Oesophageal carcinoma

Arjun Pennathur, Michael K Gibson, Blair A Jobe, James D Luketich

Lancet 2013; 381: 400–12

Department of Cardiothoracic Surgery (A Pennathur MD, Prof B A Jobe MD, Prof J D Luketich MD) **and Division of Hematology-Oncology, Department of Medicine** (M K Gibson MD), **University of Pittsburgh School of Medicine, Pittsburgh, PA, USA; and University of Pittsburgh Cancer Institute, Pittsburgh, PA, USA** (A Pennathur, M K Gibson, Prof B A Jobe, Prof J D Luketich)

Correspondence to: Prof James D Luketich, Department of Cardiothoracic Surgery, University of Pittsburgh, Pittsburgh, PA 15213, USA
luketichjd@upmc.edu

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]

See Online for appendix

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 to 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 colleagues[4] 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]

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: "esophageal cancer", "epidemiology", "pathophysiology", "prevention", "esophagectomy", "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.

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

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 slamon-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 adaption.[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 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.

***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.

Diagnosis

Barium oesophagography is widely used as the initial assessment in patients who present with symptoms of oesophageal carcinoma.[55] However, oesophagogastroduodenoscopy 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.

	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
IIIB	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
IIIB	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. Reproduced from reference 58 by permission of American Joint Cancer Committee on Cancer.

Table 1: **Stage classification for oesophageal carcinoma in the 2010 TNM staging system**

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

^{18}F-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

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.

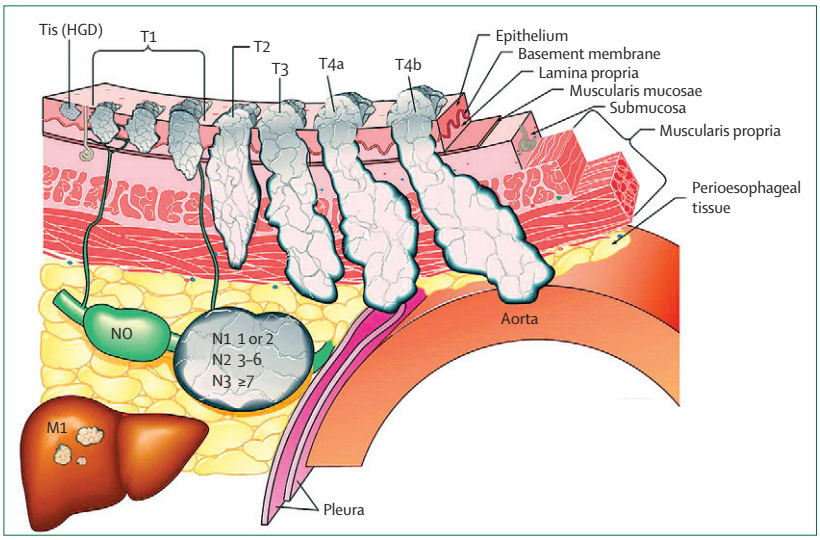

Figure: **Features used to stage oesophageal carcinoma according to the latest version of the TNM classification system**

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%) adenocarinoma	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 esophagectomy,[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 surival 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 platinums, 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 colleagues[115] 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 oesophagogastric 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 oesophagogastric 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/m² plus cisplatin 75 mg/m² on day 1, followed by fluorouracil 750 mg/m² 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/m² on day 1 and capecitabine 1000 mg/m² 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/m² on day 1 and capecitabine 1250 mg/m² 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/m² on day 1, oxaliplatin 130 mg/m² on day 1, and capecitabine 625 mg/m² 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/m² fluorouracil daily by IV infusion on days 1–5, or 1000 mg/m² capecitabine twice daily on days 1–14, plus 80 mg/m² 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/m² on day 1 and S-1 (fluoropyrimidine) 50 mg/m² 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 angiolymphatic invasion, should be assessed in addition to nodal (N) and metastatic (M) status. Ell and colleagues[121] 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, angiolymphatic 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 5RO1 CA090665 09.

References

1 Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010; **127:** 2893–917.

2 Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin* 2009; **59:** 225–49.

