

Oesophageal cancer

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Abstract | Oesophageal cancer is the sixth most common cause of cancer-related death worldwide and is therefore a major global health challenge. The two major subtypes of oesophageal cancer are oesophageal squamous cell carcinoma (OSCC) and oesophageal adenocarcinoma (OAC), which are epidemiologically and biologically distinct. OSCC accounts for 90% of all cases of oesophageal cancer globally and is highly prevalent in the East, East Africa and South America. OAC is more common in developed countries than in developing countries. Preneoplastic lesions are identifiable for both OSCC and OAC; these are frequently amenable to endoscopic ablative therapies. Most patients with oesophageal cancer require extensive treatment, including chemotherapy, chemoradiotherapy and/or surgical resection. Patients with advanced or metastatic oesophageal cancer are treated with palliative chemotherapy; those who are human epidermal growth factor receptor 2 (HER2)-positive may also benefit from trastuzumab treatment. Immuno-oncology therapies have also shown promising early results in OSCC and OAC. In this Primer, we review state-of-the-art knowledge on the biology and treatment of oesophageal cancer, including screening, endoscopic ablative therapies and emerging molecular targets, and we discuss best practices in chemotherapy, chemoradiotherapy, surgery and the maintenance of patient quality of life.

As a disease entity, oesophageal cancer principally comprises two epidemiologically and pathologically distinct diseases that share an anatomical site: oesophageal squamous cell carcinoma (OSCC) and oesophageal adenocarcinoma (OAC) (TABLE 1). OSCC and OAC have divergent risk factors and incidence trends. OSCC is the most common type worldwide, but its incidence is declining in most parts of the world. By contrast, OAC incidence rates have risen sharply in developed countries over the past four decades^{1–3}. Biologically, OSCC shares many characteristics with squamous cell carcinoma of the head and neck, whereas OAC resembles chromosomally unstable gastric adenocarcinoma in its genetic makeup⁴. Dysplastic precursor lesions can be detected for both OSCC and OAC using endoscopy and non-invasive screening methods, but routine screening is not currently recommended in low-risk areas or for low-risk individuals⁵. Local ablative treatment of these dysplastic lesions results in excellent long-term outcomes, without the requirement for extensive oesophageal resection or intensive oncological treatment, and some early cancers may also be treated successfully with endoscopic resection^{6,7}. Patients with locally advanced cancer frequently develop recurrent disease, although the use of chemotherapy or chemoradiotherapy as an adjunct to surgery has improved the prognosis⁶. Of note, definitive chemoradiotherapy (that is, chemoradiotherapy

without subsequent oesophagectomy) is only a standard of care for OSCC. In advanced or metastatic oesophageal cancer, combination chemotherapy regimens extend survival. However, the current median survival time is still <1 year^{8–11}. To improve overall survival, novel therapies tailored to the molecular composition of the tumour are urgently required. Finally, as oesophageal cancer treated with curative or palliative intent results in a substantial symptom burden and changes in quality of life (QOL), paying attention to symptom control and other patient-reported outcomes is important^{12,13}.

In this Primer, we provide an up-to-date overview of findings regarding the epidemiology, pathogenesis and treatment of oesophageal cancer, including endoscopic, surgical and medical oncology approaches, as well as the effect of the disease on the QOL of patients, and emerging data on screening and chemoprevention. As OSCC and OAC are associated with divergent histology and biology, anatomical sites of disease and aetiological factors, we discuss their epidemiology, pathogenesis and molecular biology separately below (TABLE 1).

Epidemiology

Oesophageal cancer is the sixth most common cause of cancer-associated death globally. In 2012, there were an estimated 456,000 diagnoses of oesophageal cancer worldwide. Of the total number of oesophageal cancers

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diagnosed, 398,000 diagnoses were OSCC and 52,000 were OACs³. The case mortality rate for patients diagnosed with oesophageal cancer is high; the 5-year survival rate for all patients is less than 20%, even in developed countries such as the United States¹⁴. The incidence of oesophageal cancer increases with age; for example, 56% of cases in the United Kingdom occur in patients who are ≥ 70 years of age¹⁵. Patients with oesophageal cancer may have comorbidities that are related to risk factors associated with specific histological subtypes (for example, smoking-related and alcohol-related comorbidities for OSCC, and obesity-related comorbidities for OAC).

OSCC

OSCC accounts for almost 90% of cases of oesophageal cancer worldwide, and is especially prevalent in the East, East Africa and South America (FIG. 1a). The incidence of OSCC is particularly high in the so-called oesophageal cancer belt, which stretches from northern China (where annual incidence rates are up to 100 per 100,000 individuals) through central Asia to northern Iran¹. In many countries, the incidence of OSCC has fallen substantially in recent years, possibly owing to changes in diet, and tobacco and alcohol use. For example, OSCC incidence rates in the United States fell by 3.6% annually between 1998 and 2003 (REF. 16), and a similar fall of 3.3% was observed in the annual standardized incidence rate in China from 1989 to 2008 (REF. 17). Decreased incidence rates are also apparent in high-incidence areas within China, such as in Cixian¹⁸. In addition, OSCC mortality has decreased in specific areas owing to endoscopic screening programmes and early treatment¹⁹.

OAC

The prevalence of OAC is relatively high in the Americas, Europe and Australia, and OAC is now even the predominant subtype in some of these areas³ (FIG. 1b). In contrast to the falling incidence rates of OSCC¹⁶, a substantial and sustained rise in the incidence of OAC has been observed in Western industrialized countries. The average age-adjusted incidence rates have increased over

the past four decades; the average annual increase has ranged from 3.5% (95% CI: 3.3–3.7) per year in Scotland to 8.1% (95% CI: 6.4–10.0) per year in Hawaii^{2,20}.

Mechanisms/pathophysiology**OSCC**

Risk factors. OSCC develops from the squamous epithelial cells that make up the inner lining of the oesophagus. Recurrent chemical or physical insults to the oesophageal mucosa increase the risk of OSCC. In non-endemic areas, OSCC is predominantly associated with tobacco smoking and the overconsumption of alcohol. Tobacco smoke contains carcinogens, such as polycyclic hydrocarbons, nitrosamines and acetaldehyde, and active smoking is associated with a 5-fold to 9-fold increase in the overall risk of OSCC²¹, but the relative risk is lower in endemic areas (for example, the risk is increased just 1.3-fold for smokers relative to non-smokers in Linxian, China²²). The deleterious effects of alcohol on the oesophageal mucosa are mediated by acetaldehyde, secondary to oxidation by the oral microbiota and salivary products. Pharmacogenetic differences in alcohol metabolism in Asian populations increase acetaldehyde exposure in this population²³. Smoking and alcohol synergize to increase the risk of OSCC²⁴.

A low intake of fruit and vegetables is also associated with increased OSCC risk, as are specific regional marginal micronutrient deficiencies (for example, deficiencies in vitamin A and vitamin E)^{25–27}. Many of these risk factors for OSCC are associated with lower socioeconomic status, and accordingly, OSCC is more common in economically deprived groups and regions²⁸. Recurrent thermal injury due to the ingestion of high-temperature beverages such as tea may be contributory to regional variation in OSCC incidence in, for example, northern Iran²⁹. Finally, human papillomavirus (HPV) infection has been suggested to be associated with OSCC. However, data from The Cancer Genome Atlas (TCGA) have demonstrated that OSCC has a molecular profile that is consistent with HPV-negative squamous cell carcinoma, suggesting that HPV-associated OSCC may reflect the heterogeneity of HPV prevalence globally rather than reflecting a causative effect^{4,30}.

The role of inherited genetic variants on OSCC cancer risk is modest apart from in rare familial cases. Tylosis is an autosomal dominant disorder caused by a germline mutation in *RHBDF2* (which encodes rhomboid 5 homologue 2, a protein that is also known as iRHOM2). The disorder is associated with palmar and plantar hyperkeratosis, and with a 90% cumulative risk of developing OSCC by 70 years of age³¹. Large-scale genome-wide association studies (GWAS) in China have identified susceptibility loci with an odds ratio (OR) of 1.3–1.4 for OSCC at the following chromosomal locations: 10q23 (which encodes phospholipase Cε1, an enzyme associated with growth, differentiation and apoptosis); 5q31.2 (which encodes transmembrane protein 173, a protein associated with the type I interferon response to microbial infection); 17p13.1 (which encodes sodium/potassium-dependent ATPase subunit β2; this gene is localized in close proximity to *TP53* (which encodes p53));

and, specifically in high-risk areas, the HLA class II region (6p21.32)^{32–34}. Variability in genes involved in detoxification processes may also modify environmental influences on OSCC susceptibility. For example, functional variants in the enzymes alcohol dehydrogenase 1B and aldehyde dehydrogenase 2 synergize with lifestyle factors to increase OSCC risk in the Japanese population³⁵.

Pathogenesis and molecular characterization. OSCC develops from basal cell hyperplasia and dysplasia (low to high grade) to carcinoma *in situ* (Tis) (FIG. 2). The molecular progression from dysplasia to OSCC, which is invasive, has not been well studied, but dysregulation of *TP53* and the genes that encode other cell cycle regulators (such as cyclin-dependent kinase inhibitor 2A (*CDKN2A*) and retinoblastoma-associated protein (RB; encoded by *RB1*)) is a prominent characteristic of OSCC; these changes can already be detected in precursor lesions³⁶. Abnormal p53 expression has been demonstrated in oesophageal tissue adjacent to dysplasia or OSCC, and increased levels of *CDKN2A* and RB have been associated with a stepwise progression from inflammation to cancer in oesophageal lesions^{37,38}. Differentiating between normal and dysplastic tissue for accurate risk stratification is challenging, but the evaluation of genes that are differentially expressed in normal oesophageal mucosa and OSCC has identified two candidate biomarkers that could aid in the future diagnosis of dysplasia or invasive OSCC. Indeed, the expression of *TNFAIP3* (which encodes tumour necrosis factor-induced protein 3) and *CHN* (which encodes chimerin 1) increases during the transition from normal tissue to dysplasia to carcinoma³⁹.

Several recent large-scale sequencing and multi-platform studies have evaluated the mutational, transcriptomic and epigenetic profiles of OSCC. According to TCGA data, point mutations and small insertions or deletions (indels) were most commonly detected

in *TP53*, *KMT2D* (which encodes lysine methyltransferase 2D; also known as *MLL2*) and *NFE2L2* (which encodes nuclear factor erythroid 2-like 2), whereas amplifications were frequently identified in *SOX2*, *TP63* and *FGFR1* (which encode SRY-box 2, tumour protein 63 and fibroblast growth factor receptor 1, respectively) (TABLE 2). These data confirm the results of several previous studies^{4,40–42}. Dysregulated pathways that are of therapeutic interest in OSCC include cell cycle regulation, receptor tyrosine kinase signalling, chromatin remodelling and embryonic pathways such as the Hippo signalling pathway (via the amplification of *YAP1* (which encodes Yes-associated protein 1), or deletion of *VGLL4* (which encodes vestigial-like family member 4) or *ATG7* (which encodes autophagy-related gene 7)). According to TCGA, *CDKN2A* was inactivated in 76% of tumours, and amplifications of *CCND1* (which encodes cyclin D1) were present in 57%, confirming other studies^{40,41}. The epidermal growth factor receptor (EGFR) signalling pathway was activated via mutation or amplification in 19% of tumours, and phosphoinositide 3-kinase catalytic subunit-α (PIK3CA) was activated in 13% of tumours. Each of these pathways has been successfully targeted using tyrosine kinase inhibitors that are currently approved for use in other types of tumour.

