Oesophageal cancer

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Oesophageal cancer is a clinically challenging disease that requires a multidisciplinary approach. Extensive treatment might be associated with a considerable decline in health-related quality of life and yet still a poor prognosis. In recent decades, prognosis has gradually improved in many countries. Endoscopic procedures have increasingly been used in the treatment of premalignant and early oesophageal tumours. Neoadjuvant therapy with chemotherapy or chemoradiotherapy has supplemented surgery as standard treatment of locally advanced oesophageal cancer. Surgery has become more standardised and centralised. Several therapeutic alternatives are available for palliative treatment. This Seminar aims to provide insights into the current clinical management, ongoing controversies, and future needs in oesophageal cancer.

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Introduction

Oesophageal cancer is the ninth most common cancer and the sixth most common cause of cancer death globally.[1] This cancer is associated with extensive treatment requirements, a considerable decline in health-related quality of life (HRQoL), and poor prognosis. Curative treatment typically includes chemotherapy or chemoradiotherapy followed by extensive surgery, often resulting in morbidity and persistent reductions in HRQoL.[2] However, recent developments have improved prognosis and survivorship.

Clinical presentation, signs, and symptoms

Most patients seek medical attention following a period of progressive dysphagia and involuntary weight loss. Older men (aged ≥60 years) are over-represented in both main histological types—ie, oesophageal squamous cell carcinoma and oesophageal adenocarcinoma. The mean male to female ratio is 3:1 for oesophageal squamous cell carcinoma and 6:1 for oesophageal adenocarcinoma, although this ratio varies considerably across geographical regions.[3,4] Many patients with oesophageal squamous cell carcinoma have a history of heavy tobacco and alcohol use, and patients with oesophageal adenocarcinoma are more likely to be obese than those with squamous cell carcinoma, and are more likely to have chronic gastro-oesophageal reflux disease.

Incidence and prognosis

Globally, oesophageal squamous cell carcinoma is the most common histological subtype of oesophageal cancer, particularly in high-incidence areas of eastern Asia and in eastern and southern Africa.[1,5,6] In the highest-risk region (the so-called oesophageal cancer belt) from northern Iran through Central Asia to north-central China, approximately 90% of patients with oesophageal cancer have oesophageal squamous cell carcinomas.[1,5,6] Although the incidence of oesophageal squamous cell carcinoma has decreased in many regions, a marked increase in the incidence of oesophageal adenocarcinoma has been observed in Europe, North America, and Australia during the past four decades, which appears to be sustained.[7] Thus, the incidence of oesophageal adenocarcinoma has surpassed that of oesophageal squamous cell carcinoma in many western countries.

The prognosis of oesophageal cancer varies between geographical areas, but population-based studies have shown an improvement in the overall 5-year survival from less than 5% in the 1960s to about 20% in the past decade in some European countries, the USA, and China.[8–10] Prognostic factors include tumour stage, tumour subsite and histology, patients' performance status and comorbidities, and HRQoL.[8,11]

Pathophysiology, risk factors, and prevention

Squamous cell carcinoma

The pathophysiological pathway of oesophageal squamous cell carcinoma is typically initiated by carcinogenic compounds in direct contact with the oesophageal mucosa. Mechanical injury (eg, from achalasia, radiation therapy, or from swallowing hot beverages or sodium hydroxide) increases susceptibility to carcinogenic compounds. The main risk factors for oesophageal squamous cell carcinoma are tobacco smoking (including swallowed toxins from cigarette smoke) and alcohol overconsumption, particularly when in combination.[12] Among dietary factors, fruit and vegetable intake is protective,[13] whereas intake of red meat[14] and the consumption of very hot beverages are risk factors.[15] Genetic factors are also involved; a pooled analysis[16] of three genome-wide association studies found new susceptibility loci for oesophageal squamous cell carcinoma. Tobacco smoking cessation is probably the single most effective primary preventive measure.[17]

Search strategy and selection criteria

We searched PubMed, Cochrane Library, MEDLINE, and Embase databases for publications in English using the search terms "(o)esophageal" or "(o)esophagus" in combination with the terms "cancer" or "neoplasm" or "adenocarcinoma" or "squamous cell carcinoma". We largely selected publications from the past 5 years. Review articles and book chapters are cited to provide readers with more details and more references than this Seminar has room for.

	Oesophageal squamous cell carcinoma	Oesophageal adenocarcinoma
Receptor tyrosine kinases		
*ERBB2**	3%	32%
*EGFR**	19%	15%
*VEGFA**	3%	28%
*KRAS**	7%	14%
*PIK3CA**	13%	3%
*FGFR1**	12%	4%
Cell cycle regulators		
CDKN2A†	76%	76%
*CCND1**	57%	15%
*CDK6**	16%	14%
*CCNE1**	4%	14%
RB†	9%	0%
Proliferation and differentiation		
*MYC**	23%	32%
SMAD4†	8%	24%
*GATA4**	1%	19%
*GATA6**	3%	21%
TP63 or *SOX2**	48%	11%
Chromatin remodelling		
KDM6A†	19%	4%
KMT2D†	14%	1%

*Gene dysregulation causes signalling pathway activation. †Gene dysregulation causes signalling pathway inactivation. Dysregulation might occur via amplification, deletion, mutation, or epigenetic modulation.

***Table 1*: Alteration frequencies of dysregulated genes in oesophageal squamous cell carcinoma and oesophageal adenocarcinoma[25]**

Adenocarcinoma

The main pathophysiological pathway of oesophageal adenocarcinoma is likely to be chronic gastro-oesophageal reflux disease (reflux), causing metaplasia from the native squamous cell mucosa to a specialised columnar epithelium, known as Barrett's oesophagus.[18] This condition can progress to low-grade dysplasia, high-grade dysplasia, and invasive oesophageal adenocarcinoma.[18] The main risk factors for oesophageal adenocarcinoma are reflux, obesity, and male sex, while *Helicobacter pylori* infection and dietary intake of fruit and vegetables, and possibly also non-steroidal anti-inflammatory drugs, are protective.[19] The increasing prevalence of reflux and obesity, combined with a decreasing prevalence of *Helicobacter pylori* infection, probably contributes to the increasing incidence of oesophageal adenocarcinoma.[19] Research has now identified risk loci for Barrett's oesophagus-associated carcinogenesis.[20–23] These findings could aid research examining tailored prevention in individuals at high risk of oesophageal adenocarcinoma. Scientific evidence to support specific preventive measures in oesophageal adenocarcinoma is scarce,[24] but aspirin and antireflux therapy are being investigated in a randomised controlled trial of patients with Barrett's oesophagus (AspECT).