3 Enzinger PC, Mayer RJ. Esophageal cancer. *N Engl J Med* 2003; **349:** 2241–52.

4 Lepage C, Rachet B, Jooste V, Faivre J, Coleman MP. Continuing rapid increase in esophageal adenocarcinoma in England and Wales. *Am J Gastroenterol* 2008; **103:** 2694–99.

5 Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. *J Natl Cancer Inst* 2005; **97:** 142–46.

6 Pennathur A, Farkas A, Krasinskas AM, et al. Esophagectomy for T1 esophageal cancer: outcomes in 100 patients and implications for endoscopic therapy. *Ann Thorac Surg* 2009; **87:** 1048–55.

7 Pennathur A, Luketich JD. Resection for esophageal cancer: strategies for optimal management. *Ann Thorac Surg* 2008; **85:** S751–56.

8 Polednak AP. Trends in survival for both histologic types of esophageal cancer in US surveillance, epidemiology and end results areas. *Int J Cancer* 2003; **105:** 98–100.

9 Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol* 2006; **24:** 2137–50.

10 Umar SB, Fleischer DE. Esophageal cancer: epidemiology, pathogenesis and prevention. *Nat Clin Pract Gastroenterol Hepatol* 2008; **5:** 517–26.

11 Eslick GD. Epidemiology of esophageal cancer. *Gastroenterol Clin North Am* 2009; **38:** 17–25, vii.

12 Brown LM, Devesa SS, Chow WH. Incidence of adenocarcinoma of the esophagus among white Americans by sex, stage, and age. *J Natl Cancer Inst* 2008; **100:** 1184–87.

13 Crane LM, Schaapveld M, Visser O, Louwman MW, Plukker JT, van Dam GM. Oesophageal cancer in The Netherlands: increasing incidence and mortality but improving survival. *Eur J Cancer* 2007; **43:** 1445–51.

14 Stavrou EP, McElroy HJ, Baker DF, Smith G, Bishop JF. Adenocarcinoma of the oesophagus: incidence and survival rates in New South Wales, 1972–2005. *Med J Aust* 2009; **191:** 310–14.

15 Yang SJ, Wang HY, Li XQ, et al. Genetic polymorphisms of ADH2 and ALDH2 association with esophageal cancer risk in southwest China. *World J Gastroenterol* 2007; **13:** 5760–64.

16 Ahsan H, Neugut AI. Radiation therapy for breast cancer and increased risk for esophageal carcinoma. *Ann Intern Med* 1998; **128:** 114–17.

17 Brown LM, Hoover R, Silverman D, et al. Excess incidence of squamous cell esophageal cancer among US Black men: role of social class and other risk factors. *Am J Epidemiol* 2001; **153:** 114–22.

18 Taylor PR, Qiao YL, Abnet CC, et al. Prospective study of serum vitamin E levels and esophageal and gastric cancers. *J Natl Cancer Inst* 2003; **95:** 1414–16.

19 Abnet CC, Lai B, Qiao YL, et al. Zinc concentration in esophageal biopsy specimens measured by x-ray fluorescence and esophageal cancer risk. *J Natl Cancer Inst* 2005; **97:** 301–06.

20 Abnet CC, Qiao YL, Mark SD, Dong ZW, Taylor PR, Dawsey SM. Prospective study of tooth loss and incident esophageal and gastric cancers in China. *Cancer Causes Control* 2001; **12:** 847–54.

21 Risk JM, Mills HS, Garde J, et al. The tylosis esophageal cancer (TOC) locus: more than just a familial cancer gene. *Dis Esophagus* 1999; **12:** 173–76.

22 De Stefani E, Barrios E, Fierro L. Black (air-cured) and blond (flue-cured) tobacco and cancer risk. III: Oesophageal cancer. *Eur J Cancer* 1993; **29A:** 763–66.

23 Vaughan TL, Davis S, Kristal A, Thomas DB. Obesity, alcohol, and tobacco as risk factors for cancers of the esophagus and gastric cardia: adenocarcinoma versus squamous cell carcinoma. *Cancer Epidemiol Biomarkers Prev* 1995; **4:** 85–92.

24 Gammon MD, Schoenberg JB, Ahsan H, et al. Tobacco, alcohol, and socioeconomic status and adenocarcinomas of the esophagus and gastric cardia. *J Natl Cancer Inst* 1997; **89:** 1277–84.