OAC

Risk factors. OAC arises primarily from Barrett oesophagus (a preneoplastic tissue in which the squamous oesophageal epithelium is replaced by a columnar intestinal-type mucosa). Its predominant localization is the lower oesophagus, and the tumour has a glandular structure. Gastro-oesophageal reflux of acid and/or bile is the most important risk factor for OAC. In a population-based case-control study and a meta-analysis, gastro-oesophageal reflux disease is associated with an OR of 12.00 (95% CI: 7.64–18.70) for Barrett oesophagus and 4.64 (95% CI: 3.28–6.57) for OAC^{43,44}.

Table 1 | Key differences between OSCC and OAC

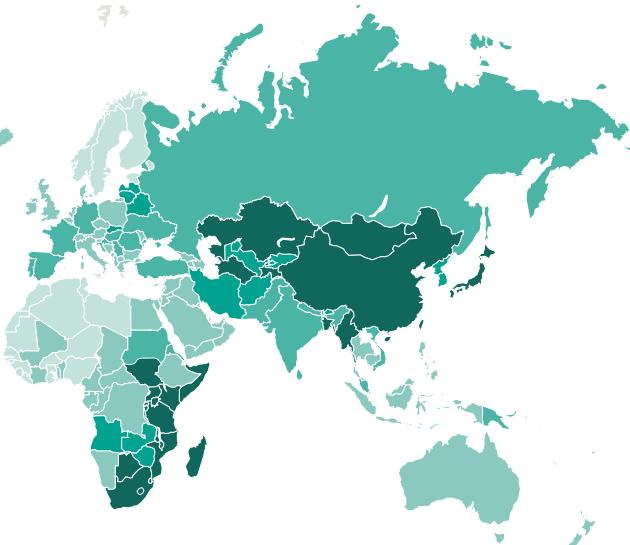
Differences	OSCC	OAC
Geographical distribution	Most common in East Asia and the Middle East (the ‘oesophageal cancer belt’)	Most common in developed regions in western Europe, North America and Australia
Main risk factors	Tobacco smoking, alcohol use, thermal injury and regional micronutrient deficiency	Acid or bile reflux, Barrett oesophagus, and central or visceral obesity
Molecular characteristics	See TABLE 2	See TABLE 2
Tumour location	Throughout the oesophagus, more common in the upper and middle third	More common in the distal oesophagus
Frequent comorbidity	Liver cirrhosis, chronic obstructive pulmonary disease, synchronous and metachronous cancer of the aero-digestive tract, and atherosclerosis	Obesity and atherosclerosis
Diagnosis and symptoms	Similar	Similar
Curative treatment	Definitive chemoradiotherapy, or chemoradiotherapy followed by surgery	Neoadjuvant or perioperative chemotherapy followed by surgery, or neoadjuvant chemoradiotherapy followed by surgery
Palliative treatment	Chemotherapy, radiotherapy or stenting	Chemotherapy (plus trastuzumab if HER2-positive), radiotherapy or stenting

HER2, human epidermal growth factor receptor 2; OAC, oesophageal adenocarcinoma; OSCC, oesophageal squamous cell carcinoma.

Obesity, and, in particular, central (visceral) obesity, is the second strongest risk factor for Barrett oesophagus and OAC (OR for individuals with a high body mass index (BMI): 2.69 (95% CI: 1.62–4.46))^{43,45,46}. In addition, reflux and obesity can have a synergistic effect. Obesity is associated with increased intra-abdominal pressure, which can increase reflux, and the obesity-related metabolic syndrome is also a risk factor for Barrett oesophagus independent of reflux symptoms⁴⁷.

Tobacco smoking is a moderately strong risk factor for OAC, but its association with Barrett oesophagus is less clear, and alcohol consumption does not seem to substantially increase the risk of Barrett oesophagus and OAC^{43,48,49}. Other risk factors for OAC include male sex (there is a male-to-female ratio of 7:1), high red meat intake (OR: 1.91 (95% CI: 1.07–3.38) for the highest versus the lowest tertile of red meat intake), and low fruit and vegetable intake (OR: 0.86 (95% CI: 0.80–0.93)

a Oesophageal squamous cell carcinoma



b Oesophageal adenocarcinoma

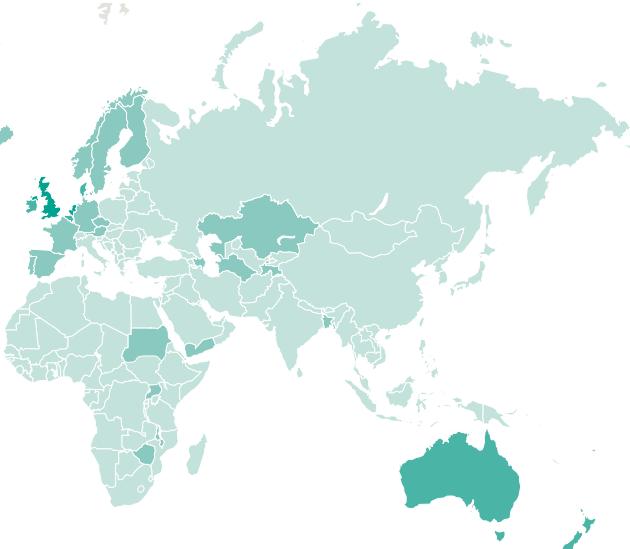
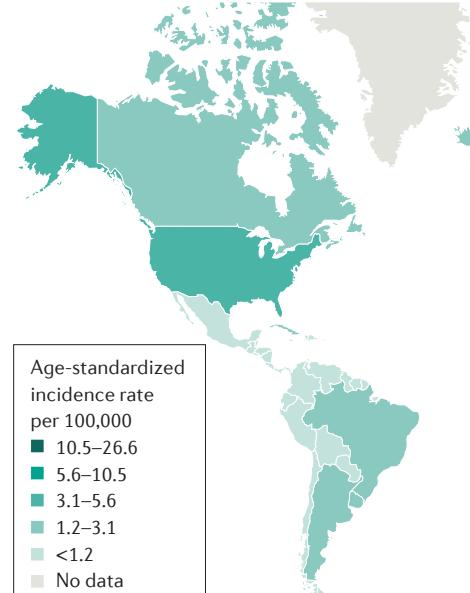


Figure 1 | The global annual incidence of OSCC and OAC. Age-standardized incidence rates per 100,000 men in 2012 are shown. **a** | The incidence of oesophageal squamous cell carcinoma (OSCC) is high in the so-called oesophageal cancer belt, which extends from China to Iran. In addition, a high incidence is also observed in East Africa and South America. **b** | The incidence of oesophageal adenocarcinoma (OAC) is highest in Western industrialized nations, including the United States, Canada, Australia and Europe; a lower incidence is seen in developing areas, including Africa and China. From REF. 3. Reproduced from Global incidence of oesophageal cancer by histological subtype in 2012, Arnold, M., Soerjomataram, I., Ferlay, J. & Forman, D., **64**, 381–387, 2015, with permission from BMJ Publishing Group Ltd.

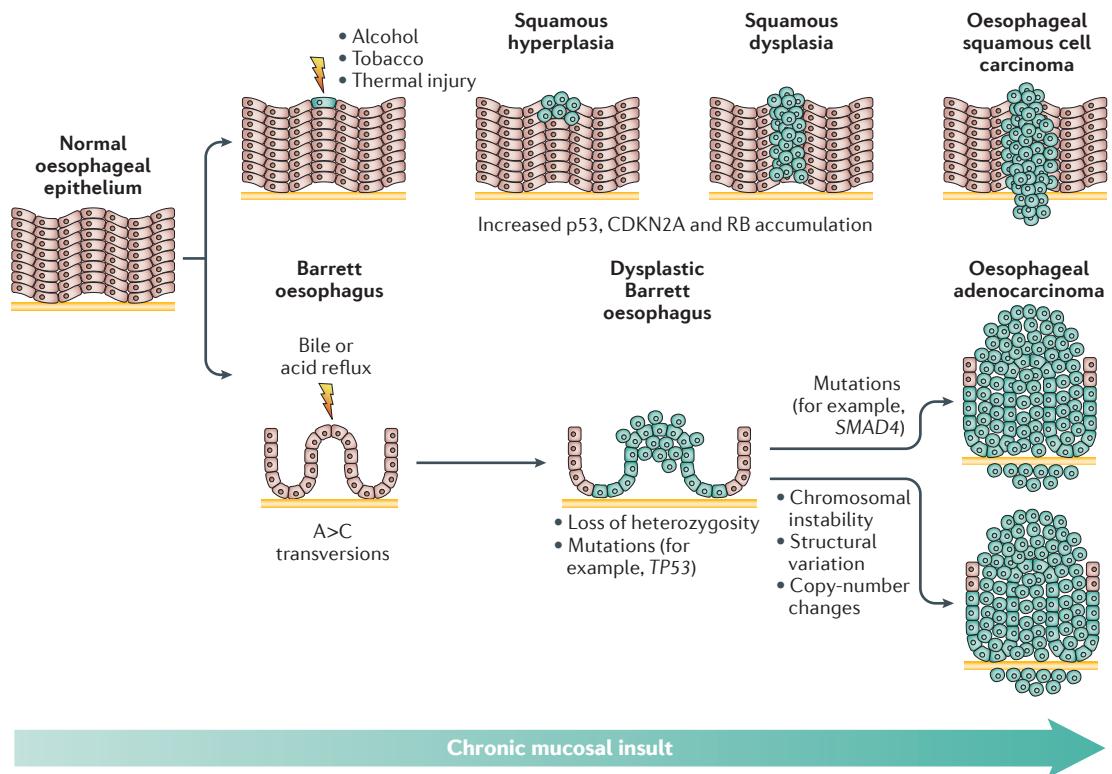


Figure 2 | The pathogenesis of OSCC and OAC. The oesophageal mucosa is exposed to repeated insults, which result in changes to the squamous oesophageal mucosa. Molecular changes also accumulate, and this ultimately leads to a malignant phenotype. In oesophageal squamous cell carcinoma (OSCC), squamous hyperplasia precedes low-grade and high-grade squamous dysplasia, which then develops into invasive cancer. In oesophageal adenocarcinoma (OAC), a metaplastic epithelium (Barrett oesophagus) is transformed through low-grade and high-grade dysplasia to invasive cancer. CDKN2A, cyclin-dependent kinase inhibitor 2A; RB, retinoblastoma-associated protein.

per portion of fruit or vegetables per day)^{43,50,51}. By contrast, *Helicobacter pylori* infection demonstrates an inverse association with Barrett oesophagus and OAC risk, and decreasing population seropositivity for *H. pylori* owing to improved socioeconomic conditions might contribute to the rising rates of OAC^{52,53}.

