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Oesophageal Cancer

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Abstract

Oesophageal cancer is the sixth most common cause of cancer death worldwide, and is therefore a major global health challenge. The two major subtypes of oesophageal cancer are oesophageal squamous cell carcinoma (OSCC) and adenocarcinoma (OAC) which are epidemiologically and biologically distinct. Pre-neoplastic 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 cytotoxic chemotherapy; those who are 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 review best practices in chemotherapy, chemoradiotherapy, surgery, and maintenance of patient quality of life.

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Conflict of interest

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Introduction

As a disease entity, oesophageal cancer is principally comprised of two epidemiologically and pathologically distinct diseases which share an anatomic site; these are oesophageal squamous cell cancer (OSCC) and adenocarcinoma (OAC). SCC and OAC have divergent risk factors and incidence trends; whereas the incidence of OSCC is declining in most parts of the world, 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, whilst OAC resembles chromosomally unstable gastric cancer in its genetic makeup.4 Precursor dysplastic lesions are detectable for both OSCC and OAC using endoscopy and non-invasive screening methods, however routine screening is not currently recommended outside high risk areas, or for low risk individuals.5 Local ablative treatment of dysplastic lesions results in excellent long term outcomes, without the requirement for extensive oesophageal resection or intensive oncological treatment, and early cancers may also be treated successfully with endoscopic resection.6,7 Patients with locally advanced cancer frequently develop recurrent disease following surgery alone, and either chemotherapy or chemoradiotherapy is recommended as an adjunct to (or instead of for OSCC patients) surgery for such patients.6,7 In advanced or metastatic oesophageal cancer, combination chemotherapy regimens extend survival, however in order to improve overall survival beyond the current median of less than one year, novel therapies tailored to the molecular composition of the tumour are urgently required in order to improve patient outcomes. Finally, as oesophageal cancer treated with either curative or palliative intent results in a substantial symptom burden and changes in quality of life, attention to symptom control and other patient reported outcomes is important.8,9 In this Primer we review up-to-date findings on the epidemiology, pathogenesis and treatment of oesophageal cancer, including endoscopic, surgical and medical oncology approaches, as well as effect on patients' quality of life, in addition to emerging data on screening and chemoprevention.

Epidemiology

Oesophageal cancer is a global problem and the sixth most common cause of cancer death annually. In 2013 there were an estimated 442,000 diagnoses of oesophageal cancer worldwide, and 440,000 deaths occurred from this disease, demonstrating the high fatality rate associated with an oesophageal cancer diagnosis. Because OSCC and OAC are associated with divergent histology and biology, anatomic sites of disease, and aetiological factors, their pathogenesis and molecular biology will be discussed separately below.

Epidemiology

Oesophageal squamous cell carcinoma—OSCC accounts for 70% of cases of oesophageal cancer globally, and is particularly common in a so-called "oesophageal cancer belt" which stretches from northern China (where annual incidence rates are up to 100/100,000 population) through the central Asian republics to Northern Iran (Figure 1).1 In many countries, the incidence of OSCC has fallen substantially in recent years due to improved living conditions and OSCC mortality has reduced due to endoscopic screening programmes. For example, US OSCC incidence rates have fell C by 3.6% annually

1998-2003 and a similar fall of 3.3% occurred in the annual standardised incidence rate in China from 1989-2008; decreased incidence rates are also apparent in high incidence areas within China such as Cixian10–12

Oesophageal adenocarcinoma—In contrast to the falling incidence rates of OSCC, a significant and sustained rise in the rate of OAC has been observed in Western industrialised countries (average annual proportional increase in age adjusted incidence ranges from 3.5% (95% CI 3.3 to 3.7) per year in Scotland to 8.1% (95% CI 6.4 to 10) per year in Hawaii), where OAC is now the predominant subtype observed.2,3,13

Mechanisms/pathophysiology

Oesophageal squamous cell carcinoma

Risk factors—Recurrent chemical or physical insult to the oesophageal mucosa increases the risk of OSCC. In non-endemic areas, OSCC is predominantly associated with tobacco and alcohol use, whereas in high risk geographic areas these factors are often less important Tobacco smoke contains carcinogens such as polycyclic hydrocarbons, nitrosamines and acetaldehyde, and active smoking is associated with a 5 to 9-fold increased risk of OSCC overall, although in high risk areas the relative risk is lower (e.g. 1.3 in Linxian, China).14–16 The deleterious effects of alcohol on the oesophageal mucosa are mediated by acetaldehyde, secondary to oxidation from the oral microbiota and salivary products, and pharmacogenetic differences in alcohol metabolism in Asian populations increase acetaldehyde exposure in this population.17,18 Smoking and alcohol synergise to increase the risk of OSCC by threefold.19 Low intake of fruit and vegetables is also associated with increased OSCC risk, as are specific regional marginal micronutrient deficiencies, particularly in endemic areas.20–22 Many of these risk factors for OSCC are associated with lower socioeconomic status and accordingly, OSCC is more common in economically deprived groups and regions.23 Recurrent thermal injury due to ingestion of high temperature beverages such as tea may be contributory to regional variation in OSCC incidence, for example in Northern Iran. 24 Finally, although human papillomavirus (HPV) infection has been suggested to be associated with OSCC, the recent oesophageal The Cancer Genome Atlas (TCGA) demonstrated OSCC to have a molecular profile consistent with HPV-negative squamous cell carcinoma, suggesting that HPV-associated OSCC may reflect heterogeneity of HPV prevalence globally rather than a causative effect.4,25

The role of inherited genetic variants on OSCC cancer risk is modest apart from rare familial cases. Tylosis is an autosomal dominant disorder caused by germline mutation in *RHBDF2* (encoding for iRhom2)which is associated with palmar/plantar hyperkeratosis and a 90% cumulative risk of OSCC by 70 years of age.26 Large-scale GWAS studies in China have identified a susceptibility locus (OR 1.3 - 1.4) for OSCC at: 10q23 (encoding PLCE1; associated with growth, differentiation and apoptosis); 5q31.2 *(*encoding TMEM173; associated with Type 1 interferon response to microbial infection); 17p13.1 (encoding ATP1B2; near TP53) and specific to high-risk areas, in the HLA class II region (6p21.32). 27–29 Genetic variability in detoxification processes may also modify environmental influences on OSCC susceptibility; for example functional variants in alcohol

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dehydrogenase IB (ADH1B) and aldehyde dehydrogenase 2 (and ALDH2) enzymes synergise with lifestyle factors to enhance OSCC risk in the Japanese population.30

Pathogenesis and molecular characterisation—OSCC develops from basal cell hyperplasia and dysplasia (low and high grade) to carcinoma in situ, which can be identified at endoscopy by Lugol's voiding patches and biopsied (Figure 2). The molecular progression from dysplasia to invasive OSCC has not been well studied, however dysregulation of *TP53* and cell cycle regulators are prominent characteristics of OSCC, which may also be detected in precursor lesions.31 Abnormal P53 protein accumulation has been demonstrated in oesophagitis adjacent to dysplasia and carcinoma and increased expression of CDKN2A/RB1 has been associated with stepwise progression from inflammation to cancer in oesophageal lesions.32,33 Differentiation between normal and dysplastic tissue for accurate risk stratification is challenging, however evaluation of genes differentially expressed in normal oesophageal mucosa and OSCC has identified two candidate biomarkers; *TNFAIP3* and *CHN*, levels of which increase through the normal tissue-dysplasia-carcinoma sequence, implying these could aid in future diagnosis of dysplasia or invasive OSCC.34

Several recent large-scale sequencing and multiplatform studies have evaluated the mutational, transcriptomic and epigenetic profile of invasive OSCC. Within the TCGA dataset, most commonly mutated genes (point mutations and small indels) included *TP53* (91%), *MLL2* (17%) and *NFE2L2* (14%), whereas amplifications were frequently identified in SOX2/TP63 (48%) and FGFR1 (12%). These data confirm the results of several previous studies (Table 2).4,35–37 Dysregulated pathways of therapeutic interest in OSCC include cell cycle regulators, tyrosine kinase receptors, chromatin remodelling and embryonic pathways such as Hippo (via YAP1 amplification or VGLL4/ATG7 deletion). In the TCGA, CDKN2a was inactivated in 76% tumours and amplification of CCND1 was present in 57%, confirming study findings.35,36 The EGFR signalling pathway was activated via mutation or amplification in 19% of tumours, and PIK3CA in 24%. Each of these pathways has been successfully targeted using tyrosine kinase inhibitors in other solid tumours.