25 Lee CH, Wu DC, Lee JM, et al. Carcinogenetic impact of alcohol intake on squamous cell carcinoma risk of the oesophagus in relation to tobacco smoking. *Eur J Cancer* 2007; **43:** 1188–99.

26 Reid BJ, Li X, Galipeau PC, Vaughan TL. Barrett's oesophagus and oesophageal adenocarcinoma: time for a new synthesis. *Nat Rev Cancer* 2010; **10:** 87–101.

27 Engel LS, Chow WH, Vaughan TL, et al. Population attributable risks of esophageal and gastric cancers. *J Natl Cancer Inst* 2003; **95:** 1404–13.

28 Lagergren J, Bergström R, Adami HO, Nyrén O. Association between medications that relax the lower esophageal sphincter and risk for esophageal adenocarcinoma. *Ann Intern Med* 2000; **133:** 165–75.

29 Islami F, Kamangar F. *Helicobacter pylori* and esophageal cancer risk: a meta-analysis. *Cancer Prev Res (Phila)* 2008; **1:** 329–38.

30 Poynton AR, Walsh TN, O'Sullivan G, Hennessy TP. Carcinoma arising in familial Barrett's esophagus. *Am J Gastroenterol* 1996; **91:** 1855–56.

31 Lagergren J, Bergström R, Lindgren A, Nyrén O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med* 1999; **340:** 825–31.

32 Anderson LA, Watson RG, Murphy SJ, et al. Risk factors for Barrett's oesophagus and oesophageal adenocarcinoma: results from the FINBAR study. *World J Gastroenterol* 2007; **13:** 1585–94.

33 Kubo A, Corley DA. Body mass index and adenocarcinomas of the esophagus or gastric cardia: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2006; **15:** 872–78.

34 Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999–2004. *JAMA* 2006; **295:** 1549–55.

35 Fisher BL, Pennathur A, Mutnick JL, Little AG. Obesity correlates with gastroesophageal reflux. *Dig Dis Sci* 1999; **44:** 2290–94.

36 Whiteman DC, Sadeghi S, Pandeya N, et al, and the Australian Cancer Study. Combined effects of obesity, acid reflux and smoking on the risk of adenocarcinomas of the oesophagus. *Gut* 2008; **57:** 173–80.

37 Shaheen NJ, Richter JE. Barrett's oesophagus. *Lancet* 2009; **373:** 850–61.

38 Sharma P. Clinical practice. Barrett's esophagus. *N Engl J Med* 2009; **361:** 2548–56.

39 Ronkainen J, Aro P, Storskrubb T, et al. Prevalence of Barrett's esophagus in the general population: an endoscopic study. *Gastroenterology* 2005; **129:** 1825–31.

40 Voutilainen M, Sipponen P, Mecklin JP, Juhola M, Färkkilä M. Gastroesophageal reflux disease: prevalence, clinical, endoscopic and histopathological findings in 1,128 consecutive patients referred for endoscopy due to dyspeptic and reflux symptoms. *Digestion* 2000; **61:** 6–13.

41 Iascone C, DeMeester TR, Little AG, Skinner DB. Barrett's esophagus. Functional assessment, proposed pathogenesis, and surgical therapy. *Arch Surg* 1983; **118:** 543–49.

42 Vaezi MF, Richter JE. Role of acid and duodenogastroesophageal reflux in gastroesophageal reflux disease. *Gastroenterology* 1996; **111:** 1192–99.

43 Jovov B, Van Itallie CM, Shaheen NJ, et al. Claudin-18: a dominant tight junction protein in Barrett's esophagus and likely contributor to its acid resistance. *Am J Physiol Gastrointest Liver Physiol* 2007; **293:** G1106–13.

44 Edelstein ZR, Farrow DC, Bronner MP, Rosen SN, Vaughan TL. Central adiposity and risk of Barrett's esophagus. *Gastroenterology* 2007; **133:** 403–11.

45 Pennathur A, Landreneau RJ, Luketich JD. Surgical aspects of the patient with high-grade dysplasia. *Semin Thorac Cardiovasc Surg* 2005; **17:** 326–32.

46 Reid BJ, Weinstein WM, Lewin KJ, et al. Endoscopic biopsy can detect high-grade dysplasia or early adenocarcinoma in Barrett's esophagus without grossly recognizable neoplastic lesions. *Gastroenterology* 1988; **94:** 81–90.