Genetics contributes up to one-third of the risk for sporadic Barrett oesophagus and OAC development, and approximately 7% of cases of Barrett oesophagus and OAC may be familial^{54–56}. GWAS have identified susceptibility loci in genes that encode proteins involved in the embryonic development of the oesophagus (for example, *FOXF1* and *BARX1* (which encode forkhead box F1 and BARX homeobox 1, respectively)), in the host immune response (that is, the HLA locus 16q24.1), and in cellular proliferation and transformation (for example, *CRTC1* (which encodes CREB-regulated transcription coactivator 1 and is found on 19p13))⁵⁷. The importance of genes that are actively transcribed in the embryonic period in the development of OAC is emphasized by the results of a large meta-analysis of all available GWAS on Barrett oesophagus and OAC (including 6,167 patients with Barrett oesophagus and 4,112 patients with OAC); this meta-analysis identified several new risk loci, including *ABCC5* (which encodes ATP-binding cassette subfamily C member 5; OR: 1.17 (95% CI: 1.11–1.24) for OAC only), which is also associated with oesophageal

development⁵⁸. Finally, germline variation in inflammation response genes, such as *MGST1* or *FOXP1* (which encode microsomal glutathione S-transferase 1 and forkhead box P1, respectively), may affect the genetically determined host response to inflammation, and thus also influence individual Barrett oesophagus and OAC risk^{59,60}.

Progression from Barrett oesophagus to OAC. Typically, damage to the oesophageal mucosa due to acid or bile exposure is the consequence of the formation of reactive oxygen species and nitric oxide, which cause DNA damage and a characteristic mutational profile with A>C transversions (FIG. 2). This base-transversion profile is common in Barrett oesophagus and OAC, lending further support to the hypothesis that these DNA-damaging factors are causally acting early in disease pathogenesis^{61–63}. Hence, it is generally agreed that Barrett oesophagus occurs as an adaptive response to recurrent injury to the squamous mucosa^{64,65}. In a minority of patients (0.12–0.60% annually), the metaplastic mucosa associated with Barrett oesophagus progresses through low-grade and then high-grade dysplasia to invasive OAC, and much effort is ongoing to understand the triggers and pathways that underlie progression, so that high-risk patients can be identified more accurately than they are at present^{66–68}.

Table 2 | Frequently dysregulated genes in OSCC and OAC

Gene	Function	OSCC		OAC	
		Frequency of dysregulation (%) [*]	Pathway regulation [‡]	Frequency of dysregulation (%) [*]	Pathway regulation [‡]
Receptor tyrosine kinases					
HER2	MAPK signalling pathway	3	↑	15–32	↑
EGFR	MAPK signalling pathway	19	↑	8–15	↑
VEGFA	Angiogenesis pathway	3	↑	5–28	↑
IGF1R	MAPK and AKT signalling pathways	2	↑	1–10	↑
KRAS	MAPK signalling pathway	7	↑	13–14	↑
PIK3CA	PI3K–AKT signalling pathway	13	↑	3–5	↑
FGFR1	MAPK and PI3K–AKT signalling pathways	12	↑	2–4	↑
FGFR2	MAPK and PI3K–AKT signalling pathways	0	NA	3	↑
Cell cycle regulators					
TP53	Maintenance of genomic integrity	91	↓	50–71	↓
CDKN2A	Negative regulator of cell cycle progression	76	↓	55–76	↓
CCND1	Regulator of cell cycle progression	57	↑	15–17	↑
CDK6	Regulator of cell cycle progression	16	↑	13–14	↑
CCNE1	Regulator of cell cycle progression	4	↑	10–14	↑
RB1	Regulator of cell cycle progression	9	↓	0	NA
Proliferation and differentiation					
MYC	Regulator of proliferation and differentiation	23	↑	16–32	↑
SMAD4	Regulator of TGF β and BMP pathways	8	↓	24–59	↓
GATA4	Transcription factor	1	↑	15–19	↑
GATA6	Transcription factor	3	↑	18–21	↑
TP63 and SOX2	Transcription factors	48	↑	7–12	↑
Chromatin remodelling					
KDM6A	Histone demethylase	19	↓	4	↓
KMT2D	Histone methyltransferase	14	↓	1	↓

BMP, bone morphogenetic protein; MAPK, mitogen-activated protein kinase; NA, not applicable; OAC, oesophageal adenocarcinoma; OSCC, oesophageal squamous cell carcinoma; PI3K, phosphoinositide 3-kinase; TGF β , transforming growth factor- β . *Percentages are based on the Oesophageal Cancer Genome Atlas and International Cancer Genome Consortium^{4,84}. [‡]Presentation of upregulation (↑) or downregulation (↓) of the specified pathway in tumours harbouring the specified mutation.

Barrett oesophagus is a preneoplastic lesion that frequently contains somatic genetic alterations that predispose to carcinogenesis. Two mechanisms of OAC generation from Barrett oesophagus have been proposed. The first mechanism involves the stepwise loss of tumour suppressor genes such as *CDKN2A* and *TP53*, and also involves mutations in *SMAD4* and the disruption of chromatin-modifying enzymes, but without an acute genome-doubling event. Indeed, mutations in *TP53* and *SMAD4* seem to occur early in tumour development. This observation might be helpful when seeking to identify patients who are at risk of progression to OAC⁶⁹.

The second mechanism involves large-scale chromosomal instability that is associated with aneuploidy following the loss of p53 regulation⁷⁰. The acquisition of loss of heterozygosity of 17p (which contains *TP53*)

in Barrett oesophagus has been associated with the development of aneuploidy and with an increased potential for malignant progression^{71,72}. A paired sequencing study of Barrett oesophagus and OAC samples from 25 patients demonstrated that a genome-doubling event in *TP53*-mutant cells commonly precedes OAC development⁷⁰. Furthermore, tumours that have undergone a genome-doubling event have distinct characteristics, including an increased number of focal genomic amplifications.

Other mechanisms — for example, chromothripsis and kataegis — may lead to chromosomal instability and accelerate the progression from Barrett oesophagus to invasive OAC. These mechanisms can explain the lack of copy-number alterations in Barrett oesophagus compared with invasive OAC, despite similar mutational signatures⁷³.

Clonal diversity is as common in Barrett oesophagus as in OAC, and greater clonal diversity is associated with an increased risk of progression from Barrett oesophagus to invasive OAC^{72–75}. This implies that sampling Barrett oesophagus requires a wide sampling field to improve the accuracy of risk stratification; as taking multiple biopsies increases the patient's risk of complications — such as perforation or haemorrhage — non-invasive strategies may be preferred in the future⁷⁶.

Epigenetic modification is another factor in OAC development. The levels of DNA methylation in both Barrett oesophagus and OAC are high relative to the levels found in normal oesophageal mucosa, although the levels are heterogeneous⁷⁷. For example, hypermethylation of the promoter of *CDKN2A* is frequent and associated with neoplastic progression in Barrett oesophagus, and, together with the loss of 9p21, it may lead to the inactivation of *CDK2NA*^{4,78,79}.

Genetics of invasive OAC. OAC has a high point-mutation burden (9.9 mutations per Mb (range: 7.1–25.2 per Mb)) relative to other cancers, but the burden is lower than that of lung cancer and melanoma^{63,80}. However, although point mutations are abundant particularly in tumour suppressor genes, such as *TP53*, *CDK2NA* and *ARID1A* (which encodes AT-rich interaction domain 1A), structural alterations dominate the OAC landscape^{4,63,69,80,81} (TABLE 2). Copy-number alterations (amplifications and deletions) are common; amplifications of potential therapeutic relevance are frequently found in the genes that encode receptor tyrosine kinases (that is, *HER2* (which encodes human epidermal growth factor receptor 2; also known as *ERBB2*), *EGFR*, *KRAS* and *FGFR2*), cell cycle regulators (for example, *CCND1* and *CDK6* (which encodes cyclin-dependent kinase 6)) and transcription factors (for example, *MYC*, *GATA4* (which encodes GATA-binding protein 4) and *GATA6*)^{4,63,82,83}. Co-amplification (that is, the amplification of more than one gene in the same tumour) of receptor tyrosine kinases is common (specifically for *HER2* and *EGFR*), and is probably associated with both *de novo* and acquired resistance to targeted therapy, which pose a challenge for drug selection and development^{84–86}. The gross chromosomal instability associated with OAC is shared with chromosomally unstable gastric cancer⁴.

The clonal heterogeneity and co-amplification profiles of OAC make targeted therapies a challenge. However, an alternative classification system based on molecular subgroups might enable the identification of different avenues for therapeutic intervention. Following whole-genome sequencing of 129 OAC samples as part of the International Cancer Genome Consortium, three subgroups were identified: one subgroup showed changes characteristic of defective homologous recombination repair; another showed a T>G mutation pattern associated with a high mutational load, and a third group had a C>A or C>T mutation pattern that was consistent with an ageing imprint⁸⁴. Effective treatments for the DNA damage repair-deficient subtype might potentially include inhibitors of poly(ADP-ribose) polymerase (PARP) and the serine/threonine-protein kinase ATR, or platinum-based

chemotherapy, whereas the subgroup with a high mutational burden might benefit from immuno-oncology therapies. However, further functional and clinical validation of these subgroups is required.

Diagnosis, screening and prevention

As the clinical symptoms and diagnosis of OAC and OSCC are similar, we discuss them together.

Diagnosis of oesophageal cancer

Owing to the muscular and expansive nature of the oesophagus, the symptoms resulting from an obstructing lesion or stricture only become apparent when the tumour has reached a relatively locally advanced or even metastatic stage. Warning symptoms include difficulty swallowing (dysphagia) or pain when swallowing (odynophagia), involuntary and progressive weight loss, and hoarseness or cough; cough can signify laryngeal nerve involvement or aspiration. Occasionally, patients may vomit blood or pass melaena (dark stool produced as a consequence of internal bleeding in the upper gastrointestinal tract). Fatigue may occur due to anaemia resulting from chronic, occult bleeding or a chronic disease burden. Clinical examination should focus on the assessment of performance status and the evaluation of clinically apparent metastatic disease (for example, evaluation of the supraclavicular lymph nodes and hepatomegaly (that is, an enlarged liver)).

Endoscopy is the gold standard for the detection and diagnosis of oesophageal cancer, as the clinical examination is often unremarkable even with locally advanced disease⁸⁷. Endoscopy can be improved by using Lugol's iodine dye (chromoendoscopy) to identify early OSCC or by using narrow-band imaging, in which light of specific wavelengths is used to improve the resolution of the surface mucosa (FIG. 3). Tumour characteristics that should be documented at endoscopy include the exact site of the tumour (relative to the gastro-oesophageal junction, extension into the stomach and distance from the teeth), the length of the lesion, circumferential involvement and the presence of obstruction⁷. Any adjacent pre-malignant lesions (that is, squamous cell dysplasia or Barrett oesophagus) should be documented and measured. As the mucosa can be friable owing to ulceration or necrosis, it is recommended that a minimum of six biopsies are analysed for histological confirmation⁸⁸.

Histology should be classified according to the WHO criteria, and the histological subtype (that is, adenocarcinoma, squamous cell carcinoma, undifferentiated cancer or rare cancer) and grade should be documented^{7,89}. If the histological subtype is difficult to determine, histochemical or immunohistochemical staining may help. Markers that may distinguish OAC from OSCC include periodic acid-Schiff staining (to identify mucus-secreting cells), cytokeratin 7 and cytokeratin 20 for OAC, whereas cytokeratin 5, cytokeratin 6 and p63 are more frequent in OSCC⁹⁰. The identification of rare cancers that can affect the oesophagus (such as small cell carcinoma, neuroendocrine tumours, lymphoma, gastrointestinal stromal tumours and melanoma) is essential as they may require specific treatment. HER2 staining

should be performed in patients with advanced tumours who are not suitable for curative therapy and in whom trastuzumab (an anti-HER2 antibody) might be a treatment option^{6,7}.

