic therapy, neodymium-doped yttrium aluminium garnet (Nd:YAG) laser therapy, and brachytherapy.¹²⁴ Self-expanding metal stents are the most commonly used oesophageal stents.¹²⁵ In a randomised trial, brachytherapy was compared with stenting. Stenting provided earlier palliation of dysphagia, but the effects of brachytherapy lasted longer with fewer complications (appendix p 8). Photodynamic therapy is used to treat obstructive endoluminal tumours and bleeding.¹²⁶ Complications after this treatment include stricture and sunburn. In a

randomised, multicentre trial of photodynamic therapy compared with Nd:YAG laser therapy in patients with obstructive oesophageal carcinoma, both approaches provided equal relief of dysphagia, but the objective tumour response was better and acute perforations were fewer in the photodynamic-therapy group.¹²⁷ Locally advanced oesophageal carcinoma can also cause tracheo-oesophageal fistulas, which are typically treated with a covered oesophageal stent.

Prevention, surveillance, and screening

Although several potential preventive measures exist, none has been proven to decrease the risk of oesophageal carcinoma in prospective well-designed trials.^{26,27}

Chemoprevention

Various nutrients and minerals have been tested for preventive effects against oesophageal carcinoma, including retinol, riboflavin, zinc, selenium, β -carotene, and α -tocopherol; none has yet shown notable preventive effects in randomised trials.^{128,129} Chemoprevention trials of black raspberries, which have a high concentration of a nitrosamine inhibitor,¹³⁰ and of selenium are in progress.¹³¹ Chemopreventive actions have been suggested for non-steroidal anti-inflammatory drugs and inhibitors of cyclo-oxygenase 2,¹³² although a randomised trial of the latter in Barrett's oesophagus showed no significant benefit.¹³³ Aspirin has shown a protective effect in population-based studies. A randomised chemoprevention trial, AspECT, is underway in the UK to assess aspirin plus twice-daily esomeprazole versus esomeprazole alone in patients with Barrett's oesophagus but without high-grade dysplasia.¹³⁴

Other suggested but as yet unproven measures to lower the incidence of oesophageal carcinoma include cessation of smoking and alcohol consumption, lifestyle modifications to increase exercise and reduce weight, and the inclusion of substantial intake of fruit and vegetables in the diet.

Screening for Barrett's oesophagus

Whether endoscopic screening programmes to detect Barrett's oesophagus in patients with chronic GORD symptoms are useful has been debated. Critics point out the high number of people in the general population who have reflux symptoms and the fact that at least 40% of patients with Barrett's oesophagus do not have reflux symptoms, and question the cost-effectiveness of screening (appendix p 9). Proponents of screening for Barrett's oesophagus point to the clear associations between reflux, Barrett's oesophagus, and oesophageal adenocarcinoma, and suggest that the rising incidence of oesophageal adenocarcinoma justifies screening. No definitive data are available on whether endoscopic screening for Barrett's oesophagus is associated with a reduction in cancer-related mortality and, therefore, screening is not routinely recommended.^{38,135}

Prevention in patients with Barrett's oesophagus

The major societies in North America and Europe support surveillance programmes after a diagnosis of Barrett's oesophagus is made,^{136,137} and a randomised trial is underway to test the usefulness of endoscopic surveillance.¹³⁸ Neither acid suppression with medical therapy nor antireflux surgery prevents progression of Barrett's oesophagus to cancer.^{139,140} Whether endoscopic therapies are useful for patients with Barrett's oesophagus without dysplasia is controversial, and the consensus is to follow up patients with endoscopic surveillance and systematic biopsy.¹⁴¹ Advances in narrow-band imaging and confocal laser microendoscopy might facilitate diagnosis and directed biopsy.^{37,38,142}

In patients with high-grade dysplasia, the options for preventive approaches include surveillance, endoscopic therapies, and surgical resection, but the optimum approach is debated. In an analysis of more than 15 studies, the mean incidence of occult adenocarcinoma in patients with a preoperative diagnosis of high-grade dysplasia treated with oesophagectomy was 41%.⁴⁵ This high incidence provides a rationale for use of oesophagectomy, but there is concern about the risk of morbidity. Use of endoscopic treatments for high-grade dysplasia has been supported in two randomised trials. In one trial of photodynamic therapy plus proton-pump inhibitors compared with proton-pump inhibitors alone, progression to cancer was significantly decreased in the photodynamic-therapy group (13% vs 28%).¹¹⁹ In the other, which assessed endoscopic radiofrequency ablation in patients with Barrett's oesophagus and high-grade dysplasia, radiofrequency ablation was more effective in eradication of high-grade dysplasia than a proton-pump inhibitor alone, and the progression to cancer was lower (4% vs 22%) during short-term follow-up.¹²⁰

Conclusions and future directions

The incidence of oesophageal carcinoma is increasing and substantial work is required to understand the causes of this rapid increase and the shift in epidemiology towards adenocarcinoma in some countries. Treatment of oesophageal carcinoma remains challenging but is best approached by a multidisciplinary team. Refinement of staging techniques, including molecular staging, is needed to understand prognosis and to tailor therapy to individuals to achieve the best possible outcomes. Technological advances in minimally invasive surgery, endoscopic treatments, and targeted agents, are being investigated and will hopefully also improve outcomes.

Contributors

AP contributed to deciding the content of the paper and to the researching, writing, and revision of all sections. MKG contributed to the researching and writing of the sections on multimodal treatments and management of advanced oesophageal carcinoma. BAJ contributed to the researching and writing of the section on endoscopic therapies for oesophageal cancer. JDL contributed to deciding the content of the paper, and to revision of all sections.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

We acknowledge the work of numerous investigators on oesophageal carcinoma that we were unable to cite owing to limitations of space. We thank Shannon Wyszomierski, University of Pittsburgh Medical Center, Pittsburgh, PA, USA, for editorial support during manuscript preparation. This work is supported by NIH grant 5R01 CA090665 09.

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