47 Schnell TG, Sontag SJ, Chejfec G, et al. Long-term nonsurgical management of Barrett's esophagus with high-grade dysplasia. *Gastroenterology* 2001; **120:** 1607–19.

48 Rastogi A, Puli S, El-Serag HB, Bansal A, Wani S, Sharma P. Incidence of esophageal adenocarcinoma in patients with Barrett's esophagus and high-grade dysplasia: a meta-analysis. *Gastrointest Endosc* 2008; **67:** 394–98.

49 Rabinovitch PS, Longton G, Blount PL, Levine DS, Reid BJ. Predictors of progression in Barrett's esophagus III: baseline flow cytometric variables. *Am J Gastroenterol* 2001; **96:** 3071–83.

50 Morales CP, Souza RF, Spechler SJ. Hallmarks of cancer progression in Barrett's oesophagus. *Lancet* 2002; **360:** 1587–89.

51 Sikkema M, Kerkhof M, Steyerberg EW, et al. Aneuploidy and overexpression of Ki67 and p53 as markers for neoplastic progression in Barrett's esophagus: a case-control study. *Am J Gastroenterol* 2009; **104:** 2673–80.

52 Daly JM, Fry WA, Little AG, et al. Esophageal cancer: results of an American College of Surgeons Patient Care Evaluation Study. *J Am Coll Surg* 2000; **190:** 562–72.

53 Portale G, Hagen JA, Peters JH, et al. Modern 5-year survival of resectable esophageal adenocarcinoma: single institution experience with 263 patients. *J Am Coll Surg* 2006; **202:** 588–96, discussion 596–98.

54 Rice TW. Diagnosis and staging of esophageal cancer. In: Pearson FG, Patterson GA, eds. Pearson's thoracic and esophageal surgery. 3rd edn. Philadelphia: Churchill Livingstone/Elsevier, 2008: 454–63.

55 Levine MS, Chu P, Furth EE, Rubesin SE, Laufer I, Herlinger H. Carcinoma of the esophagus and esophagogastric junction: sensitivity of radiographic diagnosis. *AJR Am J Roentgenol* 1997; **168:** 1423–26.

56 Faigel DO, Deveney C, Phillips D, Fennerty MB. Biopsy-negative malignant esophageal stricture: diagnosis by endoscopic ultrasound. *Am J Gastroenterol* 1998; **93:** 2257–60.

57 Krasna MJ, Reed CE, Nedzwiecki D, et al, and the CALGB Thoracic Surgeons. CALGB 9380: a prospective trial of the feasibility of thoracoscopy/laparoscopy in staging esophageal cancer. *Ann Thorac Surg* 2001; **71:** 1073–79.

58 Edge SB, Byrd DR, Compton CC, eds. AJCC cancer staging manual, 7th edn. New York, NY: Springer, 2010: 103–15.

59 Rice TW, Blackstone EH, Rusch VW. A cancer staging primer: esophagus and esophagogastric junction. *J Thorac Cardiovasc Surg* 2010; **139:** 527–29.

60 Pennathur A, Xi, L, Litle VR, et al. Gene expression profiles in esophageal adenocarcinoma predict survival following resection. American Association of Thoracic Surgery (AATS) 90th Annual Meeting; Toronto, ON; May 1–5, 2010. Abstr.

61 Xi L, Luketich JD, Raja S, et al. Molecular staging of lymph nodes from patients with esophageal adenocarcinoma. *Clin Cancer Res* 2005; **11:** 1099–109.

62 Rösch T. Endosonographic staging of esophageal cancer: a review of literature results. *Gastrointest Endosc Clin N Am* 1995; **5:** 537–47.

63 Kaushik N, Khalid A, Brody D, Luketich J, McGrath K. Endoscopic ultrasound compared with laparoscopy for staging esophageal cancer. *Ann Thorac Surg* 2007; **83:** 2000–02.

64 Meyers BF, Downey RJ, Decker PA, et al, and the American College of Surgeons Oncology Group Z0060. The utility of positron emission tomography in staging of potentially operable carcinoma of the thoracic esophagus: results of the American College of Surgeons Oncology Group Z0060 trial. *J Thorac Cardiovasc Surg* 2007; **133:** 738–45.