Staging of oesophageal cancer

As oesophagectomy is associated with considerable morbidity and changes in postoperative QOL, the careful selection of patients who meet the criteria for resection surgery (that is, patients who do not have metastatic cancer and are fit for surgery) is essential to minimize the risk of futile surgery in patients with incurable disease. Diagnostic endoscopic mucosal dissection or resection may be an alternative in very early-stage tumours (mainly in Tis–T1a tumours).

The staging of oesophageal cancer should be performed according to the tumour–node–metastasis (TNM) classification (FIG. 4) published by the current American Joint Council on Cancer⁹¹. Three classification systems are available depending on the mode of staging: namely, clinical or radiological staging (c stage), pathological staging (p stage) determined after primary surgery or endoscopy for localized disease or pathological staging after neoadjuvant therapy (yp stage).

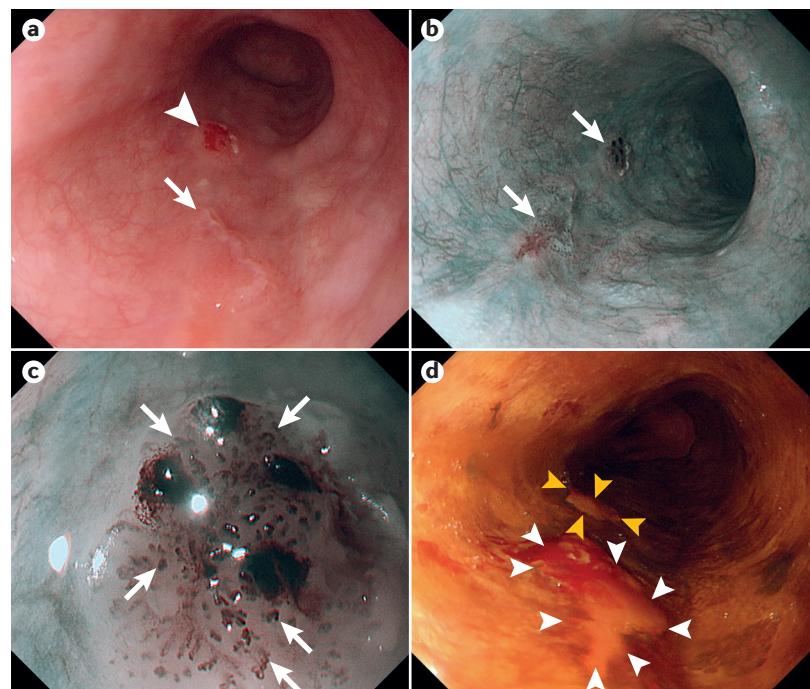


Figure 3 | An endoscopic image of early OSCC. **a** | White-light endoscopy shows an area of mucosal erythema (indicated by the arrowhead) and an additional ill-defined subtle area of reddened mucosa with a white edge (arrow). **b** | Narrow-band imaging (NBI) of the same endoscopic field shows two brown areas suspicious for early cancer (arrows). **c** | NBI magnification shows dilated intrapapillary capillary loops that are consistent with mucosal cancer (arrows). **d** | Lugol's iodine chromoendoscopy enables the precise demarcation of the two lesions (the yellow arrowheads indicate the distal lesion; the white arrowheads indicate the proximal lesion), which appear as pale mucosa (unstained lesion) surrounded by normal mucosa that is avidly stained brown by 2.5% iodine solution. Pathological analysis of the endoscopic resection specimen showed intramucosal squamous cell carcinoma with invasion of the muscularis mucosae (tumour–node–metastasis (TNM) stage pT1a, M3). OSCC, oesophageal squamous cell carcinoma. Images courtesy of M. di Pietro, University of Cambridge, Cambridge, UK.

To identify the T stage of the primary tumour, endoscopic ultrasonography is more sensitive and specific than is CT; endoscopic ultrasonography has a sensitivity and specificity of 81–92% and 94–97%, respectively⁹². In addition, endoscopic ultrasonography enables the sampling of suspicious lymph nodes to assess the N stage^{92,93} (FIG. 4). All surgical candidates should undergo PET or PET–CT, if available, to identify occult metastases (M stage); metastases are detected in approximately 15% of patients who are considered to be candidates for surgery on the basis of endoscopic ultrasonography and CT^{94,95}. Staging laparoscopy, which can be performed in patients with \geq cT3 or cN⁺ tumours at the gastro-oesophageal junction that infiltrate the cardia, may identify a similar proportion of patients with occult peritoneal disease^{95,96}. Patients with tumours at or above the carina of the trachea may undergo bronchoscopy to assess suspicious tracheal involvement, whereas those with OSCC in the context of tobacco and alcohol use should be evaluated for synchronous primary tumours of the aerodigestive tract^{6,7}.

Metabolic imaging in OAC

Changes in the degree of ¹⁸F-fluorodeoxyglucose (FDG) radionuclide uptake, as imaged by FDG-PET, are informative in patients with OAC who are treated with neoadjuvant chemotherapy. Patients who do not achieve a \geq 35% reduction in the standardized FDG uptake value following 2 weeks of platinum-fluoropyrimidine chemotherapy have worse overall survival than good metabolic responders^{97,98}. Discontinuing chemotherapy following a poor response based on FDG-PET imaging does not result in inferior survival compared with historical controls⁹⁹. The addition of radiotherapy to poor metabolic responders may improve pathological response rates and resection rates, but not survival^{99,100}. The CALGB-80803 study has reported that improved pathological complete response (pCR) rates (defined as the absence of a tumour in the surgical resection specimen) after switching to an alternative chemotherapy regimen during chemo-radiotherapy in FDG-PET determined poor metabolic responders. The pCR rate in poor metabolic responders who crossed over to a different chemotherapy was 18%, which — although lower than the pCR rate in patients who initially responded to induction chemotherapy and did not switch (26%) — is better than expected (the primary end point was a pCR of 15%); the survival results are not yet known¹⁰¹. These findings suggest that metabolic imaging can be used to identify patients with OAC who have a poor prognosis. Further investigation of PET-directed therapy is warranted.

Screening for oesophageal cancer

In Europe and North America, the majority of patients with oesophageal cancer present with locally advanced or metastatic disease that is not amenable to curative therapy. In the United Kingdom, 70–80% of patients are diagnosed with either lymph node or distant metastases¹⁵. However, although both OSCC and OAC have recognized non-invasive precursor lesions that may be treated endoscopically using ablation or resection, the low population prevalence of oesophageal cancer in

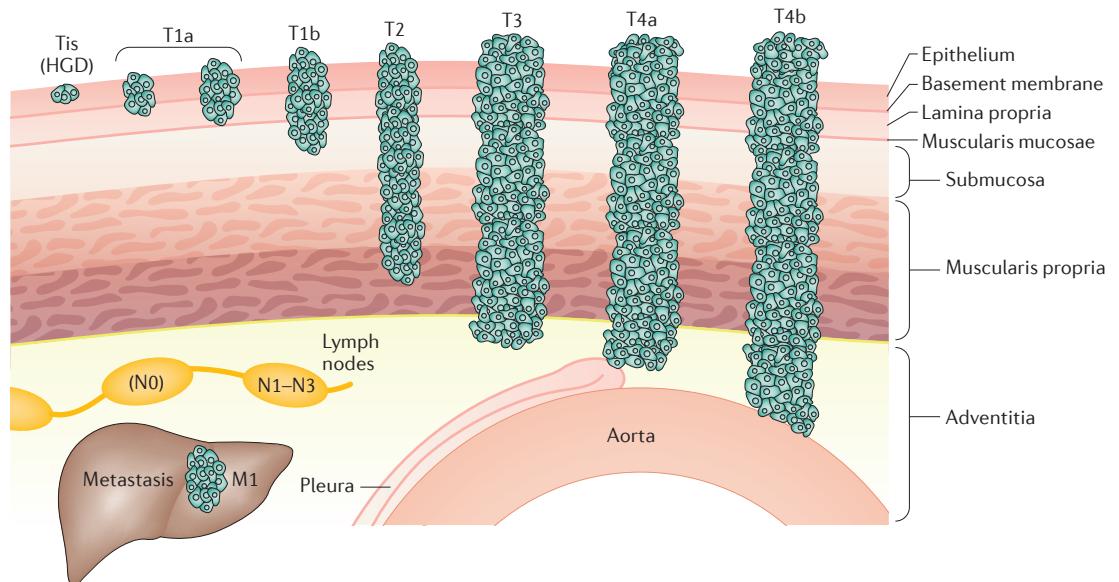


Figure 4 | Tumour–node–metastasis categories. Tumour classification according to the tumour–node–metastasis (TNM) categories. T refers to the size of the primary tumour and whether it invades the nascent tissue as shown. N refers to lymph node involvement: N0 describes no regional lymph node metastasis; N1 describes regional lymph node metastases involving one or two nodes; N2 describes regional lymph node metastases involving from three to six nodes; and N3 describes regional lymph node metastases involving seven or more nodes. M refers to distant metastasis and is categorized as M0 (no distant metastasis) or M1 (distant metastasis). HGD, high-grade dysplasia; Tis, cancer in situ. Adapted with permission from REF. 247, Elsevier.

the West is a barrier to the implementation of screening programmes¹⁰². The current American College of Gastroenterology and British Society of Gastroenterology guidelines suggest screening in patients who have a history of gastro-oesophageal reflux lasting >5 years and have multiple (≥ 2 –3) other risk factors, including male sex, Caucasian race, central obesity and current or past history of smoking. The threshold for multiple risk factors may be adjusted in the presence of a positive family history. Practices in other countries depend on country-specific guidelines^{5,103}. There are no current screening guidelines for OSCC, although studies have shown that one-off endoscopic screening using Lugol's chromoendoscopy in high-risk areas in China decreased OSCC incidence and OSCC-related mortality¹⁹.

Another impediment to introducing screening is the fact that the diagnostic modality — endoscopy — is invasive and expensive, and therefore alternative, less-invasive approaches are of interest and would enable the screening of a broader population. Transnasal endoscopy is less invasive than standard endoscopy, does not require sedation, and demonstrates equivalent sensitivity and specificity for the detection of Barrett oesophagus when tested in at-risk populations^{104,105}. However, transnasal endoscopy does require investment in equipment as well as skilled operators, and further large-scale studies in the relevant populations are needed. Other methods of screening include capsule endoscopy (the ingestion of a small video camera) and cytology-retrieval devices, such as balloons and sponges. However, capsule endoscopy has a relatively low sensitivity and specificity (73% and 78%, respectively) for the detection of Barrett oesophagus, and it is not recommended for screening by current

guidelines^{103,106}. The Cytospunge is a non-endoscopic cell-collection device comprising a sponge compressed within a gelatin capsule that expands upon swallowing and can be retrieved from the oesophagus by pulling a string¹⁰⁷. Immunohistochemistry for trefoil factor 3 (which is a marker of columnar epithelium) on cytological specimens obtained by Cytospunge yields a sensitivity (including inadequate samples in which the Cytospunge had not reached the stomach) and specificity for the diagnosis of Barrett oesophagus of 79.9% (95% CI: 76.4–83.0%) and 92.4% (95% CI: 89.5–94.7%), respectively, and the sensitivity increases markedly in patients who have long segments of Barrett oesophagus (≥ 3 cm). The sensitivity approaches 90% (89.7% (95% CI: 82.3–94.8%)) with a second swallow¹⁰⁸. The use of the Cytospunge to screen for Barrett oesophagus is now being evaluated in a large primary care trial that has a cluster randomized design and involves 9,000 patients who are receiving an acid-suppressant prescription for reflux symptoms¹⁰⁹. However, further risk stratification biomarkers are required as only a small proportion of patients with Barrett oesophagus will ultimately develop OAC, and surveillance endoscopy of all patients with Barrett oesophagus would have a substantial logistical burden^{110–113}. Aberrant p53 expression (both over-expression and loss) may be a more accurate predictor of progression than the presence of low-grade dysplasia, which is prone to inter-observer and intra-observer variability^{114,115}. The expression of p53 can be evaluated as a second-tier test on the same Cytospunge samples used for trefoil factor 3 staining. A panel of biomarkers may enable those patients who are at a low risk of progression to be spared an endoscopy^{69,76}.