Genetics

Developments in high-throughput genomic technologies have led to improved understanding of the molecular underpinnings of oesophageal squamous cell carcinoma and oesophageal adenocarcinoma. The Global Cancer Genome Atlas project characterised 164 oesophageal cancers using multiple platforms, and oesophageal squamous cell carcinoma and oesophageal adenocarcinoma had distinct profiles in copy number alterations, methylation patterns, and RNA and microRNA expression (table 1).[25] In particular, oesophageal squamous cell carcinoma was associated with a pattern of C→A substitutions, over-represented in tobacco smokers, and further comprehensive molecular characterisation suggested that oesophageal squamous cell carcinoma is more similar to squamous cell carcinoma of the head and neck than to oesophageal adenocarcinoma. Similarly, oesophageal adenocarcinoma had copy number, RNA, and methylation patterns more similar to the chromosomally unstable subtype of gastric adenocarcinoma than to oesophageal squamous cell carcinoma. The results of this study support the results from risk factor studies[26] that indicate oesophageal squamous cell carcinoma and oesophageal adenocarcinoma should be considered as different disease entities, because the genomic, transcriptomic, and epigenetic changes identified in each cancer reflect divergent aetiologies and tissues of origin.[25]

The most commonly mutated genes in oesophageal squamous cell carcinoma are *TP53*, *NFE2L2*, *MLL2*, *ZNF750*, *NOTCH1*, and *TGFBR2*, and *TP53*, *CDKN2A*, *ARID1A*, *SMAD4*, and *ERBB2* for oesophageal adenocarcinoma. Copy number changes also differ; for oesophageal squamous cell carcinoma the most commonly identified copy number alterations occur in *SOX2*, *TERT*, *FGFR1*, and *MDM1*, with common deletions of *RB1*, whereas in oesophageal adenocarcinoma amplification of *ERBB2*, *VEGFA*, *GATA6*, and *CCNE1*, and deletion of *SMAD4* are more common.[25] Combined pathway analysis[25] suggests that oesophageal squamous cell carcinoma and oesophageal adenocarcinoma have frequent alterations of cell cycle regulators, such as *CCND1*, *CCNE1*, *CDK6*, or *RB1*, via distinct mechanisms. This analysis suggests that cell-cycle-related tyrosine kinase inhibitors could be a therapeutic strategy. However, by contrast with gastric adenocarcinoma, no microsatellite instability or Epstein-Barr-driven cancers were found in patients with oesophageal cancer who were included in the Global Cancer Genome Atlas cohort.[25]

Oesophageal adenocarcinoma has also been characterised into three distinct subgroups using whole genome sequencing of 129 samples.[27] These subtypes were characterised by defects in homologous recombination

repair, a T→G mutation pattern with a high mutational load or a C→A or T mutation pattern associated with an ageing imprint. Each of these subtypes might have differential sensitivity to targeted therapy—eg, poly(ADP-ribose) polymerase inhibitors for homologous recombination repair and immunotherapy for high mutational burden. However, these findings require clinical validation.[27]

Diagnostic investigations

Diagnosis

The presence of oesophageal cancer is determined by endoscopy (figure 1) with biopsies for histopathological confirmation. Endoscopy also provides information about the tumour sublocation and local extent, and the presence and extent of Barrett's oesophagus. After the diagnosis is established, CT of the neck, chest, and abdomen to assess distant metastasis will guide whether treatment will follow a curative or palliative route.

Operability

Treatment recommendations are dependent on tumour stage and the general health of a patient. Tumour stage is based on the Union for International Cancer Control's tumour, node, and metastasis classification. In the present eighth edition of the classification,[28] clinical, pathological, and postneoadjuvant pathological staging have been separated, and the pT1 category (tumours involving the mucosa or submucosa) has been separated into pT1a (only involving the mucosa) and pT1b (involving the submucosa). Tumours with an epicentre located more than 2 cm below the oesophagogastric junction (Siewert type III) are classified as gastric cancers, even if they involve the oesophagus. The Siewert classification[29] is widely used to categorise tumours near the oesophagogastric junction. Tumours with an epicentre located 1–5 cm above this junction are categorised as type I, tumours within 1 cm above and 2 cm below this junction as type II, and tumours 2–5 cm below the junction are type III cancers.[29] In early lesions, endoscopic mucosal resection provides a good specimen for histopathological assessment. Staging measures for more advanced tumours include PET-CT and endoscopic ultrasound.[30,31] Laparoscopy is indicated if abdominal tumour spread is suspected, and bronchoscopy is indicated if tumour overgrowth on bronchi is suspected.[30,32] Laparoscopy can also identify tumoural extension on the gastric part of the tumour for junctional adenocarcinomas, identify comorbidities (eg, cirrhosis), and be used for placement of a feeding tube if required.

Little evidence is available about the evaluation of physical fitness when considering treatment recommendations. However, age, comorbidities, cardiopulmonary capacity, and nutritional status should be considered before consideration of extensive surgery, and patients should be assessed by an experienced anaesthetist.[33] Consultation of cardiologists and dietitians, and a treadmill test and spirometry can provide valuable information.[34,35] For older patients (aged >75 years), oncogeriatric assessment might be helpful before initiating therapy. HRQoL measures can predict the general health of patients and prognosis.[11,36,37] An ongoing randomised controlled trial[38] is assessing the effect of prehabilitation (including physical, nutritional, and psychological care) of patients before curative treatment.