Oesophageal adenocarcinoma

Risk factors—OAC has a glandular structure and arises primarily from Barrett's mucosa in the lower oesophagus. Gastro-oesophageal reflux, including acid and bile, is the most important risk factor for OAC and in population-based case-control studies and meta-analysis, gastro-oesophageal reflux is associated with an odds ratio (OR) of 12.0 (95% Confidence Interval (CI) 7.64-18.7) and 4.64 (95% CI 3.28 - 6.57) for Barrett's oesophagus (BE) and OAC respectively.38,39 After reflux, obesity, and in particular central (visceral) obesity, is the second strongest risk factor for BE/OAC and these two factors display synergy.38,40–42 Obesity can increase reflux through elevated intra- abdominal pressure and the obesity-related metabolic syndrome is also a risk factor for Barrett oesophagus, independent of reflux symptoms.43 Although smoking is a moderately strong risk factor for OAC, its association with BE is less clear and alcohol does not appear to substantially increase the risk.38,44,45 Other risk factors for BE/OAC include male gender (male:female incidence 7:1), high red meat intake (OR 1.91 (1.07-3.38) for highest vs. lowest tertile), and

lower fruit/vegetable intake (OR 0.86 95%CI 0.80–0.93) per portion fruit or vegetable/day).38,46–49 In contrast *Helicobacter pylori* infection demonstrates an inverse association with BE/OAC risk, and decreasing population seropositivity for *Helicobacter pylori* due to improved socioeconomic conditions may also contribute to rising rates of OAC.50,51

Host genetics also contribute up to a one-third of the risk for sporadic BE and OAC development and approximately 7% of cases of BE and OAC may be familial.52–54 Genome wide association studies (GWAS) have identified risk loci linked to oesophageal embryonic development (*FOXF1*, *BARX1*), host immune response (MHC locus 16.24) and cellular proliferation and transformation [*CRTC1* (19p13)].55 The importance of embryonically active genes in OAC risk is emphasised by the results of a large meta-analysis of all available GWAS studies of BE/OAC (including 6167 patients with BE and 4112 patients with OAC) which identified several new risk loci including *ABCC5* (1·17, 95% CI 1·11–1·24; $p=1{\cdot}64 \times 10^{8}$ for OAC only) which in common with FOXF1 and BARX1 is associated with oesophageal development.56 Finally, the genetically determined host response to inflammation caused by germline variation in inflammation response genes such as microsomal glutathione-S-transferase 1 (*MGST1*) or *FOXP1* may also determine individual BE and OAC risk 57,58

Pathogenesis: Barrett's oesophagus and malignant transformation—Typically, the oesophageal mucosa is exposed to reflux of acid and bile and is injured due to reactive oxygen species and nitric oxide production leading to DNA damage and a characteristic mutational profile of A>C transversions has been attributed to reflux-induced damage (Figure 2). This base transversion profile is common to BE and OAC lending further support to the hypothesis that these DNA damaging factors are causally acting early in the disease pathogenesis.59–61 Hence, although the cell or origin is unclear it is generally agreed that BE occurs as an adaptive response to recurrent injury to squamous mucosa.62,63 In a minority of patients (0.12 – 0.6 % annually) this metaplastic mucosa may then progress through high and low grade dysplasia to invasive OAC and much effort is ongoing to understand the triggers and pathways underlying progression so that high risk patients can be identified more accurately.64–66

As Barrett's mucosa is a pre-neoplastic tissue where squamous oesophageal epithelium is replaced by a columnar intestinal type mucosa, it frequently contains somatic genetic alterations which predispose to carcinogenesis. However only a small proportion of mutated genes, i.e. *TP53* and *SMAD4*, seem to occur in a stage-specific manner, which may be helpful for identification of patients at risk of progression to OAC.67 Other genetic abnormalities which are common in BE include loss of heterozygosity of multiple loci, in particular 17p and 9p which contain the tumour suppressor genes *TP53* and *CDKN2A*.68,69

Dysregulation of p53 signalling plays a key role in progression of BE to invasive OAC. Acquisition of loss of heterozygosity of 17p in BE has been associated with development of aneuploidy and an increased potential for malignant progression.68,70 A paired sequencing study of BE and OAC samples from 25 patients demonstrated that a genome doubling event in a *TP53* mutant cell commonly precedes OAC development. 71 Furthermore tumours that had undergone a genome doubling event had distinct characteristics, including an increase in

focal genomic amplifications. Thus, two mechanisms of OAC generation from BE are proposed, the first through the stepwise acquisition of loss of tumour suppressor genes such as *CDKN2A* and *TP53* and also involving mutations in *SMAD4* and disruption of chromatin modifying enzymes, but without an acute genome doubling event and a second mechanism involving large-scale chromosomal instability associated with aneuploidy following loss of p53 regulation.(66) Other pathways, e.g. chromosomal crises causing chromothripsis and kategis, may also cause sudden accelerations towards invasion. These findings may explain the lack of copy number alterations in BE compared to invasive OAC, despite similar mutational signatures.72 Clonal diversity is also as common in BE as in OAC, and greater clonal diversity is associated with an increased risk of progression from BE to invasive OAC. 68,72–74 These data imply that sampling BE requires a wide sampling field to improve accuracy of risk stratification; as multiple biopsies increase patient risk, non-invasive strategies may be preferred in the future.75

Epigenetic modification is another factor in OAC development; both BE and OAC are frequently highly methylated compared to normal oesophageal mucosa although levels are heterogeneous.76 For example, hypermethylation of the promoter of *CDKN2A* (p16INK4a) is frequent and associated with neoplastic progression in BE, and together with loss of 9p21 loss this may lead to inactivation of *CDK2NA* which is a common finding in invasive OAC. 77–79

Pathogenesis: genetics of invasive oesophageal adenocarcinoma—OAC has a high mutation burden compared to other cancers [9.9/Mb (range 7.1–25.2/Mb; 9.9/Mb on average for other cancers).61 However, although point mutations are abundant in particular in tumour suppressors such as TP53, CDK2NA and ARID1A, structural alterations dominate the OAC landscape.61,67,79–81 Copy number alterations (amplifications and deletions) are common: amplifications of potential therapeutic relevance are frequently found in receptor tyrosine kinases involved in cell signalling (*ERBB2*, *EGFR*, *KRAS*, *FGFR2*), in cell cycle regulators (*CCND1*, *CDK6*) and in transcription factors (*MYC*, *GATA4*, *GATA6*).61,79,82,83 However, in OAC, co-amplification of receptor tyrosine kinases is common (e.g. *ERBB2* and *EGFR*) and is probably associated with both *de novo* and acquired resistance to targeted therapy, posing a challenge for drug development (see section on emerging therapies).84–86 The gross chromosomal instability associated with OAC is shared with chromosomally unstable (CIN) gastric cancer. 79 The heterogeneity and co-amplification profiles of OAC make targeted therapies a challenge; however, alternative means of identifying molecular subgroups may suggest avenues for therapeutic intervention. Following whole genome sequencing of 129 OAC as part of the International Cancer Genome Consortium, three subgroups were exemplified by either a defective homologous recombination repair, a T>G mutation pattern associated with a high mutational load, or a C>A/T mutation pattern in keeping with an aging imprint.84 Putatively effective treatments for a DNA damage repair deficient subtype could include PARP/ATR inhibitors or platinum-based chemotherapy, whereas the subgroup with a high mutational burden could benefit from immuno-oncology therapies. However, further functional and clinical validation of these subgroups is required.

Diagnosis, screening and prevention

Diagnosis of oesophageal cancer (OAC and OSCC)

Due to the muscular and expansive nature of the oesophagus, symptoms from an obstructing or stricturing lesion may only become apparent when the tumour has reached a relatively locally advanced or even metastatic stage. Warning symptoms include difficulty or pain on swallowing (dysphagia or odynophagia), involuntary and progressive weight loss and hoarseness or cough (which can signify laryngeal nerve involvement or aspiration). Occasionally patients may vomit blood or pass melaena. More commonly fatigue may occur due to anaemia in the presence of chronic, occult bleeding or due to the disease burden. Clinical examination should focus on assessment of performance status and evaluation of clinically apparent metastatic disease (e.g. supraclavicular lymph nodes and hepatomegaly), but endoscopy (which may be enhanced using narrow band imaging or Lugol's solution for squamous dysplasia) is the mainstay of evaluation since often the clinical examination is unremarkable even with locally advanced disease.87

Tumour characteristics which should be documented at endoscopy include exact site (relative to the gastro-oesophageal junction, extension into the stomach and distance from the teeth), length of the lesion, circumferential involvement and presence of obstruction.7 Any adjacent pre-malignant lesions, i.e. squamous dysplasia or BE should be documented and measured. Since the mucosa can be friable with ulceration a minimum of six biopsies are recommended for histological confirmation.88 Histology should be classified according to WHO criteria, and histological subtype and grade should be documented.7,89,90 In the presence of a poorly differentiated tumour when the histological subtype cannot be determined using a microscope, immunohistochemistry staining may help to distinguish between adenocarcinoma (periodic acid staining (PAS) or cytokeratin 7/20) and squamous cell carcinoma (cytokeratin 5/6 and p63). Identification of rare histologies, e.g. neuroendocrine tumours, lymphoma, gastrointestinal stromal tumours and melanoma which have individual treatment paradigms is also essential. Assessment of HER2 staining should be performed in patients with advanced tumours not suitable for curative therapy in whom trastuzumab might be a treatment option.6,7

Staging of oesophageal cancer (OAC and OSCC)

As oesophageal cancer surgery is associated with considerable morbidity and changes in postoperative quality of life, careful attention to patient selection for resection is essential in order to minimise the risk of futile surgery in patients with incurable disease.