Oesophageal cancer prevention

The primary prevention of oesophageal cancer is based on the avoidance of risk factors, and includes tobacco avoidance and the moderation of alcohol intake for the prevention of OSCC, the maintenance of a healthy weight for the prevention of OAC, and increasing fresh fruit and vegetable intake with a reduction in red meat consumption for both.

For patients with Barrett oesophagus, secondary prevention could potentially include pharmacological therapy with proton pump inhibitors (PPIs) or NSAIDs, locally ablative therapies to remove neoplastic precursor lesions and anti-reflux surgery¹¹⁶. PPIs are frequently used in the setting of chronic reflux, and some cohort studies and meta-analyses suggest that patients with Barrett oesophagus who are treated with PPIs have lower rates of dysplasia and OAC than do those who are not treated with PPIs^{117–119}. Although bias caused by the severity of reflux is a potential confounder of these studies, it may be reasonable to discuss PPI treatment even with patients who have asymptomatic Barrett oesophagus. The use of NSAIDs including aspirin has been associated with reduced cancer risk in several cancer types, including oesophageal cancer^{120–122}. However, NSAIDs are associated with non-trivial toxicities. A higher grade of evidence than currently available is required to institute an NSAID-based chemoprevention strategy in Barrett oesophagus, and the ongoing phase III randomized AspECT trial¹²³ might be informative regarding this approach.

Preventing the progression of dysplastic Barrett oesophagus to OAC is now achievable for many patients using ablative therapies. Patients who have Barrett oesophagus with nodular lesions should undergo endoscopic mucosal resection to determine the grade and extent of the lesion; the presence of dysplasia or carcinoma then determines further treatment. For patients with flat, high-grade dysplasia, ablation (using radiofrequency ablation or photoablation) provides equivalent efficacy to surgery with respect to long-term survival and has much less associated morbidity than does oesophagectomy. For patients with low-grade dysplasia, ablation decreases progression both to high-grade dysplasia and to invasive OAC^{124–126}. Patients often require a combination of endoscopic mucosal resection and ablation therapy^{127,128}. As patients with Barrett oesophagus without signs of dysplasia have a low risk of progression to OAC, and as there are adverse effects associated with treatment, ablative therapy is not recommended for this patient group¹⁰³. It is also important to note that endoscopic monitoring is still recommended following ablation therapy owing to the risk of recurrence¹⁰³. In the future, assessment of the molecular status of the tumour may reduce the reliance on a subjective diagnosis of dysplasia to identify patients who need therapy.

Patients with OSCC precursor lesions may also benefit from endoscopic ablative therapy, but neoplastic progression and strictures after ablation seem to be more common in patients with squamous dysplasia than in those with Barrett oesophagus; strictures may occur in up to 21% of patients with squamous dysplasia

who have undergone ablation^{129–131}. In high-incidence populations in China, studies of chemopreventive strategies that aimed to replace deficient dietary micro-nutrients have demonstrated that increasing β-carotene, vitamin E and selenium intake did not reduce OSCC incidence or OSCC-associated mortality¹³². Finally, as aspirin and other NSAIDs decrease the risk of OSCC¹³³, these treatments should be prospectively evaluated in well-controlled clinical trials.

Management

The management of oesophageal cancer is dependent on the characteristics of the patient (including fitness) and those of the tumour, mainly the TNM stage. Very early-stage tumours may be suitable for endoscopic resection, whereas locally advanced cancers are treated with chemotherapy, chemoradiotherapy, surgical resection or combinations of these. Patients with oesophageal cancers that are not suitable for surgical management are treated with systemic chemotherapy (FIG. 5).

Endoscopic management

Endoscopic management is an option for very early-stage oesophageal cancers that have minimal local involvement (stage T1a (and sometimes T1b)), and an absence of lymph node involvement and metastasis. Although these types of tumour represent only a small proportion of all tumours, the number has been increasing with the increased use of endoscopy for various indications together with the screening and surveillance of Barrett oesophagus in individuals who are at risk¹³⁴. Endoscopic treatment is most well-established for Barrett oesophagus and OAC; it might also be an option for OSCC, but the literature on this is limited.

When OAC is confined to the mucosa and there are no metastases (stage T1a, N0, M0), local endoscopic treatments with endoscopic mucosal resection or endoscopic submucosal dissection — frequently combined with radiofrequency ablation — have replaced oesophagectomy as the first-line treatment. These local treatments have been demonstrated to be less invasive, are safer, provide a better QOL and have an equally good long-term prognosis^{5,6,135} (BOX 1). Focal endoscopic mucosal resection followed by radiofrequency ablation might be recommended before stepwise or complete endoscopic mucosal resection owing to the higher rates of complications (that is, strictures, perforation and bleeding) following endoscopic mucosal resection, whereas the risk of OAC recurrence is equally low (1.4%)¹³⁶. All endoscopic procedures should be carried out by specialized endoscopists working at well-equipped high-volume centres⁵.

For more-advanced OAC tumour stages (that is, stage T1b, N0, M0), oesophagectomy remains the standard of care because submucosal tumour involvement has a 17–26% risk of lymph node metastasis, with the highest rates for tumours that are poorly differentiated, and show lymphovascular invasion and submucosal invasion >500 μm (REFS 137,138). However, for patients with T1b tumours who are not fit enough to undergo surgery or definite chemoradiotherapy (for example, because of

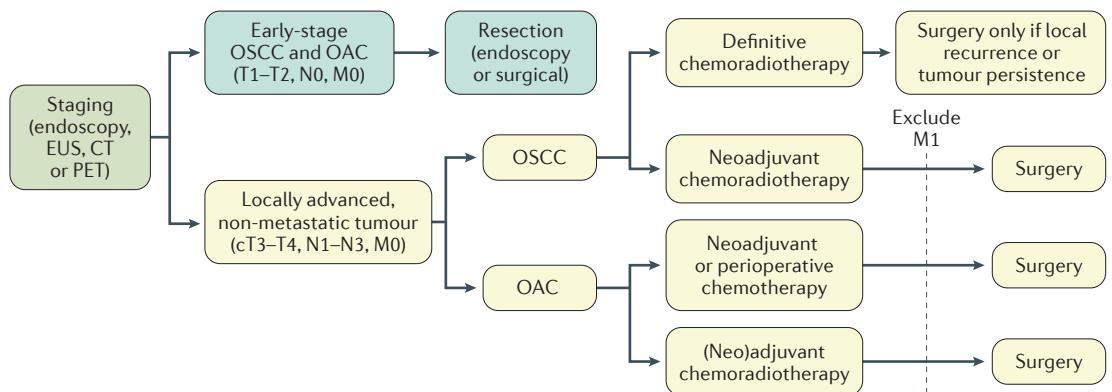


Figure 5 | An algorithm for the management of localized oesophageal cancer. The algorithm depicts the treatment options for early-stage and locally advanced oesophageal squamous cell carcinoma (OSCC) and oesophageal adenocarcinoma (OAC), in the absence of metastasis. EUS, endoscopic ultrasonography.

advanced age or severe comorbidities), endoscopic therapy can be attempted if the tumour is associated with good prognostic characteristics (that is, if the tumour shows submucosal level 1 invasion, is well-differentiated and does not show lymphovascular invasion)⁵.

Surgical management

Procedures. Locally advanced, non-metastatic OAC and OSCC tumours (stage T1b–T4, N1–N3, M0) frequently require resection. Several approaches for the resection of oesophageal cancer exist, including variations in approach and the extent of lymphadenectomy. For tumours located in or near the gastro-oesophageal junction, the resection procedure can consist of an oesophagectomy combined with the resection of the proximal part of the stomach or, alternatively, total gastrectomy combined with resection of the distal oesophagus. A systematic review of 10 cohort studies including 3,356 patients found no difference between these approaches in terms of 5-year survival or morbidity¹³⁹. The two approaches also had similar overall survival rates in a recent cohort study of 4,996 patients from the United States¹⁴⁰.

Outcomes following transhiatal and transthoracic surgery have been compared in a meta-analysis of 8 studies (including 3 randomized controlled trials (RCTs)) involving 1,155 patients; no differences in overall survival were observed¹⁴¹. A smaller meta-analysis of 6 studies (including 647 patients) contradicted this finding in 2016, as a slight survival benefit was noted in the transthoracic group¹⁴². The risk of pulmonary complications seems to be higher following the transthoracic approach than following the transhiatal approach, whereas the long-term health-related QOL might not differ much between the two approaches^{141,143}.

Minimally invasive oesophagectomy has emerged during the past few years as a feasible and safe procedure for oesophagectomy¹⁴⁴. Minimally invasive oesophagectomy could include hybrid operations that combine laparoscopy with open thoracotomy, or thoracoscopy with open laparotomy, completely minimally invasive procedures (FIG. 6) and robot-assisted surgery. A systematic review of 17 studies (including various combinations

of minimally invasive surgery) including 1,598 patients found no difference in long-term survival following minimally invasive surgery compared with open surgery¹⁴⁵. A Dutch RCT compared minimally invasive oesophagectomy ($n=59$) with open transthoracic oesophagectomy ($n=56$) and found a decreased risk of postoperative pulmonary infection (relative risk: 0.35 (95% CI: 0.16–0.78)), and better physical activity, global health and pain after 1 year in the minimally invasive oesophagectomy group^{146,147}. Studies examining short-term postoperative QOL indicate improvements in selected outcomes following minimally invasive procedures compared with following open surgery, but long-term follow-up of patient-reported outcomes is needed to assess the overall potential of minimally invasive approaches.

The optimal extent of lymphadenectomy in surgery for oesophageal cancer is a matter of controversy. Several studies have indicated a better overall prognosis when more-extensive lymphadenectomy is performed¹⁴⁸. However, some recent studies have indicated that removing more lymph nodes does not have a survival benefit over a standard approach in patients with or without metastasis, especially not in patients who have received neoadjuvant therapy^{149–151}. These findings indicate that a tailored approach regarding the extent of lymphadenectomy is needed in the era of multimodality therapy. Sentinel node biopsy (the assessment of tumour cell presence in the first lymph node to which the cancer cells are most likely to have spread) might be a future alternative for determining the extent of lymphadenectomy needed, although the unpredictability with which these tumours spread presents a challenge to this approach¹⁵².