65 Lordick F, Ott K, Krause BJ, et al. PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the MUNICON phase II trial. *Lancet Oncol* 2007; **8:** 797–805.

66 Luketich JD, Friedman DM, Weigel TL, et al. Evaluation of distant metastases in esophageal cancer: 100 consecutive positron emission tomography scans. *Ann Thorac Surg* 1999; **68:** 1133–36, discussion 1136–37.

67 Luketich JD, Schauer P, Landreneau R, et al. Minimally invasive surgical staging is superior to endoscopic ultrasound in detecting lymph node metastases in esophageal cancer. *J Thorac Cardiovasc Surg* 1997; **114:** 817–21, discussion 821–23.

68 Pennathur A, Zhang J, Chen H, Luketich JD. The "best operation" for esophageal cancer? *Ann Thorac Surg* 2010; **89:** S2163–67.

69 Hagen JA, DeMeester SR, Peters JH, Chandrasoma P, DeMeester TR. Curative resection for esophageal adenocarcinoma: analysis of 100 en bloc esophagectomies. *Ann Surg* 2001; **234:** 520–30, discussion 530–31.

70 Orringer MB, Marshall B, Iannettoni MD. Transhiatal esophagectomy: clinical experience and refinements. *Ann Surg* 1999; **230:** 392–400, discussion 400–03.

71 Altorki N, Kent M, Ferrara C, Port J. Three-field lymph node dissection for squamous cell and adenocarcinoma of the esophagus. *Ann Surg* 2002; **236:** 177–83.

72 Swanson SJ, Batirel HF, Bueno R, et al. Transthoracic esophagectomy with radical mediastinal and abdominal lymph node dissection and cervical esophagogastrostomy for esophageal carcinoma. *Ann Thorac Surg* 2001; **72:** 1918–24; discussion 1924–5.

73 Visbal AL, Allen MS, Miller DL, Deschamps C, Trastek VF, Pairolero PC. Ivor Lewis esophagogastrectomy for esophageal cancer. *Ann Thorac Surg* 2001; **71:** 1803–08.

74 Mathisen DJ, Grillo HC, Wilkins EW Jr, Moncure AC, Hilgenberg AD. Transthoracic esophagectomy: a safe approach to carcinoma of the esophagus. *Ann Thorac Surg* 1988; **45:** 137–43.

75 Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. *N Engl J Med* 2002; **346:** 1128–37.

76 Dimick JB, Pronovost PJ, Heitmiller RF, Lipsett PA. Intensive care unit physician staffing is associated with decreased length of stay, hospital cost, and complications after esophageal resection. *Crit Care Med* 2001; **29:** 753–58.

77 Hulscher JB, Tijssen JG, Obertop H, van Lanschot JJ. Transthoracic versus transhiatal resection for carcinoma of the esophagus: a meta-analysis. *Ann Thorac Surg* 2001; **72:** 306–13.

78 Chu KM, Law SY, Fok M, Wong J. A prospective randomized comparison of transhiatal and transthoracic resection for lower-third esophageal carcinoma. *Am J Surg* 1997; **174:** 320–24.

79 Goldminc M, Maddern G, Le Prise E, Meunier B, Campion JP, Launois B. Oesophagectomy by a transhiatal approach or thoracotomy: a prospective randomized trial. *Br J Surg* 1993; **80:** 367–70.

80 Hulscher JB, van Sandick JW, de Boer AG, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. *N Engl J Med* 2002; **347:** 1662–69.

81 Omloo JM, Lagarde SM, Hulscher JB, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the mid/distal esophagus: five-year survival of a randomized clinical trial. *Ann Surg* 2007; **246:** 992–1000, discussion 1000–01.

82 Nishihira T, Hirayama K, Mori S. A prospective randomized trial of extended cervical and superior mediastinal lymphadenectomy for carcinoma of the thoracic esophagus. *Am J Surg* 1998; **175:** 47–51.

83 Lerut T, Nafteux P, Moons J, et al. Three-field lymphadenectomy for carcinoma of the esophagus and gastroesophageal junction in 174 R0 resections: impact on staging, disease-free survival, and outcome: a plea for adaptation of TNM classification in upper-half esophageal carcinoma. *Ann Surg* 2004; **240:** 962–72.