Staging of oesophageal cancer should be performed according the current American Joint Council on Cancer (AJCC), 8th edition.91 Staging may be assessed clinically/radiologically (e.g cT2,), pathologically (e.g. pT2) or following neoadjuvant treatment (e.g. ypT2). All patients should first undergo computerised tomography (CT) to rule out distant metastatic disease.6,7 If metastatic disease is not detected on CT, endoscopic ultrasound (EUS), positron emission tomography (PET) or PET-CT, and/or laparoscopy (for OAC) may be considered. EUS is more sensitive and specific than CT for identification of T- stage of oesophageal cancer (sensitivity and specificity for T stages is 81%–92% and 94%–97%,

respectively), and is also useful for sampling suspicious lymph nodes (Figure 4).92,93 EUS may be helpful in patients with very early stage (cT1) (Figure 3B) or locally advanced (cT4b) cancers when it can confirm or refute the possiblity of endoscopic resection or surgery.94 Diagnostic EMR may also be helpul in very early stage tumours. All surgical candidates (who do not have metastatic cancer and are fit for surgery) should undergo PET-CT if available, as PET or PET-CT can identify occult metastases in approximately 15% of patients.94,95 Staging laparoscopy performed in patients with ≥cT3 or cN+ tumours of the gastro-oesophageal junction infiltrating the cardia may identify a similar proportion of patients with occult peritoneal disease.95,96 Patients with tumours at or above the carina may undergo bronchoscopy to assess potential tracheal involvement, whereas those with OSCC in the context of tobacco and alcohol use should be carefully evaluated for synchronous primary tumours of the aerodigestive tract.6,7

Metabolic imaging in OAC—Changes in the degree of radionucleotide uptake of 2-deoxy-2-[18F]-fluoro-D-glucose (18F-FDG PET) are informative in OAC patients treated with neoadjuvant chemotherapy. Patients who do not achieve a ≥35% reduction in SUV (standardized uptake value) following two weeks of platin-fluoropyrimidine chemotherapy have worse overall survival than good metabolic responders.97,98 Discontinuing chemotherapy following a poor PET response does not result in inferior survival compared to historical control; however conversely, the addition of radiotherapy to metabolic poor responders may improve pathological response rates and resection rates, but not survival. 99,100 The CALGB 80803 study has recently reported improved pathological complete response (pCR) rates after switching to an alternative chemotherapy regimen during CRT in PET non-responders to induction therapy (15% pCR) however, this pCR rate remains low for induction chemotherapy followed by CRT, and survival results are not yet known.101 These findings suggest that metabolic imaging identifies a biologically poor prognosis group of OAC patients; and further investigation of PET-directed therapy is warranted.

Screening for oesophageal cancer (OAC and OSCC)

In Europe and North America, many patients with oesophageal cancer present with locally advanced or metastatic disease, not amenable to curative therapy; in the United Kingdom 70-80% of patients are diagnosed with either lymph nodes or distant metastases, and 37-42% have distant metastases at diagnosis.7,102 However, although both squamous and glandular oesophageal cancers have recognised non-invasive precursor lesions which may be treated endoscopically using ablation or resection, the low population prevalence of oesophageal cancer in the West is a barrier to screening implementation.103 Current American and British Society of Gastroenterology guidelines suggest screening in patients with a history of reflux >5 years, male gender, Caucasian race and with a family history of BE or OAC, each of which are established risk factors for OAC.104,5 There are no current screening guidelines for OSCC, however in high-risk areas in China, one-off endoscopic screening using Lugol's staining (Figure 3A) decreases OSCC incidence and OSCC-related mortality.105

One impediment for introducing screening is the diagnostic modality - endoscopy is the gold standard for diagnosis of oesophageal cancer but it is invasive and expensive, and therefore

alternative approaches to broaden the test-population are of interest. Transnasal endoscopy is less invasive and demonstrates equivalent sensitivity and specificity to standard endoscopy for detection of BE when tested in enriched cohorts, however it requires investment in equipment as well as skilled operators and further large-scale studies in the relevant populations are needed.106,107 Non-endoscopic methods of screening include video capsule endoscopy and cytology retrieval devices such as balloons and sponges. However, video capsule endoscopy has a relatively low sensitivity and specificity (73% and 78% respectively) for detection of BE, and is not recommended for screening by current guidelines.104,108 The Cytosponge is a non-endoscopic cell collection device which comprises a sponge compressed within a gelatin capsule which expands on swallowing and can be retrieved from the oesophagus by pulling a string enabling cytological analysis of retrieved cells to be performed.109 Immunohistochemistry for the Trefoil factor 3 (TTF3) protein on Cytosponge cytological specimens yields a sensitivity (including inadequate samples in which the Cytopsonge had not reached the stomach) and specificity for diagnosis of BE of 79.9% (95% CI 76.4%-83.0%) and 92.4% (95% CI 89.5%-94.7%), respectively; and sensitivity increases markedly in patients with ≥3cm BE segments, and approaches 90% [89.7% (95% CI 82.3%-94.8%)] with a second swallow.110 This is now being evaluated in a large primary care trial of 9,000 patients in a cluster randomised design (ISRCTN68382401). However, further risk stratification biomarkers are required because even if more patients with BE are identified, only a small proportion of these will ultimately develop OAC (0.12 – 0.6% per year incidence of OAC) and surveillance endoscopy of all BE patients is a substantial logistical burden.111–114 Aberrant P53 expression (both overexpression and loss) may be a more accurate predictor of progression than the presence of low grade dysplasia, which is prone to inter and intra-observer variability.115,116 p53 can be evaluated on the same Cytosponge samples used for TFF3 staining as a second tier test and a panel of biomarkers may enable those patients at low risk of progression to be spared an endoscopy.67,75

Oesophageal cancer prevention

Primary prevention of oesophageal cancer includes tobacco avoidance, moderation of alcohol intake (both for OSCC prevention), maintenance of a healthy weight (for OAC prevention), and increasing fresh fruit and vegetable intake with a reduction in red meat consumption.(17, 42, 43) For patients with BE, secondary prevention could include pharmacologic therapy with proton pump inhibitors (PPIs), non-steroidal anti-inflammatory drugs (NSAIDs),locally ablative therapies to neoplastic precursor lesions and anti-reflux surgery.117 PPIs are frequently employed in the setting of chronic reflux, and some cohort studies and meta-analyses suggest that PPI treated patients with BE have lower rates of dysplasia and OAC than those who are not treated with PPIs, and although bias caused by severity of reflux is a potential confounder of these studies, it may be reasonable to discuss PPI treatment even with asymptomatic BE patients.106,118–120 Use of NSAIDs including aspirin has been associated with reduced cancer risk in multiple cancer types, including oesophageal cancer.121–123 However aspirin and NSAIDs are associated with non-trivial toxicities and a higher grade of evidence is required to institute an NSAID-based chemoprevention strategy in BE; the ongoing phase III randomised AspECT trial (NCT00357682) might be informative regarding this approach. Finally, prevention of

progression of dysplastic BE to OAC is now achievable for many patients using ablative therapies. Patients with BE who have nodular lesions detected should undergo endoscopic mucosal resection (EMR) 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 (HGD), ablation provides equivalent efficacy to surgery with respect to long-term survival and has much less associated morbidity than oesophagectomy, whereas for patients with low grade dysplasia, ablation decreases progression both to HGD and invasive OAC.124–126 Patients often require a combination of EMR and ablation therapy.127,128 As BE patients with no dysplasia have a low risk of progression to OAC and there are side-effects associated with treatment, ablative therapy is not recommended for this patient group.104 It is also important to appreciate that following ablation therapy, endoscopic monitoring is still recommended due to the risk of recurrence.104 In the future it is hoped that assessment of the molecular status may aid identification of patients for therapy and reduce the reliance on a subjective diagnosis of dysplasia.

Patients with OSCC precursor lesions may also benefit from endoscopic ablative therapy, however neoplastic progression and strictures appear to be more common with squamous dysplasia than with ablation of BE; strictures may occur in up to 21% of patients.129–131 In high-incidence OSCC populations in China chemopreventive strategies replacing dietary micronutrients demonstrated that increasing beta carotene, vitamin E and selenium intake did not reduce OSCC incidence or mortality.132 Finally, as aspirin and other NSAIDs decrease the risk of OSCC in addition to OAC, this approach could be prospectively evaluated in clinical trials.133

Management

Management of oesophageal cancer is dependent on characteristics of the patient (including fitness) and tumour, mainly the TNM-stage; early tumours may be suitable for endoscopic removal, whereas more locally advanced cancers are treated with chemotherapy, chemoradiotherapy, surgical resection or combinations of these (Figure 5). Patients with oesophageal cancers which are not suitable for operative management are treated with systemic chemotherapy.

Endoscopic management

Early stage oesophageal cancers represent only a small proportion of all tumours, however an increased use of endoscopy for various indications together with screening and surveillance of BE has generated more patients with early lesions. Most knowledge in endoscopic treatment is derived from BE and OAC, while the literature covering SCC is more limited. Similar to dysplastic BE discussed earlier, when oesophageal cancer is confined to the mucosa and without any metastases (stage T1a, N0, M0), local endoscopic treatments with endoscopic mucosal resection or dissection combined with radiofrequency ablation have replaced oesophagectomy as first-line treatment, because they are less invasive, safer, provide better quality of life and have equally good long-term prognosis.5,6,134 Some research indicates that endoscopic submucosal dissection may be recommended rather than endoscopic mucosal resection because of a higher rate of complete

resection (92.7% versus 52.7%) and a lower rate of local tumour recurrence (0.3% versus 11.5%) of early tumours. Focal endoscopic mucosal resection followed by radiofrequency ablation might be recommended before stepwise or complete endoscopic mucosal resection due to higher rates of complications (strictures, perforation, and bleeding) following the latter strategy, while the risk of OAC recurrence is equally low (1.4%).135 Such procedures should be carried out by specialised endoscopists working at well-equipped high-volume centres.136 For more advanced tumour stages, oesophagectomy (surgical removal of the oesophagus) remains the standard of care, because submucosal tumour involvement (T1b) has a 17-26% risk of lymph node metastasis, with the highest rates for tumours of poor differentiation, lympho-vascular invasion and submucosal invasion >500μm. 137,138 However, for patients with T1b tumour who are not fit enough to undergo surgery or definite chemoradiotherapy, e.g. because of advanced age and severe co-morbidities, endoscopic therapy can be attempted if the tumour is associated with good prognostic characteristics, i.e., submucosal 1 invasion, well differentiated and without lympho-vascular invasion.”.5

Surgical management (OAC and OSCC)