Thus, existing systematic meta-analyses and individual studies of predominantly observational design indicate that the above variations in surgical approaches have a limited difference in terms of survival but might affect postoperative complications, morbidity and health-related QOL. Thus far, only very few RCTs have been conducted to compare the surgical approaches, and existing observational studies are heterogeneous and often provide inconsistent results; thus, these findings need to be cautiously interpreted.

Box 1 | Definitions

- Endoscopic mucosal resection: an endoscopic procedure that is used to resect and remove a defined area of the oesophageal mucosa.
- Endoscopic submucosal dissection: an endoscopic procedure that is used to dissect and remove a defined mucosal area of the oesophagus, but with wider margins than those used during endoscopic mucosal resection.
- Oesophagectomy: surgical removal of the oesophagus.
- Radiofrequency ablation: an endoscopic procedure that uses heat energy to destroy superficial mucosal lesions of the oesophagus, mainly in patients with Barrett oesophagus.
- Transhiatal surgery: a surgical method for oesophagectomy that uses an abdominal approach combined with neck dissection; thoracotomy or thoracoscopy is not used.
- Transthoracic surgery: a surgical method for oesophagectomy in which thoracotomy or thoracoscopy is used, often in combination with an abdominal approach and sometimes also with neck dissection.

Surgeon characteristics. Some factors directly related to the surgeon have a strong influence on the long-term prognosis of oesophageal cancer. The annual number of oesophagectomies per surgeon is an important and independent prognostic factor for both short-term and long-term survival, even after adjustment for the hospital annual volume of these procedures^{153–155}. Proficiency gain curves have mainly been established for minimally invasive surgery, but learning curves have also recently been identified for open oesophagectomies^{156,157}. The learning curves are longer for achieving a stable long-term survival than for stabilizing short-term mortality^{156,157}. The age of the surgeon might be an independent prognostic factor, even after adjustment for surgeon volume and other prognostic factors, and there seems to be an optimal 5-year prognosis if the surgeon is 52–56 years of age¹⁵⁸. Finally, surgery later in the week is also an independent prognostic factor and could be associated with the alertness of the surgeon¹⁵⁹.

Patient characteristics. Older age is a prognostic factor for surgery outcome, but its influence has declined with medical specialization in surgery. In fact, the negative effect of age only becomes evident after 80 years of age, and is related to comorbidities rather than age itself^{160–162}. A higher Charlson Comorbidity Index (which assigns a score that is based on the presence and severity of 22 comorbid conditions) and previous heart conditions worsen the prognosis after oesophageal cancer surgery, and comorbidities (such as cardiac or respiratory disease) also negatively influence the long-term health-related QOL following oesophagectomy^{12,162}. Ethnicity also has a role; white individuals have lower mortality rates corrected for tumour stage than do individuals of non-white ethnicity, but they are also more likely to undergo surgery and have surgery conducted at high-volume centres^{163,164}. Results from meta-analyses have consistently shown that having a higher BMI is associated with

more postoperative complications but a better overall survival^{165,166}. Tobacco smoking is negatively associated with overall survival and more so for current smokers than previous smokers¹⁶⁷. Tumour stage-specific survival among alcohol drinkers is worse than that of non-drinkers¹⁶⁸. Finally, among socioeconomic factors, a longer education is followed by better overall survival independent of other prognostic factors, particularly in early tumour stages and in tumours with a squamous cell carcinoma histology¹⁶⁹. Further research is needed to confirm and fully understand the role of these factors on prognosis after surgery.

Chemotherapy and chemoradiotherapy

Survival for patients with $\geq T2$ or N^+ cancers following surgery alone is poor; the overall survival rate 10 years after surgery even for stage 1b is only 50%¹⁷⁰. Thus, therapies in addition to surgery are required for these patients (FIG. 5). Current guidelines recommend adjunctive treatment comprising neoadjuvant or perioperative chemotherapy, radiotherapy or chemoradiotherapy for patients with $\geq T2$ OAC and OSCC tumours^{6,7}. Most oesophageal cancers are diagnosed at a locally advanced stage ($>T2$ and/or N^+); for these patients, the purpose of neoadjuvant and perioperative chemotherapy or chemoradiotherapy is to reduce the primary tumour bulk, increase the likelihood of radical (R0) resection, treat micro-metastatic disease and decrease the risk of future systemic recurrence. Neoadjuvant therapy also relieves dysphagia and improves nutritional status in the majority of patients, and it may avoid the requirement for feeding tube placement¹⁷¹. By contrast, node-negative T2 lesions with low-risk features (<2 cm and well differentiated) can be considered for oesophagectomy alone in the case of both OAC and OSCC, or considered for definitive chemoradiotherapy in the case of OSCC^{6,7}.

Although patients with OSCC or OAC have historically been treated using similar paradigms, clear biological differences between these two histological subtypes exist⁴. This heterogeneity has implications for responses to radiotherapy, patterns of metastatic spread and the interpretation of trial results. In particular, the high sensitivity of OSCC to radiotherapy leads to complete and durable pathological responses in a high proportion of patients (up to 40% of patients are progression-free at 2 years) following chemoradiotherapy, and in a subgroup of complete responders surgery even becomes unnecessary^{6,7,172,173}. In contrast to patients with OSCC, patients with OAC are recommended to undergo surgical resection even in the setting of a good clinical response to chemoradiotherapy because the complete histopathological response rate to chemoradiotherapy is lower for OSCC than for OAC, and the rate of microscopic-positive disease at the primary tumour site is higher^{6,7}.

In all cases, the multidisciplinary planning of neoadjuvant chemotherapy or chemoradiotherapy and surgery is mandatory, and close attention should be paid to performance and nutritional status, in addition to comorbidities, during preoperative assessment^{6,7}.

A team of experts from various disciplines should review the patients with respect to staging and likely treatment tolerability, and develop a consensus before starting therapy.

Neoadjuvant and perioperative chemotherapy.

The evidence base for neoadjuvant chemotherapy in the curative treatment of patients with OSCC or OAC is substantial (TABLE 3). An evaluation of surgery alone versus two cycles of neoadjuvant cisplatin and fluorouracil prior to surgery in the OE02 trial¹⁷⁴ showed that patients treated with neoadjuvant chemotherapy had an absolute overall survival benefit of 5.9% at 5 years. The overall survival benefit was not significantly different between OAC and OSCC (5% versus 8%, respectively)¹⁷⁵. However, in practice, chemoradiotherapy — and not chemotherapy — is preferred for patients with OSCC owing to the excellent responses associated with radiotherapy in this population.

For patients with OAC, the addition of epirubicin to cisplatin and capecitabine chemotherapy (ECX) and extending preoperative therapy to four cycles did not improve overall survival in the OE05 study¹⁷⁶, and therefore doublet chemotherapy is the preferred neoadjuvant treatment. The MAGIC trial and the FNCLCC/FFCD trial randomized patients with OAC or gastric cancer to groups that received perioperative chemotherapy or surgery alone, and demonstrated almost identical improvements in 5-year overall survival in both groups^{177,178}. In addition, patients treated with docetaxel plus oxaliplatin and 5-fluorouracil (known as the FLOT regimen) showed better pathological response rates than those treated with ECX in the FLOT4-AIO RCT for localized gastric cancers, including OAC. The survival results from this study have been presented in the form of a conference abstract and demonstrate superior survival among patients treated with the FLOT regimen relative to those treated with ECX (50 months versus 37 months; hazard ratio (HR): 0.77 (95% CI: 0.63–0.94); $P=0.012$)^{179,180}. Meta-analyses support the consistency

of these findings, and it is recommended that patients with OAC are treated with either neoadjuvant or perioperative platinum-based and fluoropyrimidine-based chemotherapy (including an adjuvant component, if tolerated)^{6,7,181}.

Neoadjuvant chemoradiotherapy. Chemoradiotherapy is also an effective preoperative treatment for OSCC and OAC, but especially for OSCC (TABLE 3). However, in patients with very early-stage cancers, neoadjuvant chemoradiotherapy does not lead to a survival advantage when compared with surgery alone¹⁸². Radiotherapy for patients with oesophageal cancer should be planned using CT simulation and conformal treatment planning⁷. Intensity-modulated radiation therapy may be used if dose reductions to specific organs cannot be achieved using standard 3D planning mechanisms⁷.

A comparison of weekly carboplatin and paclitaxel in addition to radiotherapy (known as the CROSS regimen) versus surgery alone in the CROSS trial¹⁸³ showed that neoadjuvant chemoradiotherapy resulted in improved overall survival for all patients, although the magnitude of this benefit was greater for patients with OSCC than for patients with OAC (HR: 0.453 (95% CI: 0.243–0.844) versus 0.732 (95% CI: 0.524–0.998) for OSCC and OAC, respectively). These results have led to the widespread adoption of the CROSS regimen as a standard treatment option for oesophageal cancer, especially for OSCC, thus replacing older and more-toxic regimens, although there are some concerns¹⁸⁴. Notably, patients with lymph node-positive cancers did not seem to derive the same magnitude of survival benefit following subgroup analysis. Concerns regarding the adequacy of the systemic dose of chemotherapy in the CROSS regimen are mitigated by a clear decrease in the occurrence of distant metastases in patients treated with chemotherapy (HR: 0.63 (95% CI: 0.46–0.87)), albeit only for the first 2 years following surgical resection¹⁸⁵.

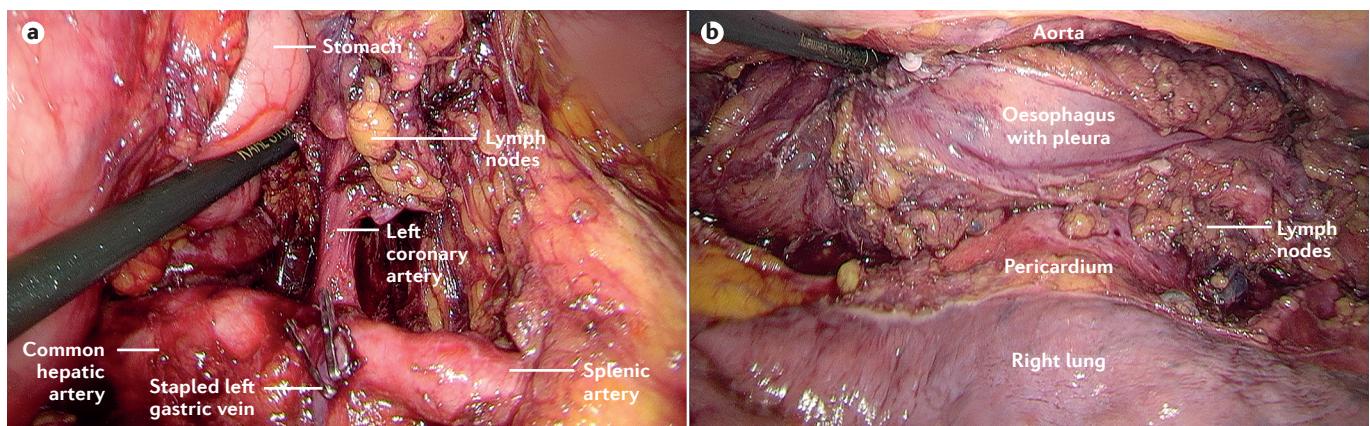


Figure 6 | Minimally invasive oesophagectomy for oesophageal cancer.