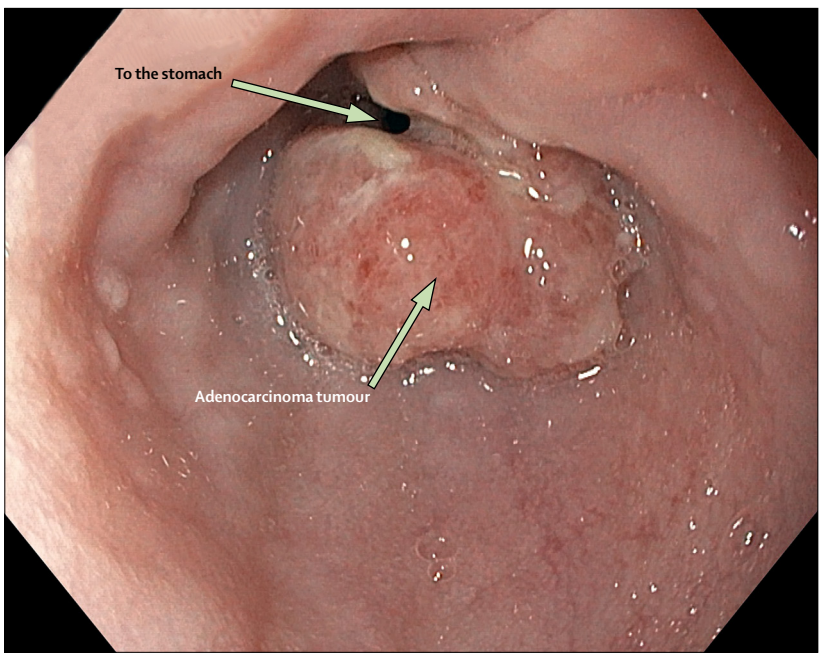

Figure 1: **Endoscopic photograph of an adenocarcinoma partly obstructing the distal oesophagus**

Treatment recommendations

Multidisciplinary assessment and determination of a treatment plan has been shown to improve clinical decision making in oesophageal cancer and should be mandatory.[39–41] Ideally, the multidisciplinary team should have expertise in pathology, radiology, endoscopy, medical oncology, radiotherapy, surgery, nursing, dietetics, and other relevant specialists as needed (eg, laryngologists, physiotherapists, and social workers).[42] Treatment plans depend on clinical tumour stage, subsite, and histology of the tumour, performance status, and comorbidity. Multidisciplinary team meetings provide an opportunity to follow up treatment results and to discuss recruitment of patients for research studies.

Curative treatment

Endoscopic treatment

Endoscopic techniques, mainly radiofrequency ablation, endoscopic mucosal resection, and endoscopic submucosal dissection, are increasingly used for the prevention and curative treatment of early oesophageal lesions.[43,44] Most research has examined Barrett's oesophagus and early oesophageal adenocarcinoma, but some studies[45,46] also support ablation therapies in early

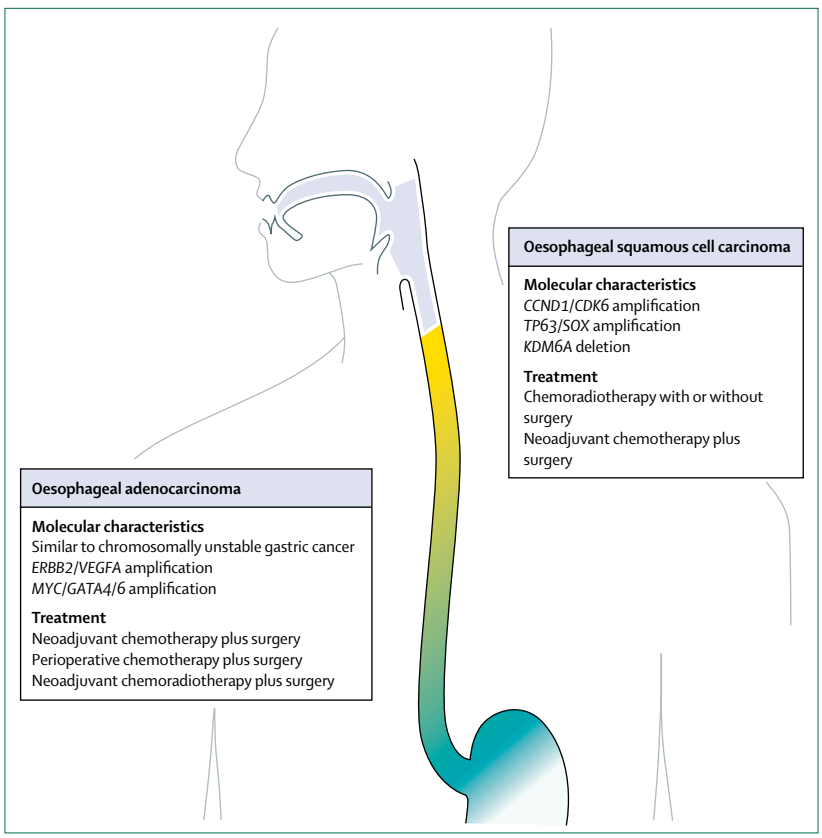

Figure 2: **Molecular characteristics and treatment recommendations for locally advanced oesophageal adenocarcinoma and squamous cell carcinoma**

oesophageal squamous cell carcinomas. Endoscopic mucosal resection combined with radiofrequency ablation can successfully prevent cancer progression in patients with high-grade dysplasia, and are increasingly also used in patients with low-grade dysplasia, even if multifocal.[47–50] Endoscopic removal for the small proportion of patients with early (T1) oesophageal cancer has increased during the past few years.[43] Superficial oesophageal cancer can be successfully removed by endoscopic submucosal dissection in 90% (95% CI 87–93%) of patients; the main complication is a 5% (3–8%) risk of stenosis, which can be managed with endoscopic dilatation.[51] Compared with endoscopic mucosal resection, endoscopic submucosal dissection offers a higher rate of complete resection of early cancer (92·7% *vs* 52·7%) and a lower rate of local tumour recurrence (0·3% *vs* 11·5%).[52] These organ-sparing procedures offer substantial HRQoL benefits compared with oesophagectomy, and clinical guidelines recommend endoscopic mucosal resection or endoscopic submucosal dissection rather than surgery for T1a oesophageal adenocarcinoma in specialised centres.[39] However, a 5% risk of lymph node metastasis exists in intramucosal (T1a) cancer and a 17% risk in submucosal cancer (T1b).[43] Moreover, endoscopic therapy is associated with an increased risk of local tumour recurrence compared with surgery.[53] Thus, in patients with superficial submucosal infiltration (T1b) oesophagectomy optimises the prognosis, whereas in patients unfit for surgery or definite chemoradiotherapy, endoscopic resection is a good alternative. The learning curve associated with these therapies indicates the need for centralisation.[54]