Procedures—There are several alternative approaches for the resection of oesophageal cancer, including variations in approach and extent of lymphadenectomy. For tumours located in or near the gastro-oesophageal junction, the resection may be oesophagectomy combined with 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 and 3356 patients found no difference in 5-year survival or morbidity between these approaches.139 Similar overall survival rates were also found also in a recent cohort study of 4996 patients from the United States.140 Outcomes following transhiatal and transthoracic surgery were compared in a meta-analysis of eight studies (including three RCTs) and 1,155 patients, and no survival differences were observed.141 This finding was contradicted in a smaller, but more recent meta-analysis of 6 studies (647 patients), in which slight survival benefits were noted in the transthoracic group.142 The risk of pulmonary complications seems to be higher following the transthoracic approach, while the longer term health-related quality of life might not differ much between these approaches.141,143 Minimally invasive surgery has during the last years emerged as a feasible and safe procedure for oesophagectomy.144 Such surgery could include hybrid operations combining laparoscopy with open thoracotomy or thoracoscopy with open laparotomy, total minimally invasive procedures (Figure 6) and robot-assisted surgery. A systematic review of 17 studies (including various combinations of minimally invasive surgery) and 1598 patients found no difference in long-term survival following minimally invasive compared to open surgery.145 A Dutch RCT compared minimally invasive oesophagectomy (n=59) with open transthoracic oesophagectomy (n=56) and indicated a decreased risk of postoperative pulmonary infection (RR 0.35, 0.16-0.78), and better physical activity, global health and pain 1 year after surgery the minimally invasive group (PMID:26037024).146,147 Studies examining short-term postoperative quality of life indicate improvements in selected outcomes following minimally invasive procedures, but long-term follow-up of patient-reported outcomes is needed to assess potential overall benefits of minimally invasive surgery for oesophageal cancer.

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The optimal extent of lymphadenectomy in surgery for oesophageal cancer is a matter of controversy. Several studies have indicated better overall prognosis with more extensive lymphadenectomy.148 However, some recent studies indicated no survival benefit from removing more nodes, with or without metastasis, especially not in patients having received neoadjuvant oncological therapy.149–151 These findings indicate that a more tailored approach regarding the extent of lymphadenectomy may be warranted in an era of multi-modality therapy, and sentinel node biopsy might be a future alternative.152

Thus, existing systematic meta-analyses and single studies of predominantly observational design indicate that the above variations in approaches are followed by no or limited differences in the long-term oncological outcomes, while these approaches may more differently influence postoperative complications, morbidity and health-related quality of life. Thus far, only very few randomised clinical trials have been conducted to compare the above surgical approaches and existing observational studies are heterogeneous and often provide inconsistent results, which stress that these findings need to be cautiously interpreted.

Surgeon characteristics—In contrast to the lack of clear survival differences between surgical approaches, some factors directly related to the surgeon seem to have stronger influence on the long-term prognosis in oesophageal cancer. The annual number of oesophagectomies per surgeon has been established as an important and independent prognostic factor for both short-term and long-term survival, which remains after adjustment for hospital annual volume of these procedures.153–155 Proficiency gain curves have been associated mainly with minimally invasive surgery, and recently, “learning curves” have also identified among surgeons conducting open oesophagectomies, and these curves seem to be longer for achieving a stable long-term survival than for stabilising short-term mortality.156,157 Some early data indicate that the age of the surgeon might be an independent prognostic factor, even after adjustment for surgeon volume and other prognostic factors, with a plateau in 5-year prognosis in patients if the surgeon is aged 52-56 years.158 Finally, later weekday of surgery might be an independent prognostic factor in oesophageal cancer, which may be associated with the alertness of the surgeon.159

Surgery and patient characteristics

Several patient characteristics may influence the outcomes following surgery for oesophageal cancer. Older age is a prognostic factor, but its influence has declined with more specialised surgery and is more evident only after the age of 80 years, and rather related to co-morbidities than age itself.160–162 Higher Charlson Co-morbidity Index (which assigns a score based on the presence and severity of 22 comorbid conditions) and previous heart conditions seem to reduce the prognosis after oesophageal cancer surgery, and co-morbidities may also negatively influence the long-term health-related quality of life following oesophagectomy.8,162 Ethnicity seems to influence the prognosis following surgery for oesophageal cancer, with Caucasians having lower tumour stage-specific mortality rates, being more likely to undergo surgery, and have their surgery conducted at high-volume centres.163,164165,166 Results from meta-analyses have consistently shown that higher BMI is associated with more postoperative complications, but a better overall

survival.167–169 Tobacco smoking seems to negatively influence overall survival, and more so for current smokers than previous smokers.170 Tumour stage-specific survival among alcohol drinkers is seemingly worse than that of non-users.171 Finally, among socio-economic factors a longer education seems to be followed by better overall survival independent of other prognostic factors, particularly in early tumour stages and squamous cell carcinoma histology.172 Further research is required in order to fully understand and reduce these apparent disparities.

Chemotherapy and chemoradiotherapy

Survival for patients with ≥T2 or N+ cancers following surgery alone is poor (~ 50% 10 year overall survival for OSCC and OAC Stage IB), therefore therapies in addition to surgery are required for these patients (Figure 5).173 Current guidelines recommend adjunctive treatment for patients with ≥T2 tumours, although node-negative T2 lesions with low risk features (<2cm and well differentiated) may be considered for oesophagectomy alone (OAC and OSCC) or definitive chemoradiotherapy (OSCC).6,7 However, most oesophageal cancers are diagnosed at a more locally advanced stage (>T2 and/or N+); for these patients the purpose of chemotherapy or chemoradiotherapy (CRT) is to reduce the primary tumour bulk, to increase the likelihood of radical (R0) resection and to treat micro-metastatic disease and decrease the risk of future systemic recurrence. Neoadjuvant therapy also relieves dysphagia and improves nutritional status in a majority of patients, and may avoid the requirement for feeding tube placement.174

Although historically patients with OSCC or OAC have been treated using similar paradigms, clear biological differences between these two histological subtypes exist.79 This heterogeneity has implications for response to radiotherapy, patterns of metastatic spread, and interpretation of trial results. In particular, the high sensitivity of OSCC to (chemo)radiotherapy leads to complete and durable pathological responses in a high proportion of patients following CRT, which may render surgery unnecessary in a subgroup of complete responders and this is an area ripe for research.6,7,175,176 In contrast to OSCC patients, patients with OAC are recommended to undergo surgical resection even in the setting of a good clinical response, because of the lower sensitivity of OAC to radiotherapy, which leads to a lower complete histopathological response rate to CRT and a higher rate of microscopic positive disease at the primary tumour site.6,7 In all cases, multidisciplinary planning of neoadjuvant chemotherapy or CRT and surgery is mandatory and close attention should be paid to performance and nutritional status, in addition to co-morbidities during preoperative assessment.6,7 Prior to commencing therapy, a team of experts from various disciplines should review the patients with respect to staging and likely treatment tolerability and develop a consensus prior to starting therapy.

Neoadjuvant and perioperative chemotherapy—Neoadjuvant chemotherapy is an evidence-based component of potentially curative treatment for patients with OSCC or OAC. In the OE02 trial 802 patients (OSCC:OAC 31%:66%) were randomised to surgery alone or two cycles of neoadjuvant cisplatin and infused fluorouracil (CF) prior to surgery.177 (Table 3) Patients treated with neoadjuvant CF had an absolute survival benefit of 5.9% at 6 years; this was 5% for OAC and 8% for OSCC, with no significant heterogeneity of treatment

effect.178 However, in practice, CRT is preferred for OSCC patients due to the excellent responses associated with CRT in this population. For patients with OAC, addition of epirubicin to cisplatin and capecitabine chemotherapy (ECX) and extending preoperative therapy to four cycles did not improve overall survival in the OE05 study, therefore doublet chemotherapy is preferred neoadjuvant treatment.179 Additionally, docetaxel plus oxaliplatin and 5-fluorouracil showed better pathologic response rates than ECX in a recent randomised trial for localised gastric cancer including OAC, survival results from this study have been presented in abstract form and demonstrate superior survival for the FLOT regimen compared to ECX (50 months vs 37 months 0.77 [0.63 - 0.94]; p = 0.012).180,181 The MAGIC and FNCLCC/FFCD trials randomised patients with OAC or gastric cancer to perioperative chemotherapy vs. surgery alone and demonstrated almost identical improvements in 5-year overall survival for chemotherapy treated patients (23% vs. 36% and HR 24% vs. 38% respectively).182,183 Meta-analysis supports the consistency of these findings, and therefore patients with OAC are recommended treatment with either neoadjuvant or perioperative platinum and fluoropyrimidine based chemotherapy (including an adjuvant component, if tolerated).6,7,184