Minimally invasive oesophagectomy involves two minimally invasive procedures: one in the abdomen, followed by another in the thorax. **a** Following port placement to access the abdomen, the greateromentum is mobilized and lymphadenectomy is performed. The image shows the

arteries that join and constitute the celiac trunk following lymphadenectomy, with the stomach pushed against the abdominal wall. **b** The thoracic part of the procedure involves the mobilization of the oesophagus, whereby the oesophagus is separated from the adjacent tissue. After the removal of the tumour, the oesophagus is closed by stapling.

A comparison of chemoradiotherapy versus chemotherapy has only been done in one small study showing equivalent survival outcomes¹⁸⁶. However, several large randomized phase III trials are currently evaluating chemoradiotherapy versus chemotherapy. The findings will be of particular interest in view of the improved survival results recently presented for perioperative FLOT chemotherapy, which are equivalent to those demonstrated in the CROSS trial for chemoradiotherapy¹⁸⁶.

Combining induction chemotherapy to reduce distant metastases with chemoradiotherapy that improves local control would seem to be an attractive option. However, the role of induction chemotherapy before neoadjuvant chemoradiotherapy has not yet been confirmed, and results from small RCTs are inconsistent^{187,188}.

Definitive chemoradiotherapy. Definitive chemoradiotherapy is recommended for cervical OSCC tumours, and can be considered as an alternative standard of care for OSCC of the mid and lower oesophagus^{6,7}. Compared with chemoradiotherapy followed by surgery, definitive chemoradiotherapy has been associated

with an equivalent survival of patients with OSCC but higher rates of local relapse in two RCTs^{172,173}. The standard dose of radiotherapy in definitive protocols is 50.4 Gy, despite recent technical developments in radiotherapy delivery; the use of dose-escalated radiotherapy has not yet been validated in RCTs¹⁸⁹. If salvage oesophagectomy is considered as a therapeutic strategy, doses higher than 55 Gy should be avoided because they are linked with increased postoperative mortality and morbidity¹⁹⁰.

However, as local relapse rates are substantial, surgery might still be required following definitive chemoradiotherapy. There are no data that compare prospectively whether salvage surgery upon relapse following chemoradiotherapy is superior to neoadjuvant chemoradiotherapy followed by surgery; ongoing clinical trials are investigating this question. In the past, salvage oesophagectomy was associated with a higher rate of postoperative complications (for example, anastomotic leak rate) than was planned oesophagectomy, but the use of risk-reduction approaches — such as omental transposition and anastomosis outside the irradiated

Table 3 | Landmark studies on chemotherapy or chemoradiotherapy in oesophageal cancer

Trial	Setup*	Survival ratio (%)	Hazard ratio (95% CI)	P-value	Comments
Neoadjuvant chemotherapy					
OE02 (REF. 174)	Surgery versus CF (2x) plus surgery	5-Year: 17 versus 23	0.84 (0.72–0.98)	0.03	n=802, of which ~65% were OAC; 90% of primary tumours were in the oesophagus and 10% were in the cardia
OE05 (REF. 176)	CF (2x) plus surgery versus ECX (4x) plus surgery	3-Year: 39 versus 42	0.92 (0.79–1.08)	0.8582	n=897, all OAC or type I and type II junctional tumours; primary tumour site not known
Perioperative chemotherapy					
FLOT4-AIO ¹⁸⁰	Surgery plus pre-surgery and post-surgery ECF/X versus surgery plus pre-surgery and post-surgery FLOT	3-Year: 48 versus 57	0.77 (0.63–0.94)	0.012	n=706, 100 of which were OAC; 56% of primary tumours were in the oesophagus or gastro-oesophageal junction, and 44% were in the stomach
MAGIC ^{177*}	Surgery versus ECF (3x pre-surgery plus 1x post-surgery) plus surgery	5-Year: 23 versus 36	0.75 (0.60–0.93)	0.009	n=503, all OAC; 14% of primary tumours were in the oesophagus, 12% were in the gastro-oesophageal junction and 74% were in the stomach
FNCLCC/FFCD ^{178*}	Surgery versus CF (3x pre-surgery and 1x post-surgery) plus surgery	5-Year: 24 versus 38	0.69 (0.50–0.95)	0.02	n=224, all OAC; 11% of primary tumours were in the oesophagus, 64% were in the gastro-oesophageal junction and 25% were in the stomach
Neoadjuvant chemoradiotherapy					
CROSS ¹⁸³	Surgery versus Carbo-Pac plus RT (41.1 Gy) plus surgery	5-Year: 34 versus 47	0.657 (0.495–0.871)	0.003	n=366, of which 275 were OAC; 73% of the primary tumours were in the oesophagus (of which 15% were in the upper-to-middle region and 58% were in the lower oesophagus) and 24% were in the gastro-oesophageal junction
CALGB 9781 (REF. 248)	Surgery versus CF, RT (50.4 Gy) plus surgery	5-Year: 16 versus 39	NA	0.002	n=56, of which 75% were OAC and 25% were OSCC; primary tumour location was not available
Definitive chemoradiotherapy					
Herskovic et al. ²⁴⁹	RT (64 Gy) versus CF plus RT (50 Gy)	2-Year: 10 versus 38	NA	<0.001	n=121, of which 7% were OAC and 93% were OSCC; all primary tumours were in the oesophagus (19%, 51% and 30% were in the upper, middle and lower regions, respectively)
PRODIGE5/ACCORD17 (REF. 193)	CF-RT (50 Gy) versus FOLFOX plus RT (50 Gy)	3-Year: 27 versus 20	0.94 (0.68–1.29)	0.70	n=267, of which ~70% were OAC; all primary tumours in the oesophagus (33%, 42% and 25% were in the upper, middle and lower regions, respectively)

Carbo-Pac, carboplatin and paclitaxel; CF, cisplatin and 5-fluorouracil (the exact regimen may vary across trials); ECF, epirubicin, cisplatin and 5-fluorouracil; ECF/X, epirubicin, cisplatin, and 5-fluorouracil or capecitabine; ECX, epirubicin, cisplatin and capecitabine; FLOT, docetaxel plus oxaliplatin and 5-fluorouracil and leucovorin; FOLFOX, oxaliplatin, 5-fluorouracil and leucovorin; NA, not applicable; OAC, oesophageal adenocarcinoma; OSCC, oesophageal squamous cell carcinoma; RT, radiotherapy. *Fluorouracil and capecitabine are fluoropyrimidines; platinum-based regimens include cisplatin, carboplatin or oxaliplatin.

oesophagus — during salvage oesophagectomy in high-volume centres may reduce this risk so that it is equivalent to that of a planned surgery^{191,192}.

Definitive chemoradiotherapy is also an option for patients with OAC who are unsuitable for or who refuse surgery, but it is not the standard approach. In definitive chemoradiotherapy, cisplatin-based, oxaliplatin-based or fluoropyrimidine-based regimens have equivalent efficacy¹⁹³.

Palliative treatment

As many oesophageal cancers are unresectable at diagnosis, and more than half of patients who are treated with curative intent will develop tumour recurrence, the majority of patients will ultimately require palliative therapy^{174,176}. Radiotherapy or stent placement might reduce the symptoms associated with the primary tumour, but palliative chemotherapy is required for systemic disease control. Few studies have evaluated the role of palliative chemotherapy solely in oesophageal cancer, and therefore data are frequently extrapolated from trials containing a mixture of oesophageal, junctional and stomach cancers. In addition, studies assessing palliative chemotherapy in OSCC versus OAC are needed^{194,195}.

Palliative chemotherapy for oesophageal cancer is predominantly platinum-based and fluoropyrimidine-based^{6,196–198}. On the basis of the results of the REAL-2 trial, oxaliplatin and cisplatin are considered to be equivalent in terms of efficacy, but not in terms of their toxicity profiles; oxaliplatin was associated with increased rates of neuropathy and diarrhoea, and cisplatin with thromboembolic events and neutropenia¹⁹⁹. Capecitabine has replaced infused 5-fluorouracil in many chemotherapy regimens as it does not require a central venous access device, but infused 5-fluorouracil plus oxaliplatin (FOLFOX) remains a popular regimen. In Asia, S1 (containing tegafur, gimeracil and oteracil) is a standard treatment for advanced gastro-oesophageal cancer in combination with cisplatin, but the pharmacogenomics affecting the tolerability of this regimen in non-Asian populations have limited the use of S1 outside of Asia^{200,201}. Patients with oesophageal cancer who progress on first-line therapy may benefit from second-line chemotherapy, such as taxanes and irinotecan. However, the median overall survival benefit associated with second-line cytotoxic chemotherapy relative to that associated with the best supportive care is approximately 6 weeks^{202–204}.

As the median overall survival in clinical trials for patients treated with palliative chemotherapy for gastro-oesophageal cancer is <1 year¹⁹⁹, a consideration of the toxicity-to-efficacy ratio is required when selecting a regimen. Chemotherapy increases overall survival relative to the best supportive care (HR: 0.37 (95% CI: 0.24–0.55))²⁰⁵. A Cochrane meta-analysis showed that triplet chemotherapy is superior to doublet chemotherapy²⁰⁵. However, although standard triplet regimens improve survival, they have increased toxicity, and careful patient selection or modification of these regimens is recommended^{206,207}.

Overexpression or amplification of HER2 is common in OAC (it is found in 30% of OAC tumours in TCGA and 32.2% of gastro-oesophageal junction tumours in the ToGA screening cohort)^{4,208}. Patients with oesophageal tumours that overexpress HER2 are usually treated with the anti-HER2 monoclonal antibody trastuzumab in combination with cisplatin plus fluoropyrimidine chemotherapy, and this was demonstrated to improve overall survival in the ToGA trial for HER2-positive gastric and gastro-oesophageal junction cancer^{6,7,209}. As OAC has recently been shown to be molecularly very similar to chromosomally unstable gastric adenocarcinoma⁴, anti-HER2 therapy in OAC has a strong biological rationale. The anti-vascular endothelial growth factor receptor 2 (VEGFR2) monoclonal antibody ramucirumab also improves overall survival both as a single agent (median overall survival: 3.8 months versus 5.2 months for the best supportive care versus ramucirumab) and in conjunction with paclitaxel (median overall survival: 7.4 months versus 9.6 months for paclitaxel versus paclitaxel plus ramucirumab), but it has only been evaluated in gastric and gastro-oesophageal junctional adenocarcinoma, although based on TCGA results, this is clearly a continuum with OAC^{4,210,211}.

Quality of life

The QOL of patients with oesophageal cancer is first negatively affected by the symptoms that are associated with the obstructing tumour and later by the adverse effects of treatment. Measurements of QOL after confirmation of the diagnosis but prior to treatment are often used as ‘baseline’. Such measurements can be valuable for the adjustment of differences between groups in statistical analyses, but they do not mirror the actual baseline level because most patients at that point in time are already seriously affected by their disease. Before diagnosis, the majority of individuals with oesophageal cancer experience dysphagia, eating difficulties and appetite loss, resulting in considerable weight loss and fatigue, which influence the daily life and QOL of patients¹³. Individuals who have advanced-stage tumours may suffer from additional problems — such as odynophagia, hoarseness and coughing — owing to tumour overgrowth or metastatic disease²¹².

Good communication between health care professionals and patients facilitates adjustment to illness and improves QOL. In conjunction with information about different treatments and their influence on QOL, patients often require information about the potential long-term benefits and consequences of treatments, including topics such as work ability, social functioning and physical symptoms. A core information set with aspects that should be discussed with patients before treatment has been developed. This set includes information on what to expect upon admission, during hospital stays (for example, information about major complications), and after treatment and discharge (for example, expected recovery milestones, and the effect of treatment on eating, long-term QOL and survival)²¹³.