84 Rizk N, Venkatraman E, Park B, Flores R, Bains MS, Rusch V, and the American Joint Committee on Cancer staging system. The prognostic importance of the number of involved lymph nodes in esophageal cancer: implications for revisions of the American Joint Committee on Cancer staging system. *J Thorac Cardiovasc Surg* 2006; **132:** 1374–81.

85 Luketich JD, Pennathur A, Awais O, et al. Outcomes after minimally invasive esophagectomy: review of over 1000 patients. *Ann Surg* 2012; **256:** 95–103.

86 Luketich JD, Pennathur A, Catalano PJ, et al. Results of a phase II multicenter study of MIE (Eastern Cooperative Oncology Group Study E2202). *J Clin Oncol* 2009; **27** (suppl)**:** 15s (abstr 4516).

87 Biere SS, van Berge Henegouwen MI, Maas KW, et al. Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicentre, open-label, randomised controlled trial. *Lancet* 2012; **379:** 1887–92.

88 Nguyen NT, Follette DM, Wolfe BM, Schneider PD, Roberts P, Goodnight JE Jr. Comparison of minimally invasive esophagectomy with transthoracic and transhiatal esophagectomy. *Arch Surg* 2000; **135:** 920–25.

89 Verhage RJ, Hazebroek EJ, Boone J, Van Hillegersberg R. Minimally invasive surgery compared to open procedures in esophagectomy for cancer: a systematic review of the literature. *Minerva Chir* 2009; **64:** 135–46.

90 Pennathur A, Luketich JD, Landreneau RJ, et al. Long-term results of a phase II trial of neoadjuvant chemotherapy followed by esophagectomy for locally advanced esophageal neoplasm. *Ann Thorac Surg* 2008; **85:** 1930–36; discussion 1936–37.

91 Kelsen DP, Ginsberg R, Pajak TF, et al. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. *N Engl J Med* 1998; **339:** 1979–84.

92 Medical Research Council Oesophageal Cancer Working Group. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. *Lancet* 2002; **359:** 1727–33.

93 Cunningham D, Allum WH, Stenning SP, et al, and the MAGIC Trial Participants. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006; **355:** 11–20.

94 Le Prise E, Etienne PL, Meunier B, et al. A randomized study of chemotherapy, radiation therapy, and surgery versus surgery for localized squamous cell carcinoma of the esophagus. *Cancer* 1994; **73:** 1779–84.

95 Bosset JF, Gignoux M, Triboulet JP, et al. Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. *N Engl J Med* 1997; **337:** 161–67.

96 Urba SG, Orringer MB, Turrisi A, Iannettoni M, Forastiere A, Strawderman M. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. *J Clin Oncol* 2001; **19:** 305–13.

97 Apinop C, Puttisak P, Preecha N. A prospective study of combined therapy in esophageal cancer. *Hepatogastroenterology* 1994; **41:** 391–93.

98 Walsh TN, Noonan N, Hollywood D, Kelly A, Keeling N, Hennessy TP. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. *N Engl J Med* 1996; **335:** 462–67.

99 Tepper J, Krasna MJ, Niedzwiecki D, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. *J Clin Oncol* 2008; **26:** 1086–92.

100 Burmeister BH, Smithers BM, Gebski V, et al, and the Trans-Tasman Radiation Oncology Group, and the Australasian Gastro-Intestinal Trials Group. Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial. *Lancet Oncol* 2005; **6:** 659–68.

101 Gebski V, Burmeister B, Smithers BM, Foo K, Zalcberg J, Simes J, and the Australasian Gastro-Intestinal Trials Group. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis. *Lancet Oncol* 2007; **8:** 226–34.

102 Khushalani NI, Leichman CG, Proulx G, et al. Oxaliplatin in combination with protracted-infusion fluorouracil and radiation: report of a clinical trial for patients with esophageal cancer. *J Clin Oncol* 2002; **20:** 2844–50.

103 Armanios M, Xu R, Forastiere AA, Haller DG, Kugler JW, Benson AB 3rd, and the Eastern Cooperative Oncology Group. Adjuvant chemotherapy for resected adenocarcinoma of the esophagus, gastro-esophageal junction, and cardia: phase II trial (E8296) of the Eastern Cooperative Oncology Group. *J Clin Oncol* 2004; **22:** 4495–99.