Neoadjuvant chemoradiotherapy—Chemoradiotherapy is also an effective preoperative treatment for OSCC and OAC, except patients with very early stage cancers who did not benefit from CRT in a randomised trial specifically focused on these patients. 185 Radiotherapy for patients with oesophageal cancer should be planned using CT simulation and conformal treatment planning.7 Intensity modulated radiation therapy may be used where dose reductions to specific organs cannot be achieved using standard 3D planning mechanisms.7 In the CROSS trial, 275 oesophageal cancer patients (OSCC:OAC 23%:75%) were randomised to CRT with weekly carboplatin and paclitaxel compared to surgery alone.186 Neoadjuvant CRT resulted in improved overall survival for all patients (Hazard Ratio (HR) 0.657; [95% CI 0.495 to 0.871]), although the magnitude of this benefit was greater for OSCC patients (HR for OSCC vs. OAC were 0.453 vs. 0.732 respectively). Additionally, neoadjuvant CRT was associated with reduction in both local and systemic disease recurrence. These results have led to widespread adoption of the CROSS regimen as a standard treatment option for oesophageal cancer, especially of OSCC, thus replacing older and more toxic regimens.187 Notably, the CROSS included ≤T3 tumour status, and patients with lymph node positive cancers and adenocarcinoma did not appear to derive the same magnitude of survival benefit on subgroup analysis. However, concerns regarding the adequacy of the systemic dose of chemotherapy in CROSS are mitigated by a clear decrease in the occurrence of distant metastases in CRT treated patients (HR 0.63, 95% CI 0.46-0.87), albeit only in the first two years following surgical resection.188 One small study directly comparing outcomes for patients treated with neoadjuvant CRT vs. chemotherapy showed equivalent survival outcomes; however this question is currently being evaluated in several large randomised phase III trials, this 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 chemoradiotherapy.189 Combining induction chemotherapy to reduce distant metastases with CRT which improves local control would appear to be an attractive option. However, the role of induction chemotherapy before

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neoadjuvant CRT is currently not confirmed and results from smaller randomised controlled trials are inconsistent.190,191

Definitive chemoradiotherapy—Definitive CRT, i.e. chemoradiotherapy without subsequent oesophagectomy, is recommended for cervical OSCC tumours, and may also be considered as a standard of care for OSCC of the mid and lower oesophagus. In OSCC, definitive CRT is associated with equivalent survival, but higher rates of local relapse, when compared to CRT followed by surgery in two randomised trials.175,176 However, there are no studies directly comparing whether salvage surgery on relapse following CRT is superior to neoadjuvant CRT followed by surgery in all patients in this setting; ongoing clinical trials are investigating this question. Previously, series comparing salvage oesophagectomy with planned oesophagectomy suggest a higher rate of postoperative complications with a salvage approach (e.g. anastomotic leak rate of 18% vs 11%), however in high volume centres use of risk reduction approaches such as omental transposition and anastomosis outside the irradiated oesophagus during salvage oesophagectomy may reduce this risk to that of a planned surgery.192,193 Definitive CRT is also an option for OAC patients who are unsuitable for or who refuse surgery, but it is not the standard approach in OAC. In definitive CRT, cisplatin or oxaliplatin-fluoropyrimidine regimens have equivalent efficacy.194 The standard dose of radiotherapy in definitive protocols is 50.4Gy, despite recent technical developments in radiotherapy delivery, and there are not yet randomised data to support the use of dose-escalated radiotherapy in this setting.195 If salvage oesophagectomy is considered as a therapeutic strategy, doses higher than 55Gy should be avoided because they are linked with increased postoperative mortality and morbidity.196

Palliative treatment

As many oesophageal cancers are unresectable, and more than half of patients who are treated with curative intent will develop tumour recurrence, ultimately a majority of patients will require palliative therapy.177,179 Reduction in symptoms due to the primary tumour may be achieved using radiotherapy or stent placement, however for systemic control of disease, palliative chemotherapy is required. There are few studies evaluating the role of chemotherapy solely in oesophageal cancer, and therefore data are frequently extrapolated from trials containing a mixture of oesophageal, junctional and stomach cancer patients. Additionally, as emerging data suggests that OSCC has biology distinct from OAC; further research in this area is warranted.4,197,198

Palliative chemotherapy for oesophageal cancer is predominantly platinum and fluoropyrimidine based, while irinotecan may be an alternative in patients unsuitable for platinum.6,199–201 Based on the results of the REAL-2 trial, oxaliplatin and cisplatin are considered equivalent in efficacy, but not in toxicity profile; in REAL-2 oxaliplatin was associated with increased rates of neuropathy and diarrhoea and cisplatin with thromboembolic events and neutropenia.202 Capecitabine has also replaced infused 5-fluorouracil in many chemotherapy regimens as it does not require central venous access device, however infused 5-fluouracial plus oxaliplatin (FOLFOX) remains a popular regimen. In Asia, S1 is a standard treatment for advanced gastro-oesophageal cancer in combination with cisplatin; however pharmacogenomics affecting tolerability in non-Asian

populations have limited S1 adoption outside Asia.203,204 Because the median overall survival in clinical trials for patients treated with cytotoxic chemotherapy for gastroesophageal cancer is less than one year, consideration of the toxicity vs. efficacy ratio is required when selecting a chemotherapy regimen. Chemotherapy increases overall survival compared to best supportive care, and in meta-analysis, triplet chemotherapy is superior to doublet.205 However standard triplet regimens enhance survival at a cost of increased toxicity, and careful patient selection or modification of these regimens is recommended.206,207 Overexpression or amplification of HER2 is common in OAC (30% amplification in TCGA, 32.2% HER2 positive gastroesophageal junction in TOGA screening cohort).79,208Whilst the landmark TOGA trial contained only patients with oesophageal or gastric cancers, patients with oesophageal tumours which overexpress HER2 are usually treated with the anti-HER2 monoclonal antibody trastuzumab in combination with cisplatin plus fluoropyrimidine chemotherapy. As OAC has recently been shown to be molecularly indistinguishable from chromosomally unstable gastric adenocarcinoma this has a strong biological rationale. Oesophageal cancer patients who progress on first line therapy may benefit from chemotherapy such as taxanes and irinotecan; however the median overall survival benefit associated with second-line cytotoxic chemotherapy compared to best supportive care is approximately six weeks.209–211 The anti-VEGFR2 monoclonal antibody ramucirumab also improves overall survival both as a single agent and in conjunction with paclitaxel; however it has been evaluated only in gastric and gastro-oesophageal junctional adenocarcinoma.212,213

Emerging therapies

With the exception of trastuzumab, development of targeted therapies in oesophageal cancer over the past decade has been disappointing. International randomised trials have investigated agents focusing on the EGFR, MET/hGF, mTOR, VEGF and FGFR pathways without success.214–221 The unmet need for trials in OSCC is highlighted by the fact that only one of these studies (COG) enrolled OSCC patients.216 For OAC, the challenges associated with biomarker selection and targeted therapy are exemplified by HER2 expression, where clear evidence of significant intra-patient heterogeneity of HER2 status and the deleterious effect of heterogeneity on response to anti-HER2 therapy has accumulated.222–224 As discussed earlier, the role of gene copy load, intra-tumoural heterogeneity and receptor tyrosine kinase co-amplification on response to targeted therapy has also been demonstrated for EGFR, FGFR and MET amplified gastro-oesophageal tumours.85,225,226 As amplification of receptor tyrosine kinases are one of the key targetable lesions in OAC (and CIN gastric cancer), identification of patients who are truly oncogenically addicted to amplified receptor tyrosine kinase signalling and who are most likely to benefit from drugs targeting these pathways is an important future challenge.

Prospective pathways for investigation of targeted therapy in oesophageal cancer include cell cycle regulators and the DNA damage response pathway (See section on genetics of OSCC and OAC). Cell cycle pathway dysregulation is present in up to 90% of OSCC and 86% of OAC, via distinct but overlapping mechanisms (Figure 7).4 The orally available CDK4/6 inhibitors ribociclib and palbociclib improve overall survival in oestrogen receptor (ER) positive breast cancer in conjunction with endocrine therapy; ER positive breast cancer is

dependent on cyclin D1 for cell cycle progression.227,228 Preclinical data in OAC demonstrates that CDK6 and CDK4 amplified OAC are addicted to CDK6/4 signalling which is inhibited by palbociclib, supporting development of tyrosine kinases targeting cell cycle regulators in OAC patients.229 Development of drugs such as PARP inhibitors which target the DNA damage response pathway in gastro-oesophageal cancer has also been hampered by inability to adequately identify biomarker selected populations with sufficient benefit.230 However, moving beyond immunohistochemistry biomarkers associated with an impaired DNA damage response such ATM deficiency to more nuanced signatures using next generation sequencing like those which have been predictive of response to PARP inhibition in ovarian cancer may be useful in future.84,231,232

Finally, oesophageal cancer is associated with a relatively high mutational load, which in other tumours is correlated with response to anti-PD-1 therapy.80,84,233,234 Data specific to oesophageal cancer using anti-PD1 therapy is preliminary but encouraging; of 23 PD-L1 positive oesophageal cancer patients treated with pembrolizumab in the phase IB KEYNOTE 028 study the objective response rate was 30% overall (40% OAC:29% OSCC), whereas a pure OSCC PD-L1 unselected population demonstrated a centrally reviewed objective response rate (ORR) of 17% (11/64) to nivolumab therapy.235,236 Patients with PD-L1 unselected gastric or gastro-oesophageal junctional adenocarcinoma were treated with nivolumab or nivolumab plus the anti-CTLA-4 antibody ipilimumab in the CHECKMATE 032 study; radiological responses were observed in PD-L1 positive and negative tumours (12% vs 27% for PD-L1 <1% and ≥1% respectively), and were increased for both PD-L1 negative and positive patients treated with combination immunotherapy.237 As a phase III randomised trial has demonstrated the superiority of nivolumab in terms of overall survival compared to best supportive care in a chemorefractory gastric cancer population, with a key finding of an improvement of one year survival from 10% to 26% in nivolumab treated patients despite a relatively low radiological response rate of 11% it is likely that pending the results of ongoing trials, checkpoint inhibitor therapy will be integrated into treatment paradigms for oesophageal cancer patients.238–241

Quality of life

Oesophageal cancer patients' quality of life is first negatively affected by the obstructing tumour and later by complex treatment, which may include extensive surgical resection. Measurements of quality of life after the diagnosis is confirmed, but prior to treatment, are often used as "baseline". Such measures can be valuable for adjustment of differences between groups in statistical analyses, but do not mirror the actual baseline level because most patients at that point in time are already seriously affected by their disease.