Oncological treatment

In patients with locally advanced (T3–T4 [tumour invading the adventitia or adjacent structures] or cN1–N3 [lymph node metastasis according to clinical evaluation]) oesophageal cancer, chemotherapy or chemoradiotherapy plus surgery is required in addition to surgery; the differential sensitivity of oesophageal squamous cell carcinoma and oesophageal adenocarcinoma to radiotherapy leads some centres to vary in treatment approaches across these histological subtypes (figure 2; table 2). Meta-analysis[62] of 24 randomised trials suggests that both neoadjuvant chemotherapy and chemoradiotherapy improve overall survival for patients with operable oesophageal cancer (hazard ratio [HR] for chemotherapy 0·87, 95% CI 0·79–0·96; HR for chemoradiotherapy 0·78, 0·70–0·88). Neoadjuvant oncological treatment for early tumours not suitable for local ablation is less well defined. One randomised clinical trial[63] found no difference between stage I and stage II tumours treated with neoadjuvant cisplatin and fluorouracil chemoradiotherapy (45 Gy in 25 fractions) compared with surgery alone. Therefore, patients with ≤T2N0 tumours are recommended to proceed directly to surgery, although reliably identifying these patients with pre-operative investigations can be challenging. For all patients undergoing neoadjuvant treatment, restaging is recommended before oesophagectomy.[39] Nutritional assessment is recommended as malnutrition is common, and if enteral feeding is required, jejunostomy placement is preferable to stenting for resectable cancer.[39,64]

Squamous cell carcinoma

In a randomised controlled trial (OE02),[55] 247 (of 802) patients with oesophageal squamous cell carcinoma were randomised to surgery alone or neoadjuvant chemotherapy with two cycles of chemotherapy with cisplatin (80 mg/m²×96 h) and fluorouracil (1000 mg/m²×96 h) followed by surgery. Long-term follow-up showed an overall survival benefit for patients with oesophageal squamous cell carcinoma treated with chemotherapy (HR 0·86, 95% CI 0·71–1·05).[56] A 2012 randomised controlled trial (CROSS)[60] evaluated a regimen of weekly chemotherapy (carboplatin with an area under the curve of 2 mg/mL per min and 50 mg/m² paclitaxel) for 5 weeks in conjunction with concurrent radiotherapy (41·4 Gy in 23 fractions 5 days a week). In 84 patients with oesophageal squamous cell carcinoma, those treated with surgery alone had a median survival of 21·1 months compared with 81·6 months in the chemoradiotherapy group (HR 0·48, 95% CI 0·28–0·83).[61] These results have led to

	Number of patients	Tumour histology	Treatment	Survival*	Hazard ratio (95% CI)	Median survival time (months)	Hazard ratio (95% CI)
Neoadjuvant chemotherapy							
OE02[55,56]	802	Squamous cell carcinoma (n=247), adenocarcinoma (n=533), undifferentiated or unknown (n=22)	Surgery (control) Neoadjuvant chemotherapy	17% 23%	..	Not reported Not reported	0·83 (0·70–0·98)
Perioperative chemotherapy							
MAGIC[57]	503	Adenocarcinoma (n=503); lower oesophageal or junctional adenocarcinoma (n=131), gastric adenocarcinoma (n=372)	Surgery (control) Perioperative chemotherapy	23% 36%	..	Not reported Not reported	0·75 (0·60–0·93)
FNCLCC-FFCD[58]	224	Adenocarcinoma (n=224); lower oesophagus or junctional adenocarcinoma (n=169); gastric adenocarcinoma (n=55)	Surgery (control) Perioperative chemotherapy	24% 38%	..	Not reported Not reported	0·69 (0·50–0·95)
FLOT-4[59]	716	Adenocarcinoma (n=716)	Epirubicin, cisplatin, and capectabine (control) FLOT	48%† 57%†	..	37 50	0·77 (0·63–0·94)
Pre-operative chemoradiotherapy							
CROSS[60,61]	366	Squamous cell carcinoma (n=84), adenocarcinoma (n=275), large-cell undifferentiated carcinoma (n=7)	Surgery (control) Neoadjuvant chemoradiotherapy	33% 47%	0·67 (0·51–0·87)	24 49	0·68 (0·53–0·88)

FLOT=fluorouracil, leucovorin, oxaliplatin, and docetaxel. *Refers to 5-year survival, unless specified otherwise. †3-year survival.

***Table 2*: Randomised clinical trials of adjunctive therapy for operable oesophageal cancer**

the adoption of the CROSS regimen as standard of care for many patients with oesophageal squamous cell carcinoma undergoing oesophagectomy. However, oesophageal squamous cell carcinoma might not always require surgery: several randomised controlled trials[65,66] have found similar survival when comparing definitive chemoradiotherapy with neoadjuvant chemoradiotherapy and surgery, especially in patients with a response to chemoradiotherapy. However, no trial results directly compare the watch-and-wait surgical approach with immediate surgery, and research in this area is ongoing. Because local recurrence rates are higher with a non-surgical approach, close surveillance and salvage surgery, when indicated, are recommended as these approaches might result in survival rates similar to that of planned chemoradiation and oesophagectomy.[67]

Adenocarcinoma

Oesophageal adenocarcinomas are less radiosensitive than oesophageal squamous cell carcinomas and all patients who are operable with oesophageal adenocarcinoma that is potentially curable should be considered for neoadjuvant chemotherapy or chemoradiotherapy followed by surgery. Standard chemotherapy is platinum-fluoropyrimidine based, which improved survival in three randomised controlled trials (OE02, MAGIC, and FNCLCC/FFCD).[55–58] In the OE02 trial,[56] 802 patients with oesophageal cancer (533 with oesophageal adenocarcinoma) were randomly assigned to two cycles of chemotherapy with cisplatin and fluorouracil plus surgery or surgery alone, showing a 5% increase in 5-year survival for patients with oesophageal adenocarcinoma treated with chemotherapy. Another randomised controlled trial (OE05)[68] compared two cycles of neoadjuvant cisplatin and fluorouracil with four cycles of epirubicin, cisplatin, and capecitabine for resectable oesophageal adenocarcinoma, and although more intensive chemotherapy was associated with an improved pathological tumour response, overall survival was similar. Therefore, whenever neoadjuvant chemotherapy alone is preferred, doublet chemotherapy is recommended.