104 Ando N, Iizuka T, Kakegawa T, et al. A randomized trial of surgery with and without chemotherapy for localized squamous carcinoma of the thoracic esophagus: the Japan Clinical Oncology Group Study. *J Thorac Cardiovasc Surg* 1997; **114:** 205–09.

105 Ando N, Iizuka T, Ide H, et al, and the Japan Clinical Oncology Group. Surgery plus chemotherapy compared with surgery alone for localized squamous cell carcinoma of the thoracic esophagus: a Japan Clinical Oncology Group Study—JCOG9204. *J Clin Oncol* 2003; **21:** 4592–96.

106 Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001; **345:** 725–30.

107 Kleinberg L, Gibson MK, Forastiere AA. Chemoradiotherapy for localized esophageal cancer: regimen selection and molecular mechanisms of radiosensitization. *Nat Clin Pract Oncol* 2007; **4:** 282–94.

108 Herskovic A, Martz K, al-Sarraf M, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *N Engl J Med* 1992; **326:** 1593–98.

109 Cooper JS, Guo MD, Herskovic A, et al, and the Radiation Therapy Oncology Group. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). *JAMA* 1999; **281:** 1623–27.

110 Stahl M, Stuschke M, Lehmann N, et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. *J Clin Oncol* 2005; **23:** 2310–17.

111 Homs MY, v d Gaast A, Siersema PD, Steyerberg EW, Kuipers EJ. Chemotherapy for metastatic carcinoma of the esophagus and gastro-esophageal junction. *Cochrane Database Syst Rev* 2006; **4:** CD004063.

112 Enzinger PC, Ilson DH. Irinotecan in esophageal cancer. *Oncology (Williston Park)* 2000; **14** (suppl 14)**:** 26–30.

113 Enzinger PC, Ilson DH, Kelsen DP. Chemotherapy in esophageal cancer. *Semin Oncol* 1999; **26** (suppl 15)**:** 12–20.

114 Enzinger PC, Ilson DH, Saltz LB, O'Reilly EM, Kelsen DP. Irinotecan and cisplatin in upper gastrointestinal malignancies. *Oncology (Williston Park)* 1998; **12** (suppl 6)**:** 110–13.

115 Van Cutsem E, Moiseyenko VM, Tjulandin S, et al, and the V325 Study Group. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol* 2006; **24:** 4991–97.

116 Cunningham D, Starling N, Rao S, et al, and the Upper Gastrointestinal Clinical Studies Group of the National Cancer Research Institute of the United Kingdom. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med* 2008; **358:** 36–46.

117 van Meerten E, Eskens FA, van Gameren EC, Doorn L, van der Gaast A. First-line treatment with oxaliplatin and capecitabine in patients with advanced or metastatic oesophageal cancer: a phase II study. *Br J Cancer* 2007; **96:** 1348–52.

118 Shah MA, Ramanathan RK, Ilson DH, et al. Multicenter phase II study of irinotecan, cisplatin, and bevacizumab in patients with metastatic gastric or gastroesophageal junction adenocarcinoma. *J Clin Oncol* 2006; **24:** 5201–06.

119 Overholt BF, Wang KK, Burdick JS, et al, and the International Photodynamic Group for High-Grade Dysplasia in Barrett's Esophagus. Five-year efficacy and safety of photodynamic therapy with Photofrin in Barrett's high-grade dysplasia. *Gastrointest Endosc* 2007; **66:** 460–68.

120 Shaheen NJ, Sharma P, Overholt BF, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. *N Engl J Med* 2009; **360:** 2277–88.

121 Ell C, May A, Pech O, et al. Curative endoscopic resection of early esophageal adenocarcinomas (Barrett's cancer). *Gastrointest Endosc* 2007; **65:** 3–10.

122 Altorki NK, Lee PC, Liss Y, et al. Multifocal neoplasia and nodal metastases in T1 esophageal carcinoma: implications for endoscopic treatment. *Ann Surg* 2008; **247:** 434–39.

123 Rees JR, Lao-Sirieix P, Wong A, Fitzgerald RC. Treatment for Barrett's oesophagus. *Cochrane Database Syst Rev* 2010; **1:** CD004060.