Before a diagnosis of oesophageal cancer is established a majority of patients have experienced dysphagia, eating difficulties and appetite loss, resulting in considerable weight loss and fatigue, which influence patients' daily living and quality of life.9 Patients with advanced tumour stage may suffer from additional problems, e.g. odynophagia, hoarseness and coughing due to tumour overgrowth or metastatic disease.242 Good communication between healthcare professionals and oesophageal cancer patients facilitates adjustment to illness and improves quality of life. In conjunction with information about treatment

alternatives and their influence upon patients' quality of life, patients often require information about potential long-term benefits and consequences of these treatments, including topics such as work ability, social functions and physical symptoms. A core information set with aspects that should be communicated with oesophageal cancer patients before treatment has been developed (Table 4). This set should include information about the experience on admission and during hospital stays (e.g. information about major complications) and experience after treatment and discharge (e.g. expected recovery milestones, impact on eating, long-term quality of life and survival).243

To prepare for curative treatment, preoperative preparing programs to optimise patients are under study.244,245 As malnourished patients are at greater risk of surgical morbidity and mortality, attention to preoperative nutritional status is mandated.246 If intervention for feeding is required because of dysphagia, jejunostomy is preferred to stenting in operable cancer.247 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 patients receiving surgery alone.248 Few studies have evaluated the influence of definitive CRT on patients' quality of life. A multi-centre RCT showed that definitive CRT negatively affects patients' quality of life during treatment with but symptoms are usually resolved within 6 months, except for persisting fatigue and insomnia.249 Patients with definitive CRT seem to recover faster than those who undergo surgery.249 Oesophagectomy has a detrimental effect on patients' quality of life in the short and long-term. Complications after surgery are the strongest known risk factor for poor quality of life and delayed and incomplete recovery.250–254 After surgery, most patients struggle with loss of appetite, difficulty eating and severe and long-standing postoperative weight loss, and the support of a dietician is warranted (Table 4).9,255 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 quality of life. The literature assessing quality of life in patients having palliative treatment is limited, but this is important an important area for future research.256

Scientific guidelines do not give much information on how oesophageal cancer patients should be followed up after treatment, e.g. regarding frequency or duration of follow-up.257 One important aim of the follow-up is to support patients in their recovery and survivorship. 255 Supportive care needs after treatment may differ substantially between patients and a tailored follow-up supported by a multidisciplinary team is recommended. A primary contact nurse can be a valuable coordinator of patients' follow-up program (Table 4). 258,259 With the increasing incidence of oesophageal cancer (adenocarcinoma) combined with improvements in survival, more patients will be eligible for long-term follow-up. To meet the burden on the outpatient clinic, nurse-led follow-ups of oesophageal cancer patients have been evaluated with encouraging results regarding patients' satisfaction and cost-effectiveness.260–262

Outlook

As multiplatform molecular characterisation studies examining oesophageal cancer continue to accumulate, it is likely that the findings of this research will begin to impact on the future management of this disease, and that treatment paradigms may further diverge for OSCC and OAC.79 Use of non-invasive screening such as Cytosponge or assessment of volatile organic solvents in exhaled breath and diagnostic procedures optimised for biomarkers specific for dysplasia and early cancer may facilitate earlier diagnosis in larger numbers of patients; this is of particular importance given the rapid rise in OAC incidence.263 This approach should also lead to increased use of curative endoscopic therapy in patients with early cancers and a reduction in oesophagectomies. For patients with locally advanced cancers who require chemotherapy or chemoradiotherapy in addition to surgery, ongoing clinical trials will inform a number of important questions. These include whether neoadjuvant chemotherapy, chemoradiotherapy or induction chemotherapy followed by CRT is the ideal treatment for resectable OAC, and when (if any) is the best time for oesophagectomy following CRT for OSCC. However, taking into account the rapidity of development of immune-oncology therapies, and the promising preliminary results demonstrated with these agents for both OSCC and OAC, it is conceivable these questions may be superseded by others, including how best to select patients for immune-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 impact positively to reduce the morbidity and mortality associated with the rising incidence of OAC in developed countries globally.

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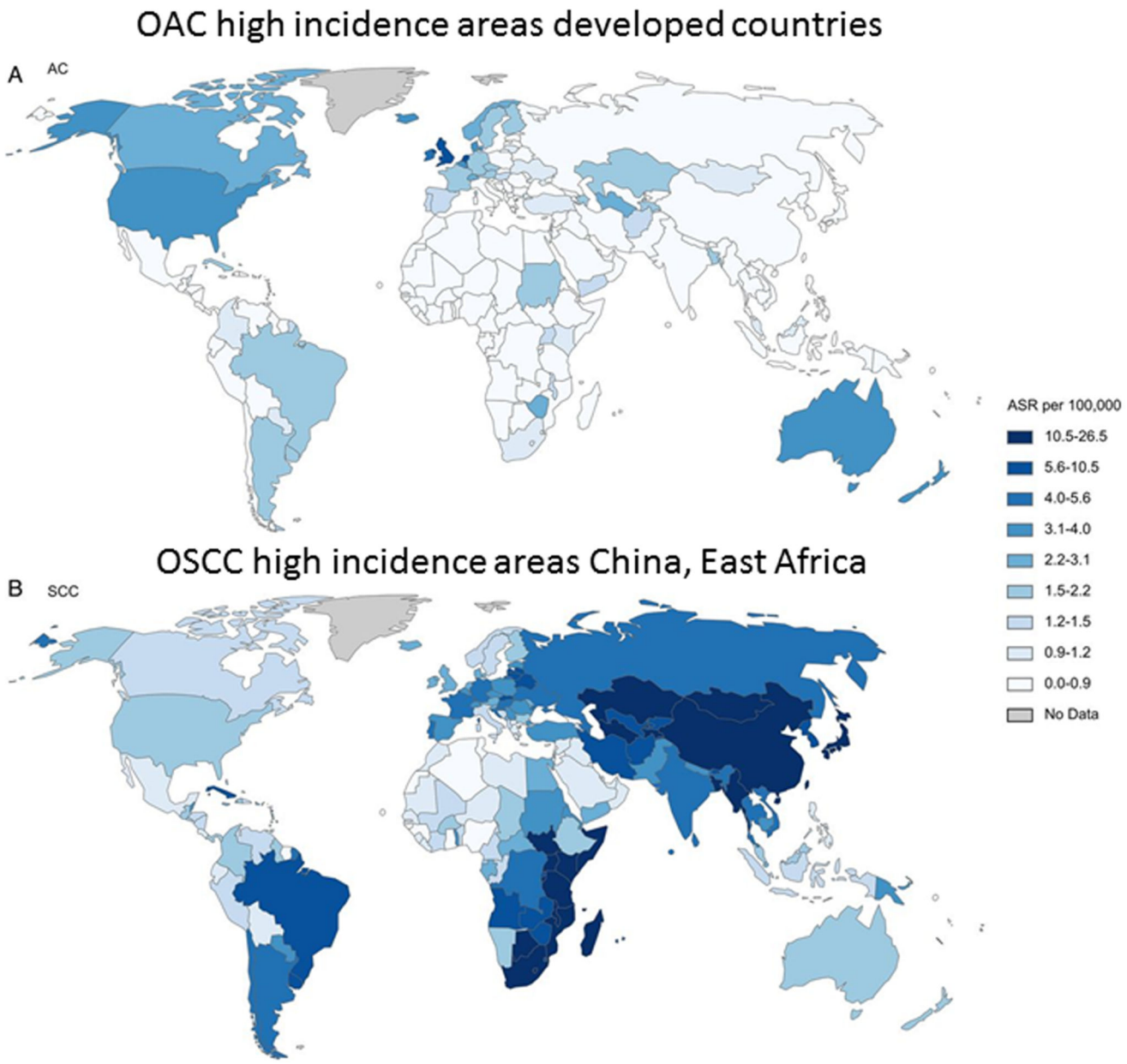

Figure 1.

Annual incidence rate of OAC and OSCC globally in men. Panel a demonstrates highest rates for OAC in Western industrialised nations including USA, Canada, Australia and European Union, and lower levels in less developed areas including Africa and China. Panel B demonstrates high levels of OSCC in China, in so called “oesophageal cancer belt” across extending to Iran, and also in East Africa.