Perioperative chemotherapy is an alternative treatment approach for oesophageal adenocarcinoma. In two randomised controlled trials (FNCLCC/FFCD,[58] which included 58 [75%] patients with oesophageal adenocarcinoma and MAGIC,[57] which included 164 [26%] patients with oesophageal adenocarcinoma) patients were randomly assigned to perioperative cisplatin plus fluorouracil or epirubicin plus cisplatin and fluorouracil regimens, respectively, and both trials reported a 13–14% improvement in 5-year survival. Results from the 2017 AIO-FLOT4 trial have been presented,[59] which suggest a substantial improvement in 3-year survival with perioperative FLOT (fluorouracil, leucovorin, oxaliplatin, and docetaxel) chemotherapy compared with ECF (epirubicin, cisplatin, and fluorouracil) or ECX (epirubicin, cisplatin, and capecitabine) regimens; thus, this might become a new standard of care. Postoperative chemotherapy was a component in these trials, and patients with adequate performance status following surgery should therefore also be treated in the adjuvant setting. Perioperative chemotherapy might enable patients who have derived the most benefit from chemotherapy to be treated in the neoadjuvant setting with further treatment following surgery. Metabolic imaging using a reduction in 18F-fluorodeoxyglucose uptake in the primary tumour with PET after one cycle of chemotherapy is predictive of overall survival in patients

with resectable oesophageal or junctional adenocarcinoma.[69–71] Although promising, evaluation of chemotherapy response using metabolic imaging, such as PET, requires validation in larger studies and is not recommended as standard practice.

Neoadjuvant chemoradiotherapy might also be considered for patients with oesophageal adenocarcinoma.[61,72] In the CROSS trial,[61] 275 of 368 patients had oesophageal adenocarcinoma and were randomly assigned to chemoradiotherapy followed by surgery or to surgery alone. Overall survival was improved in the chemoradiotherapy group (HR 0·73, 95% CI 0·55—0·98), although the magnitude of this benefit was less than that achieved for oesophageal squamous cell carcinoma and following adjustment the difference in survival for oesophageal adenocarcinoma was not statistically significant.[61] However, no significant interactions between treatment effect and histological subgroup were identified.[61] Neoadjuvant chemoradiotherapy should be restricted to patients with characteristics similar to those in the CROSS trial[60,61]—ie, ≤T3 tumours (no extension beyond the oesophageal wall) that are less than 5 cm in width and less than 8 cm in length. Alternative chemoradiotherapy regimens include cisplatin and oxaliplatin plus fluoropyrimidines.[73] No data are available that directly compare neoadjuvant chemoradiotherapy with neoadjuvant or perioperative chemotherapy, but the consensus is that both are valuable options, however, significant toxicities (≥grade 3), such as neutropenia and nausea, are less common with CROSS-type chemoradiotherapy.[57,74] Induction chemotherapy followed by chemoradiotherapy has not improved survival in several small trials[75,76] and therefore remains an investigational approach. Randomised trials comparing neoadjuvant chemotherapy with chemoradiotherapy are currently ongoing (ClinicalTrials.gov NCT01726452 and NCT02509286).

Definitive chemoradiotherapy

Chemoradiotherapy is superior to radiotherapy for patients with oesophageal squamous cell carcinoma or oesophageal adenocarcinoma who are not surgical candidates, including patients with cervical oesophageal tumours. The most frequently used definitive chemoradiotherapy regimen is cisplatin (75 mg/m²), fluororacil (1000 mg/m² infusion daily for 4 days), plus radiotherapy (50 Gy). In an randomised controlled trial,[77] patients treated with this chemoradiotherapy regimen had a median survival of 12·5 months compared with 8·9 months for those treated with 64 Gy radiotherapy alone. Oxaliplatin-based definitive chemoradiotherapy is associated with comparable survival to cisplatin-based treatment, but with a different toxicity spectrum.[73] Therefore, oxaliplatin or cisplatin are both evidence-based treatment choices in combination with radiotherapy in this setting. Notably, the radiation dose in CROSS (41·4 Gy) is less than the standard radiation dose used in definitive chemoradiotherapy regimens. Intensification of radiotherapy to higher than standard doses did not improve local control or survival in one randomised controlled trial (INT0123),[78] and no data from randomised controlled trials support the use of brachytherapy in this setting. However, intensification of radiotherapy dosing remains an area of active research as does the development of a watch-and-wait strategy following chemoradiotherapy for both oesophageal adenocarcinoma and oesophageal squamous cell carcinoma (ClinicalTrials.gov, NCT02741856, NCT01348217, NTR4834, and NCT02551458; and ISRCTN01483375[79]).

Surgical treatment

Surgery remains a single modality treatment for early tumour stages, and for cT2N0 (tumour invading the muscularis propria without lymph node metastasis) and T1a and T1b tumours after non-radical or failed endoscopic mucosal resection, or endoscopic submucosal dissection,[63] but is combined with neoadjuvant therapy for locally advanced oesophageal cancer.[80] Oesophagectomy typically includes the removal of most of the oesophagus together with the cardia and lesser curve of the stomach (figure 3). Some issues associated with oesophagectomy deserve special attention.

Surgical approach

Tumour-free resection margins are prognostically important.[81,82] These margins can be accomplished with alternative approaches, including right-sided or left-sided thoraco-abdominal or transhiatal approaches using open or minimally invasive techniques.[32,83] Earlier studies[84] that investigated minimally invasive surgery showed a high risk of complications, possibly associated with learning curve issues, whereas a 2016 study[85] showed accelerated recovery, which has prompted its increased use.[84,85] Ongoing randomised controlled trials are comparing postoperative outcomes following minimally invasive procedures and open surgery, in which HRQoL is a key outcome (ClinicalTrials.gov NCT01544790 and NTRTC2452; and ISRCTN59036820[86]). Transhiatal and minimally invasive surgery seem to be associated with less pulmonary complications than thoracoabdominal approaches.[87,88] No major differences in survival have been found between any of the established approaches.[32,83,85,89,90] Standardisation of the surgical approach might be a more important prognostic factor than selecting one specific procedure over another.[91] Alternatively, if the surgeon has sufficient experience of various surgical approaches, the approach can be tailored depending on tumour and patient characteristics. However, for surgeons the learning curve associated with the adoption of new approaches should be considered.[92]