124 Christie NA, Patel AN, Landreneau RJ. Esophageal palliation—photodynamic therapy/stents/brachytherapy. *Surg Clin North Am* 2005; **85:** 569–82.

125 Christie NA, Buenaventura PO, Fernando HC, et al. Results of expandable metal stents for malignant esophageal obstruction in 100 patients: short-term and long-term follow-up. *Ann Thorac Surg* 2001; **71:** 1797–801; discussion 1801–02.

126 Litle VR, Luketich JD, Christie NA, et al. Photodynamic therapy as palliation for esophageal cancer: experience in 215 patients. *Ann Thorac Surg* 2003; **76:** 1687–92; discussion 1692–93.

127 Lightdale CJ, Heier SK, Marcon NE, et al. Photodynamic therapy with porfimer sodium versus thermal ablation therapy with Nd:YAG laser for palliation of esophageal cancer: a multicenter randomized trial. *Gastrointest Endosc* 1995; **42:** 507–12.

128 Muñoz N, Wahrendorf J, Bang LJ, et al. No effect of riboflavine, retinol, and zinc on prevalence of precancerous lesions of oesophagus. Randomised double-blind intervention study in high-risk population of China. *Lancet* 1985; **2:** 111–14.

129 Blot WJ, Li JY, Taylor PR, et al. Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. *J Natl Cancer Inst* 1993; **85:** 1483–92.

130 Stoner GD, Wang LS, Zikri N, et al. Cancer prevention with freeze-dried berries and berry components. *Semin Cancer Biol* 2007; **17:** 403–10.

131 Limburg PJ, Wei W, Ahnen DJ, et al. Randomized, placebo-controlled, esophageal squamous cell cancer chemoprevention trial of selenomethionine and celecoxib. *Gastroenterology* 2005; **129:** 863–73.

132 Vaughan TL, Dong LM, Blount PL, et al. Non-steroidal anti-inflammatory drugs and risk of neoplastic progression in Barrett's oesophagus: a prospective study. *Lancet Oncol* 2005; **6:** 945–52.

133 Heath EI, Canto MI, Piantadosi S, et al, and the Chemoprevention for Barrett's Esophagus Trial Research Group. Secondary chemoprevention of Barrett's esophagus with celecoxib: results of a randomized trial. *J Natl Cancer Inst* 2007; **99:** 545–57.

134 Das D, Chilton AP, Jankowski JA. Chemoprevention of oesophageal cancer and the AspECT trial. *Recent Results Cancer Res* 2009; **181:** 161–69.

135 Kahrilas PJ. Gastroesophageal reflux disease. *JAMA* 1996; **276:** 983–88.

136 Wang KK, Sampliner RE, and the Practice Parameters Committee of the American College of Gastroenterology. Updated guidelines 2008 for the diagnosis, surveillance and therapy of Barrett's esophagus. *Am J Gastroenterol* 2008; **103:** 788–97.

137 Watson A, Heading RC, Shepherd NA. Guidelines for the diagnosis and management of Barrett's columnar-lined oesophagus. A report of the Working Party of the British Society of Gastroenterology. London: British Society of Gastroenterology, 2005.

138 Jankowski J, Barr H. Improving surveillance for Barrett's oesophagus: AspECT and BOSS trials provide an evidence base. *BMJ* 2006; **332:** 1512.

139 Parrilla P, Martínez de Haro LF, Ortiz A, et al. Long-term results of a randomized prospective study comparing medical and surgical treatment of Barrett's esophagus. *Ann Surg* 2003; **237:** 291–98.

140 Corey KE, Schmitz SM, Shaheen NJ. Does a surgical antireflux procedure decrease the incidence of esophageal adenocarcinoma in Barrett's esophagus? A meta-analysis. *Am J Gastroenterol* 2003; **98:** 2390–94.

141 Abela JE, Going JJ, Mackenzie JF, McKernan M, O'Mahoney S, Stuart RC. Systematic four-quadrant biopsy detects Barrett's dysplasia in more patients than nonsystematic biopsy. *Am J Gastroenterol* 2008; **103:** 850–55.

142 Wolfsen HC, Crook JE, Krishna M, et al. Prospective, controlled tandem endoscopy study of narrow band imaging for dysplasia detection in Barrett's esophagus. *Gastroenterology* 2008; **135:** 24–31.