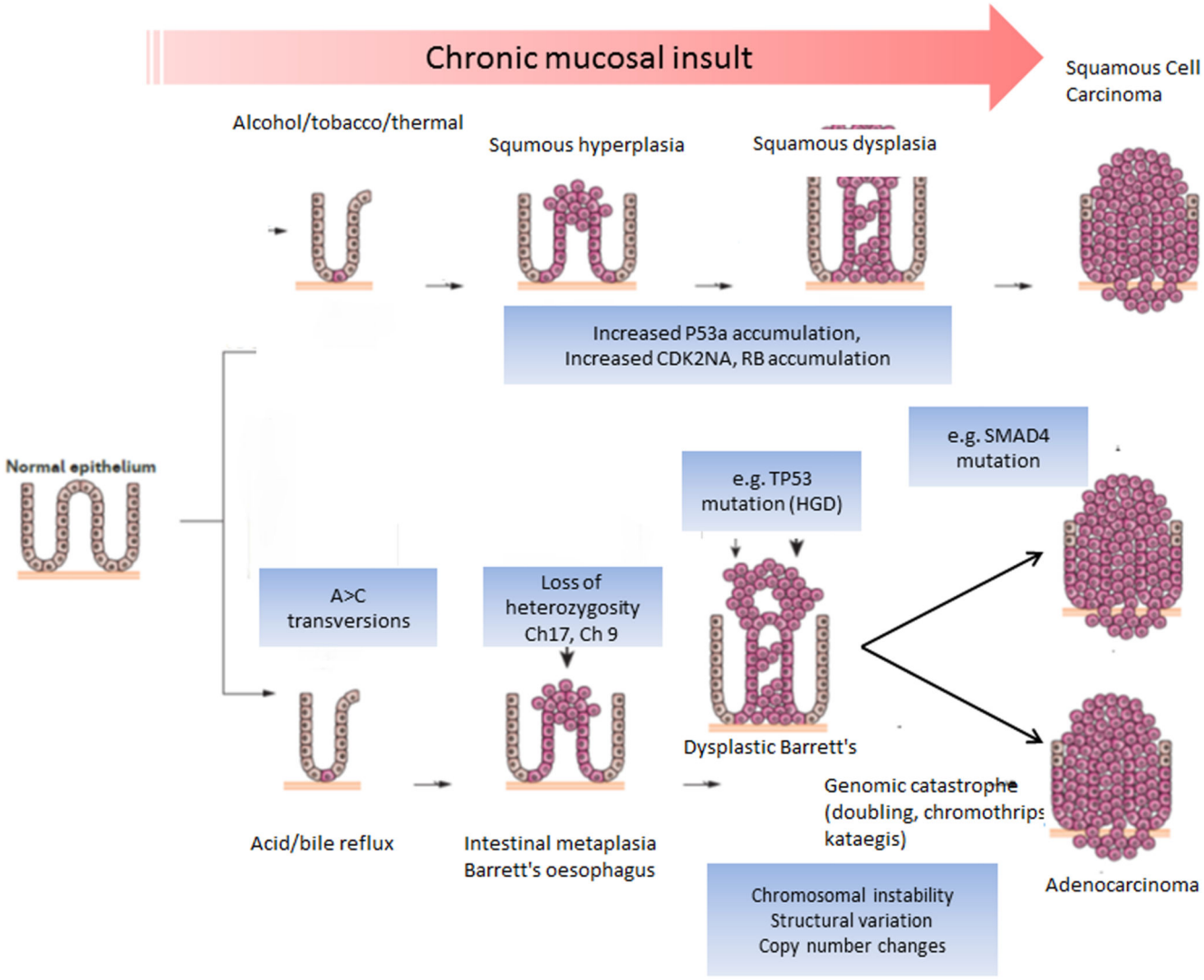

Figure 2.

Pathogenesis of oesophageal squamous cell carcinoma and adenocarcinoma. The oesophageal mucosal is exposed to repeated insult (tobacco, alcohol, hot liquids, reflux containing acid or bile) which results in changes to the squamous oesophageal mucosa. Molecular changes also accumulate ultimately leading to a malignant phenotype. In OSCC squamous hyperplasia precedes low and high grade squamous dysplasia which then develops into invasive cancer. In OAC, a metaplastic epithelium containing intestinal metaplasia is transformed through low and high grade dysplasia to invasive cancer.

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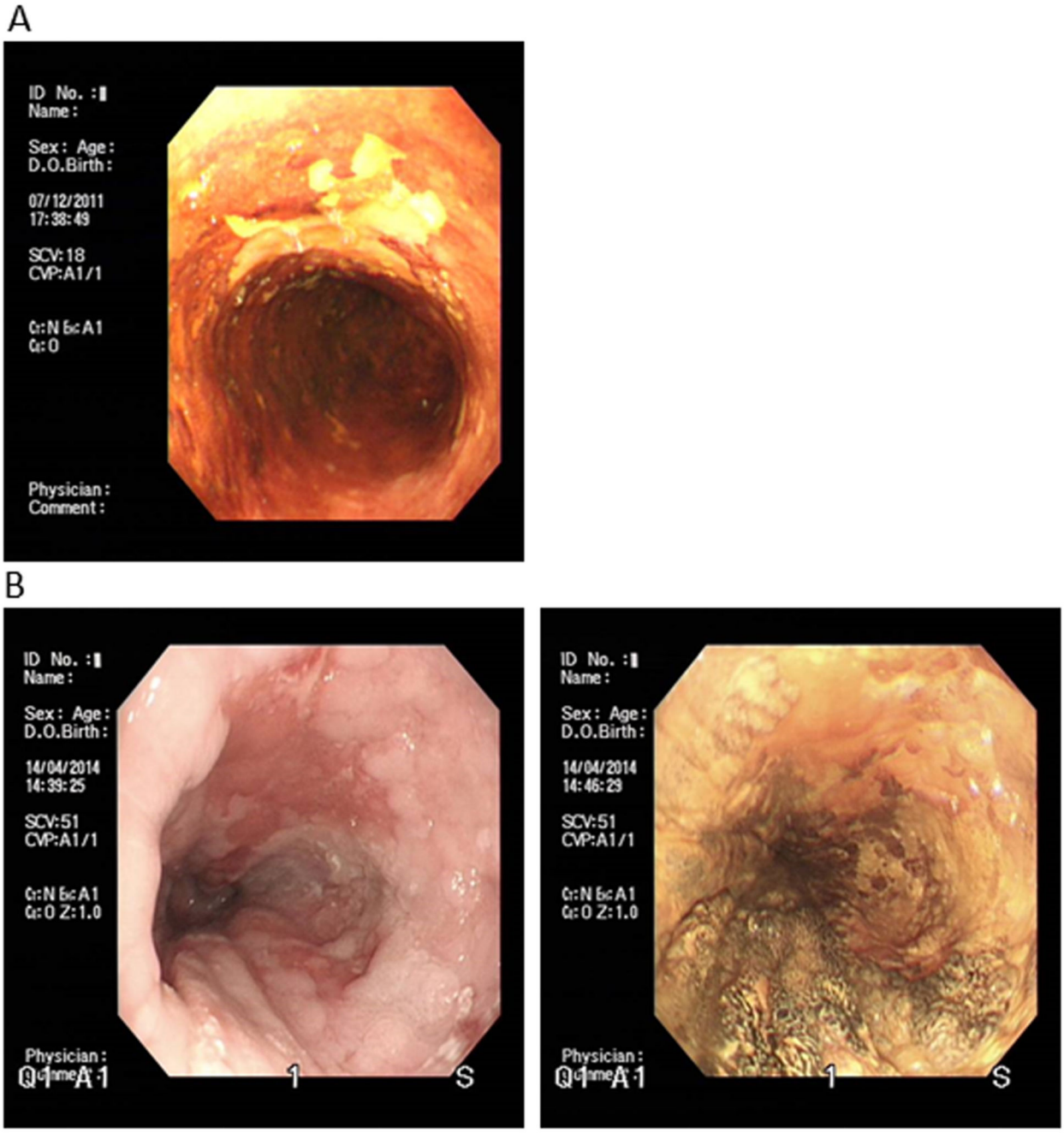

Figure 3.

A. Endoscopy image demonstrating low grade dysplasia in squamous mucosal lesion at 12 o'clock highlighted using Lugol's solution. B. Endoscopy image demonstrating intramucosal squamous lesion in a patient with achalasia. .

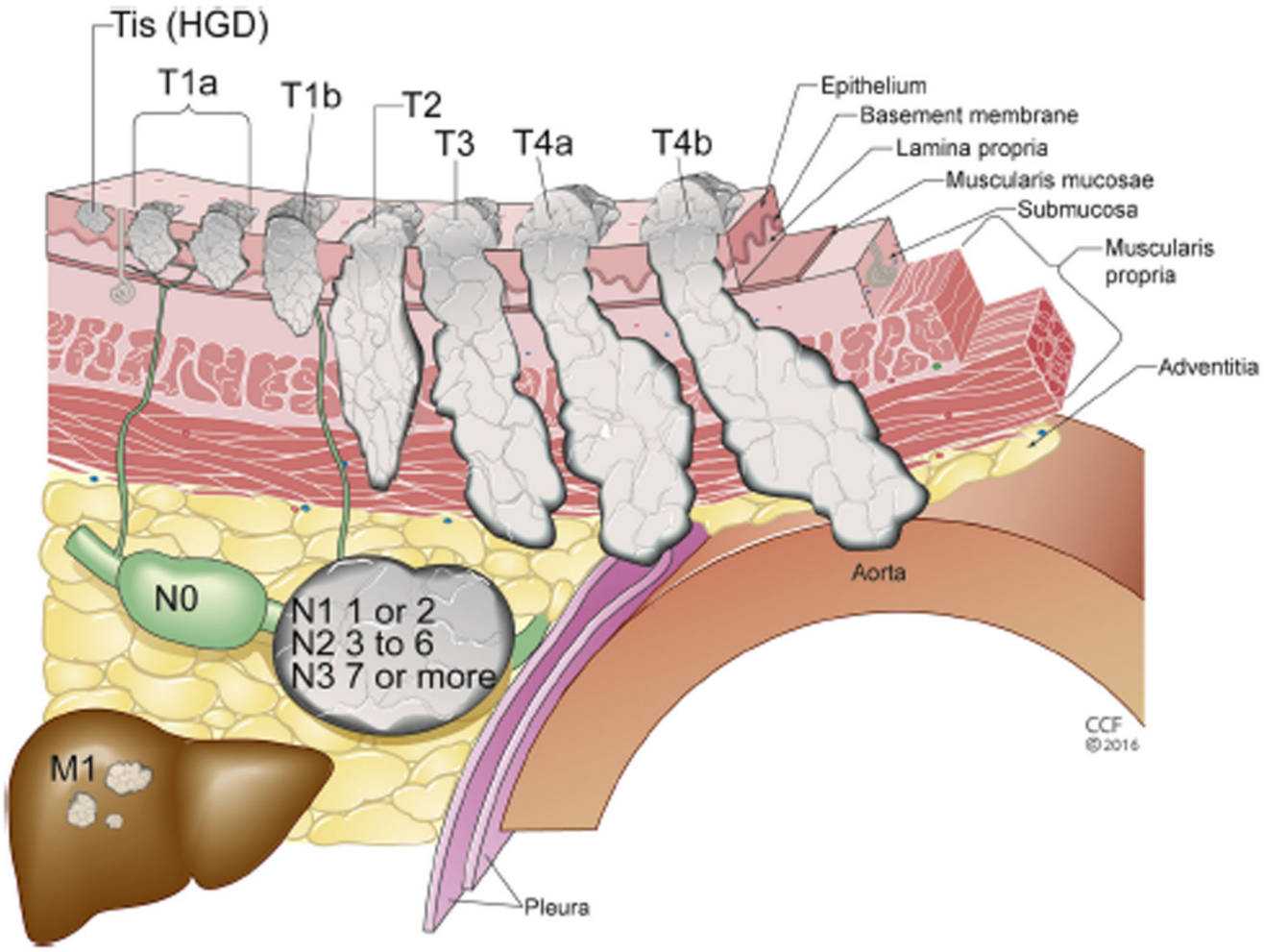

Figure 4.