Hospital and surgeon volume

The number of oesophagectomies done at one hospital or by one surgeon annually influences short-term and long-term mortality.[93] High-volume hospitals had lower overall

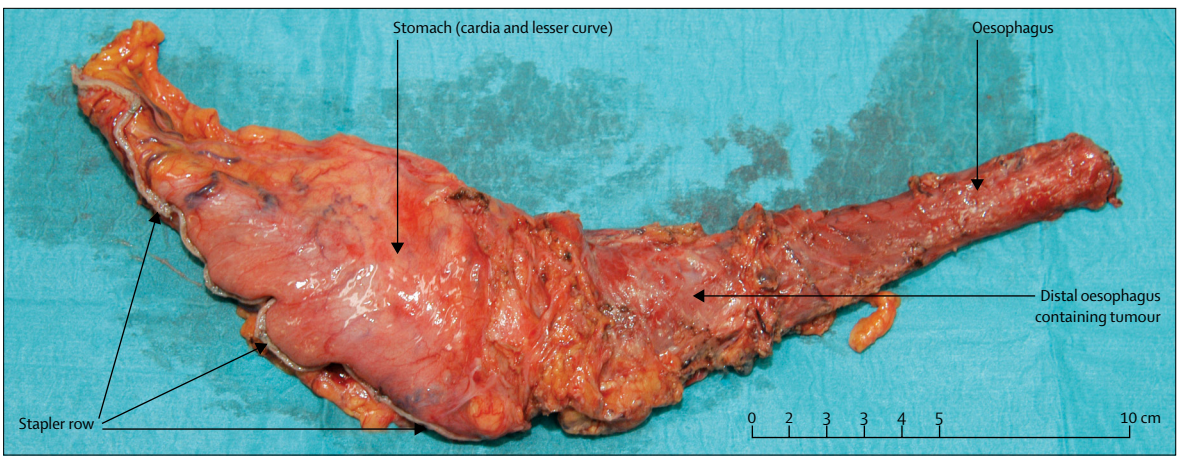

Figure 3: **An oesophageal adenocarcinoma specimen resected by oesophagectomy**

mortality compared with low-volume hospitals (HR 0·82, 95% CI 0·75–0·90). A cohort study[94] found that surgeon volume was a stronger prognostic factor than hospital volume after mutual adjustment. Even when experienced surgeons begin doing oesophagectomies they have a learning curve before the survival outcome for their patients is stabilised.[92] Taken together, available scientific evidence supports centralisation of oesophagectomy.

Lymphadenectomy

Research findings that advocate extensive lymphadenectomy[95] have been challenged in large cohort studies[96,97] showing no association between the number of resected nodes and survival after adjusting for surgeon volume. Data indicate that knowledge about location of lymph node metastasis allows for a tailored lymphadenectomy with good sampling for tumour staging and possibly better outcomes.[98,99] Moreover, extensive lymphadenectomy does not seem to have any adverse effect on patients' postoperative HRQoL.[100] Taken together, evidence indicates that a moderate and tailored lymphadenectomy providing a sufficient assessment of the pathological tumour stage is adequate.

Survivorship

Patients who have had oesophagectomy often have specific survivorship issues, including decreased HRQoL, eating difficulties and malnutrition, and poor long-term survival. A 2014 meta-analysis[101] showed long-lasting deterioration in several HRQoL aspects, including social functioning, role functioning, and increased symptoms of fatigue, pain, cough, dry mouth, and reflux. Additionally, patients often experience major social and emotional changes, and might have an increased risk of developing psychiatric disorders, which subsequently decreases survival.[102]

Some patient and tumour characteristics reduce postoperative HRQoL, including comorbidity, advanced tumour stage (III–IV), proximal tumour location, and oesophageal squamous cell carcinoma histology.[103] Neoadjuvant therapy has a negative influence on aspects of HRQoL during treatment, with the exception of dysphagia, which is usually relieved.[104,105] However, the HRQoL of most patients recovers before surgery,[106] and no difference has been observed in postoperative recovery between patients receiving neoadjuvant therapy and those undergoing surgery alone.[107] A 2015 multicentre study[108] found a detrimental effect of definitive chemoradiotherapy for localised oesophageal cancer on most HRQoL aspects, but many of these changes usually resolved within 6 months of treatment, and HRQoL recovery was faster than after oesophagectomy. Surgical technical factors, such as surgical approach, extent of lymphadenectomy, blood loss or operation length, seem to have little influence on postoperative HRQoL.[100,109,110] Early postoperative complications, however, have profound negative effects both in the short and long term.[111] A 2016 population-based cohort study[112] found that surgery can have a strong negative effect on several HRQoL measures—eg, reflux, dysphagia, and eating difficulties—up to 10 years after surgery (figure 4).

Weight loss and malnutrition, before, during, and after treatment, are major concerns in most patients with oesophageal cancer.[114] Surgical resection results in a loss of stomach reservoir and is associated with several functional and mechanical issues, and also malabsorption,[115] which contributes to eating difficulties and weight loss. Approximately two-thirds of patients lose more than 10% of their preoperative bodyweight and one in five patients lose over 20% of their preoperative weight within 6 months of oesophagectomy.[116] Nutritional deficiencies (eg, vitamin B and folate deficiency) might require vitamin or mineral supplementation. Patient counselling by a dietitian is recommended at the time of diagnosis for assessing the need for enteral nutrition during neoadjuvant therapy—eg, by supplying the patient with a jejunostomy. Additionally, some evidence

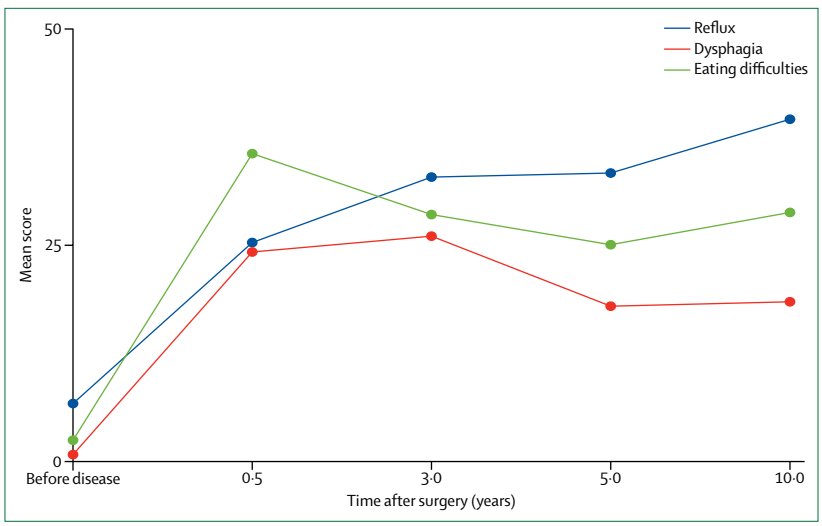

Figure 4: **Effect of surgery on reflux, dysphagia, and eating difficulties in patients with oesophageal cancer 10 years after treatment**