To prepare for curative treatment, preoperative interventions that improve patient survival and treatment success rate are being studied^{214,215}. As malnourished patients are at a greater risk of surgical morbidity and mortality, attention to preoperative nutritional status is needed²¹⁶. If intervention for feeding is required because of dysphagia, jejunostomy is preferred to stenting in operable cancer²¹⁷. Neoadjuvant therapy reduces physical fitness and social functioning, and increases fatigue, nausea and vomiting, dyspnoea, appetite loss, diarrhoea and taste problems during treatment, but recovery is usually achieved before surgery, and postoperative recovery is similar to that of patients receiving surgery alone²¹⁸. Few studies have evaluated the influence of definitive chemoradiotherapy on the QOL of patients. A multicentre RCT showed that definitive chemoradiotherapy negatively affects the QOL of patients during treatment, but the symptoms are usually resolved within 6 months, except for persisting fatigue and insomnia²¹⁹. Patients undergoing definitive chemoradiotherapy tend to recover faster than those who undergo surgery²¹⁹. Oesophagectomy has a detrimental effect on the QOL of patients in the short term and the long term. Complications after surgery are the strongest known risk factor for poor QOL, and for delayed and incomplete recovery^{220,221}. After surgery, most patients struggle with loss of appetite, difficulty eating, and severe and long-standing postoperative weight loss, and thus the support of a dietitian is warranted^{13,222}. The majority of patients are not eligible for curative treatment and will thus undergo palliative treatment, which has the main aim of prolonging survival while preserving QOL. The literature assessing QOL in patients undergoing palliative treatment is limited, but this is an important area for future research²²³.

Clinical guidelines do not provide much information on how patients with oesophageal cancer should be followed up after treatment regarding, for example, the frequency or duration of follow-up. One important aim of the follow-up is to support patients in their recovery after treatment. Supportive care needs after treatment may differ substantially between patients, and a tailored follow-up supported by a multidisciplinary team is recommended. With the increasing incidence of OAC, combined with improvements in survival, more patients will need long-term follow-up. To meet the burden on the outpatient clinic, nurse-led follow-ups have been evaluated, and studies have reported encouraging results regarding patient satisfaction and cost-effectiveness^{224–226}.

Outlook

As multiplatform molecular characterization studies examining oesophageal cancer continue to accumulate, it is likely that the findings of this research will begin to have an effect on the future diagnosis and individualized management of this disease, and that the treatments for OSCC and OAC may further diverge⁴. Earlier diagnosis in larger numbers of carefully selected high-risk patients might be facilitated by the use of non-invasive methods to obtain samples

(such as Cytosponge or the assessment of volatile organic solvents in exhaled breath) and by the optimization of biomarkers specific for dysplasia and early cancer²²⁷. This approach should lead to the increased use of curative endoscopic therapy and a reduction in oesophagectomies.

For patients with locally advanced cancers who require neoadjuvant chemotherapy or chemoradiotherapy, ongoing clinical trials will address several important questions. These questions include whether neoadjuvant chemotherapy, chemoradiotherapy or induction chemotherapy followed by chemoradiotherapy is the ideal treatment for resectable OAC, and when (if any) the best time to perform oesophagectomy following chemoradiotherapy for OSCC is.

In addition, several new therapies or treatment targets have been tested for the management of oesophageal cancer, and several promising studies are ongoing. The development of targeted therapies in oesophageal cancer over the past decade has been disappointing, with the exception of trastuzumab. International RCTs have investigated agents that target EGFR, the tyrosine-protein kinase MET (also known as hepatocyte growth factor receptor), mechanistic target of rapamycin (mTOR), and the VEGF and FGFR pathways without success^{8–11,228–231}. The unmet need for trials in OSCC is highlighted by the fact that only one of these studies (the COG trial²²⁸) enrolled patients with OSCC. For OAC, the challenges associated with biomarker selection and targeted therapy are exemplified by HER2 expression, for which clear evidence of significant intra-patient heterogeneity of HER2 and the deleterious effect of heterogeneity on the response to anti-HER2 therapy has accumulated^{232–234}. The role of gene copy load, intra-tumoral heterogeneity and receptor tyrosine kinase co-amplification on the response to targeted therapy has also been demonstrated for EGFR-amplified, FGFR-amplified and MET-amplified gastro-oesophageal tumours^{85,235,236}. As the amplification of receptor tyrosine kinases is one of the key targetable lesions in OAC (and in chromosomally unstable gastric cancer), the identification of patients in whom the tumour is truly dependent on receptor tyrosine kinase signalling and who are most likely to benefit from drugs that target these pathways is an important future challenge.

Prospective pathways that could be investigated as the targets of targeted therapy in oesophageal cancer include cell cycle regulators and the DNA damage response pathway. Cell cycle pathway dysregulation is present in up to 90% of OSCC tumours and 86% of OAC tumours via distinct but overlapping mechanisms⁴ (FIG. 7; TABLE 2). Inhibitors of CDK4 and CDK6 — such as ribociclib and palbociclib — which have been shown to improve survival in oestrogen receptor-positive breast cancer²³⁷, could be used in OAC tumours that have CDK4 and CDK6 amplifications; these tumours have been shown to depend on CDK4 and CDK6 signalling in preclinical studies²³⁸. The development of drugs such as PARP inhibitors, which target the DNA damage response pathway, in gastro-oesophageal cancer has also been hindered by the absence of biomarkers

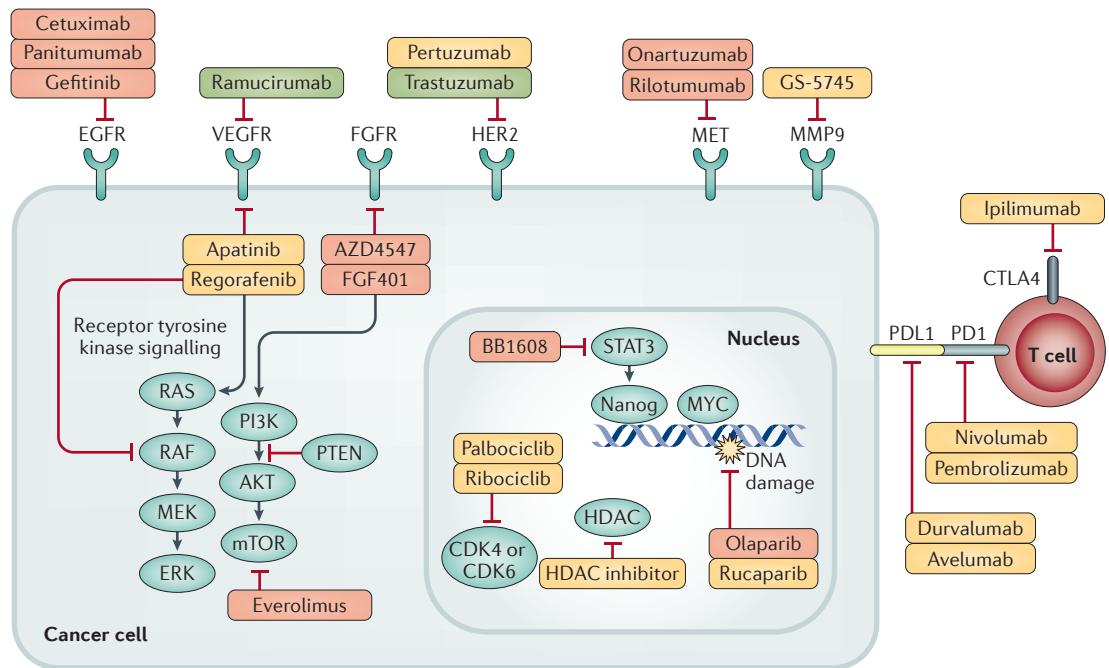


Figure 7 | Potential drug targets in oesophageal cancer. Drugs shown in red have been tested in patients with oesophageal cancer, without success. Drugs highlighted in yellow are currently being evaluated or could be evaluated on the basis of emerging data on active pathways in oesophageal cancer. Regorafenib, apatinib and nivolumab have improved the overall survival of patients with gastric cancer in randomized trials. At the time of publication, the only drugs that have achieved a survival advantage in patients with oesophageal cancer in randomized trials with a control group are trastuzumab and ramucirumab (green). CDK, cyclin-dependent kinase; CTLA4, cytotoxic T lymphocyte protein 4; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; FGFR, fibroblast growth factor receptor; HDAC, histone deacetylase; HER2, human epidermal growth factor receptor 2; MEK, MAPK/ERK kinase; MMP9, matrix metalloproteinase 9; mTOR, mechanistic target of rapamycin; PD1, programmed cell death protein 1; PDL1, PD1 ligand 1; PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homologue; STAT3, signal transducer and activator of transcription 3; VEGFR, vascular endothelial growth factor receptor.

for population selection²³⁹. However, moving beyond immunohistochemistry biomarkers associated with an impaired DNA damage response to more-nuanced signatures using next-generation sequencing — like those used to predict response to PARP inhibition in ovarian cancer — may be useful in the future^{84,240,241}.

Oesophageal cancer is associated with a relatively high mutational load, which, in other tumours, is correlated with response to therapy directed at programmed cell death protein 1 (PD1)^{80,242}. Data on the use of anti-PD1 therapy in oesophageal cancer are preliminary but encouraging. The objective response rate of 23 patients who had PD1 ligand 1 (PDL1)-positive oesophageal cancer and were treated with pembrolizumab in the phase Ib KEYNOTE-028 study was 30% overall (40% for OAC and 29% for OSCC)²⁴³. A PDL1-unselected population of 64 patients with OSCC demonstrated an independently reviewed objective response rate of 17% to nivolumab (an anti-PD1 antibody) therapy²⁴⁴. Patients with PDL1-unselected gastric or gastro-oesophageal junctional adenocarcinoma were treated with nivolumab or nivolumab plus ipilimumab (an antibody that targets cytotoxic T lymphocyte protein 4 (CTLA4)) in the CHECKMATE 032 study²⁴⁵. Nivolumab treatment induced radiological responses

in PDL1-positive and PDL1-negative tumours (27% versus 12% for PDL1 levels of $\geq 1\%$ and $< 1\%$, respectively), and these responses were more frequent in both PDL1-negative and PDL1-positive patients who were treated with combination immunotherapy²⁴⁵. A phase III RCT has demonstrated the superiority of nivolumab in terms of overall survival relative to the best supportive care in patients with chemorefractory gastric cancer, with a key finding of an improvement of 1-year survival from 10% to 26% in nivolumab-treated patients despite a relatively low radiological response rate of 11%²⁴⁶. Thus, it is likely that, pending the results of ongoing trials, checkpoint inhibitor therapy with agents such as nivolumab and ipilimumab will be integrated into treatment paradigms for patients with oesophageal cancer²⁴⁶.

Given the rapid development of immuno-oncology therapies and the promising preliminary results, other questions arise, such as how best to select patients for immuno-oncology therapy and how to integrate these treatments into other molecularly targeted and current treatment paradigms. Together, these advances in screening, diagnosis and treatment may have the positive impact of reducing the morbidity and mortality associated with oesophageal cancer.

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Competing interests

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