Data were retrieved from a nationwide Swedish cohort study[112] and symptoms were measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Oesophageal 18 (QLQ-OES18)[113] in patients who had surgery between 2001 and 2005. Mean scores range from 0 (no symptoms) to 100 (severe symptoms). Number of participants at each time point: before disease, 4910 randomly selected people in the Swedish population; 0·5 years, 402 patients; 3·0 years, 178 patients; 5·0 years, 141 patients; and 10·0 years, 92 patients.

from randomised controlled trials[117,118] shows shortened length of hospital stay and improved clinical outcomes when using jejunostomy in the postoperative period, including continued use at home.

Palliative treatment

Patient selection

Most patients diagnosed with oesophageal cancer are not eligible for curative therapy or will develop tumour recurrence despite curatively intended treatment.[56,60,61] Advanced tumour stage at diagnosis (eg, most T4 tumours [involving adjacent tissue surrounding the oesophagus] and M1 [tumour with distant metastasis]) indicates a requirement for palliative treatment. Little evidence exists about how to select patients for palliative regimen on the basis of other conditions, but selection should follow a balanced evaluation of the general health of the patient. Palliative therapy aims to control disease-related symptoms, preserve as good a HRQoL score as possible, and prolong survival. The median survival in patients with metastatic oesophageal cancer without treatment is less than 6 months.

Local treatment

Dysphagia is a predominant problem. Oesophageal stenting with self-expanding metallic stents usually offers rapid partial relief of dysphagia, and is superior to thermal and chemical ablative therapies, with regard to side-effects and need for repeat interventions.[119] Survival is not associated with whether or not the stent is covered.[120] Intraluminal brachytherapy might provide a slight survival benefit and better longer-term HRQoL compared with stenting.[119] The optimal treatment for dysphagia might be stenting plus brachytherapy.[119] A 2014 randomised controlled trial of 160 patients indicated a longer median survival if the stent was loaded with radioactive seeds (177 *vs* 147 days, p=0·0046).[121] However, if chemotherapy is planned it often provides relief of dysphagia, obviating the need for local treatment. Dysphagia might also be palliated by external radiotherapy.

Systemic treatment

Chemotherapy improves survival compared with best supportive care alone,[122] but the survival benefit is modest and must be weighed against the side-effects of chemotherapy. No randomised phase 3 trials associated with the palliative treatment of oesophageal squamous cell carcinoma have been done, and data are usually extrapolated from oesophageal adenocarcinoma studies. A thorough discussion with the patient and family should provide a realistic view of the expected advantages and disadvantages of chemotherapy. Patients with metastatic oesophageal cancer, who are eligible for clinical trials, with a good performance status (0–1) have a median survival with first-line chemotherapy of less than 1 year.[57,123,124] First-line chemotherapy usually includes platinum and a fluoropyrimidine, and the addition of a third drug might be considered for patients who are generally in good health. A non-inferiority randomised controlled trial (REAL-2)[125] showed equivalence of cisplatin and oxaliplatin, and similar outcomes for infused fluororuacil and capecitabine. Triplet combinations include epirubicin or docetaxel as a third drug, which might improve tumour response, but also increase toxicity.[57,123] In particular, the original docetaxel, cisplatin, and fluoruracil regimen is associated with high rates of neutropenia, and randomised controlled trials have evaluated modifications of this regimen to ameliorate this toxicity. Furthermore, the role of anthracylines in providing additional benefit has been challenged.[126,127] Patients with oesophageal adenocarcinoma should have their tumour tested for overexpression of the human epidermal growth factor receptor 2 (HER2) protein, and if a high level of HER2 expression is identified, the anti-HER2 monoclonal antibody trastuzumab could be used in conjunction with cisplatin–fluoropyrimidine chemotherapy. In an randomised controlled trial (ToGA),[128] patients with oesophageal adenocarcinoma who had a HER2 score of 3+ or 2+ on immunohistochemistry with positive fluorescence in-situ hybridisation results and were treated with trastuzumab plus chemotherapy had a median survival of 16·0 months compared with 11·8 months for patients treated with chemotherapy alone (HR 0·65, 95% CI 0·51–0·83).

Second-line chemotherapy might be considered for patients with maintained performance status (0–1); the mean survival benefit with cytotoxic chemotherapy is 6 weeks leading to a median overall survival of approximately 5 months.[129–131] Appropriate drugs include docetaxel, paclitaxel, and irinotecan. The anti-vascular

endothelial growth factor receptor 2 monoclonal antibody ramucirumab provides equivalent benefit to cytotoxic chemotherapy for patients with metastatic oesophageal adenocarcinoma when used as a single second-line drug.[132] In combination with paclitaxel, ramucirumab is associated with a small improvement in median survival (9·6 months *vs* 7·4 months with paclitaxel alone; HR 0·81, 95% CI 0·68–0·96).[129]

Emerging therapies

The aggressive nature of oesophageal cancer with early spread, rapid tumour recurrence, and poor prognosis highlight the need for research examining novel medical therapies.[133] Efforts to molecularly characterise oesophageal cancer have identified subgroups of patients who might benefit from targeted therapies in the future. However, with the exception of HER2-positive tumours, randomised controlled trials[134,135] of targeted therapies, including those targeting the epidermal growth factor receptor and mesenchymal-epithelial transition pathways, have not been successful. Failure to use biomarker selection or inadequate validation of biomarkers might be partly responsible for these failures. However, co-amplification of receptor tyrosine kinases, intratumour heterogeneity of copy number alteration, and mutations in oesophageal cancers also lead to attenuation of the clinical benefit of targeted therapy.[27,136,137] Targets of therapeutic interest in oesophageal cancer have emerged, including dysregulation of cell cycle regulators such as *CDK6*, which have been successfully targeted in breast cancer by palbociclib and ribociclib, and impaired DNA damage repair mechanisms, which have been exploited in ovarian cancer using olaparib and rucaparib.[138–141] Immunotherapy using checkpoint inhibitors, such as programmed cell death protein 1 (PD-1) antibodies, has resulted in survival benefits for patients with some other cancers, such as melanoma and non-small cell lung cancer, and gastro-oesophageal cancer is an attractive target for immuno-oncological intervention because of its relatively high mutation burden.[142–145] Results from early phase trials[146] in oesophageal cancer have been encouraging with response rates to the anti-PD-1 antibody pembrolizumab reported as 29% for oesophageal squamous cell carcinoma and 40% for oesophageal adenocarcinoma in a randomised controlled trial of 23 patients with positive expression of programmed death-ligand 1 (PD-L1). Patients with gastro-oesophageal cancer who are PD-L1 negative also respond to checkpoint inhibitor therapy; the radiological response rate was 12% in patients who were PD-L1 negative and treated with the anti-PD-1 antibody nivolumab, and radiological response rates were increased for patients who were PD-L1 positive and negative when the anti-cytotoxic T-lymphocyte-associated protein 4 antibody ipilimumab was added to nivolumab therapy.[147] The promise of personalised immunotherapy for solid tumours could also be realised for oesophageal cancer, as adoptive T-cell transfer of mutation-specific T cells was associated with a sustained radiological response in epithelial tumours such as cholangiocarcinoma.[148] However, as autologous adoptive T-cell transfer requires considerable expertise, alternative forms of personalised immunotherapy, such as chimeric antigen-receptor T cells, which have been successful in haematological malignancies, might be more widely applicable.[149] Chimeric antigen-receptor T cells are in early development for gastrointestinal cancers, and selection of the most safe and specific target antigen will be of key importance; targets associated with oesophageal cancer that are currently being investigated in clinical trials include HER2, mucin 1, carcinoembryonic antigen, and epithelial cell adhesion molecule.

For more on **ongoing clinical trials associated with oesophageal cancer** see www.clinicaltrials.gov

Best supportive care

Rapidly progressive dysphagia needs to be dealt with promptly and almost independently of the general condition of the patient. In a rapidly deteriorating patient, oesophageal stenting alone is recommended because it promptly secures a continuity that passes the obstructing tumour and is usually a single therapy without the need for follow-up.[119] The malnutrition seen in patients with palliative oesophageal cancer is typically worse than that of patients with most other cancers and depending on the clinical scenario enteral support might be considered. Deterioration in HRQoL is often rapid, which highlights the urgency of planning end-of-life care, and discussing the future with the patient and family members; and making early contact with the relevant health-care facilities (eg, ambulant palliative care units, hospices or hospitals that provide end-of-life care). Also in the many patients who have had curatively intended treatment, but develop tumour recurrence, it is recommended that palliative and supportive care is planned as soon as recurrent disease is identified. Well designed clinical trials using standardised measures might help improve the best supportive care in patients with oesophageal cancer.[150,151]

Controversies and uncertainties

Endoscopic treatment

Although early tumours (T1) are not often identified, evaluating when endoscopic (organ-sparing) treatment can be recommended above surgical resection is important. More large-scale observational research and randomised controlled trials are needed to answer this question.

Oncological treatment

The potential advantage of neoadjuvant chemotherapy compared with chemoradiotherapy requires clarification. Both treatments are associated with tumour downstaging, but rates of complete tumour response are higher following chemoradiotherapy, particularly for patients with oesophageal squamous cell carcinoma.[55,57,58,61] However, for patients with oesophageal adenocarcinoma, the low dose of systemic chemotherapy in neoadjuvant chemoradiotherapy regimens might negatively affect

systemic disease control. In the long-term follow-up of the CROSS trial,[61] distant metastatic recurrence was reduced overall (HR 0·63, 95% CI 0·46–0·87), but was not significantly reduced after 2 years compared with the control arm. For patients with oesophageal adenocarcinoma at high risk of metastatic recurrence, a systemic approach might be preferred. Randomised controlled trials are needed to clarify these issues.

Timing of surgery following neoadjuvant therapy

The tumour stage after neoadjuvant chemoradiotherapy seems to be a better predictor of long-term prognosis than clinical tumour stage at presentation.[152] Some studies[153,154] indicate that an increase in the time latencies between completed neoadjuvant therapy and surgery from the current 4–6 weeks to over 12 weeks might improve the tumour response to neoadjuvant therapy in oesophageal squamous cell carcinoma and oesophageal adenocarcinoma, which might increase the rate of radical resection.[153,154] The optimum interval between neoadjuvant therapy and surgery with regard to survival is being assessed in a randomised controlled trial (ClinicalTrials.gov NCT02415101).

Follow-up

Evidence is scarce regarding how to optimise the follow-up of patients who have had radical treatment for oesophageal cancer. Some studies[36,155–157] indicate that HRQoL measures can be used to identify the need for prompt interventions following treatment and to predict survival. Future research on these topics can provide further evidence that might guide future decision making about therapy choice, as well as tailored follow-up.

Outstanding research questions

Increased detection of premalignant lesions and early stage tumours would improve prognosis. However, general endoscopic screening might not be cost-effective or clinically feasible, or well tolerated by certain individuals. Future alternatives might include screening of carefully selected absolute high-risk individuals (with a combination of risk factors) in combination with the use of less invasive screening tools, such as cytosponge or breath tests,[158,159] although more research is needed before these tools can be introduced in routine clinical practice.

Many patients with oesophageal cancer have extensive therapy despite having tumour dissemination that has remained undetected before treatment. These patients might never recover from surgery before death. Thus, a need exists to develop new diagnostic measures with improved specificity and sensitivity for a more accurate assessment of the clinical tumour stage, potentially by developing novel radiotracers.

New biomarkers that can help predict treatment response and prognosis would be valuable. Beyond HER2, no biomarkers are available for treatment selection in patients with operable oesophageal cancer. Optimisation and developments in existing therapeutic tools can further improve survival in oesophageal cancer. However, novel strategies for early tumour detection and new treatment are required for breakthroughs in the prognosis of this cancer.

Contributors

All authors contributed equally to the production of this article.

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