Eight edition TNM categories. T is categorized as Tis: high-grade dysplasia (HGD). T1 is cancer that invades the lamina propria, muscularis mucosae, or submucosa and is subcategorized into T1a (cancer that invades the lamina propria or muscularis mucosae) and T1b (cancer that invades the submucosa); T2 is cancer that invades the muscularis propria; T3 is cancer that invades the adventitia; T4 is cancer that invades the local structures and is subcategorized as T4a (cancer that invades adjacent structures such as the pleura, pericardium, azygos vein, diaphragm, or peritoneum) and T4b (cancer that invades the major adjacent structures, such as the aorta, vertebral body, or trachea). N is categorized as N0 (no regional lymph node metastasis), N1 (regional lymph node metastases involving one to two nodes), N2 (regional lymph node metastases involving three to six nodes), and N3 (regional lymph node metastases involving seven or more nodes). M is categorized as M0 (no distant metastasis) and M1 (distant metastasis). Reproduced from Thomas et al. Cancer of the Esophagus and Esophagogastric Junction: An Eighth Edition Staging Primer. Journal of Thoracic Oncology, vol 12, n 1: 36-42 (2016).

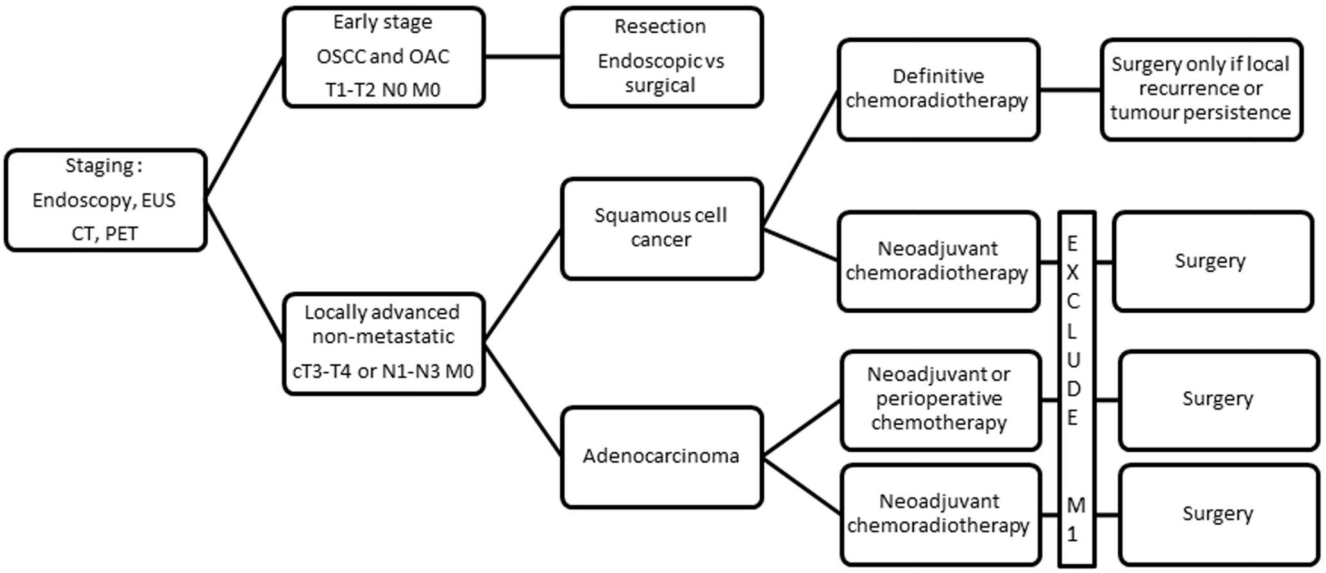

Figure 5.
Suggested algorithm for management of localised oesophageal cancer

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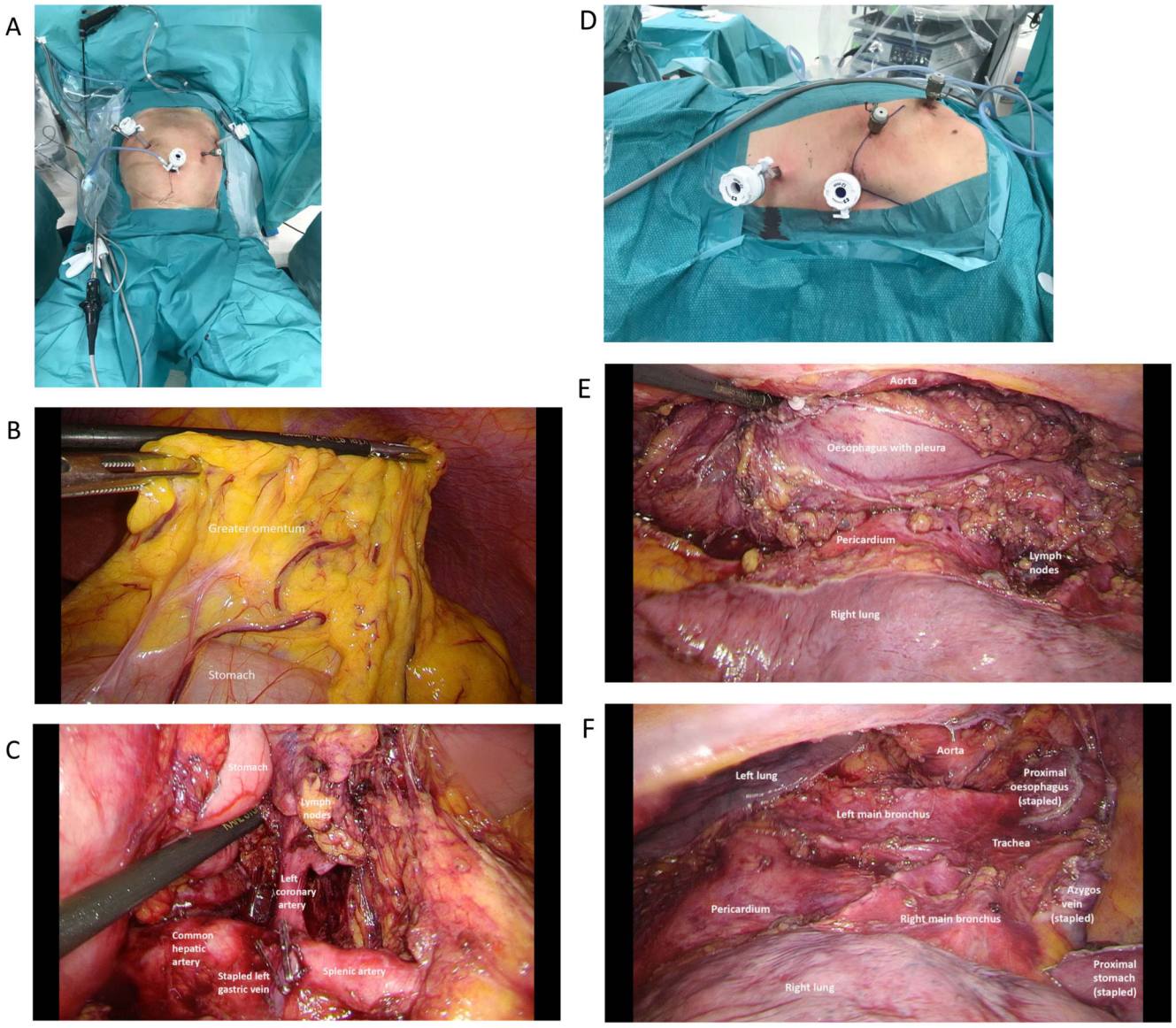

Figure 6.

These pictures illustrate a minimally invasive oesophagectomy for oesophageal cancer. Picture A shows the port placement of the abdominal part of the procedure. Picture B shows how the greater omentum has been mobilised and is pulled towards the abdominal wall. Picture C shows the arteries that join and constitute the celiac trunk following lymphadenectomy (the stomach is pushed against the abdominal wall). Picture D shows the port placement of the thoracic part of the procedure with the patients lying in his abdomen. Picture E shows how the oesophagus is mobilised and dissected from adjacent tissue (the right lunch is collapsed). Picture F shows the chest after the oesophagus has been resected, visualising the airways, pericardium and stapled proximal oesophagus and the proximal part of the gastric tube

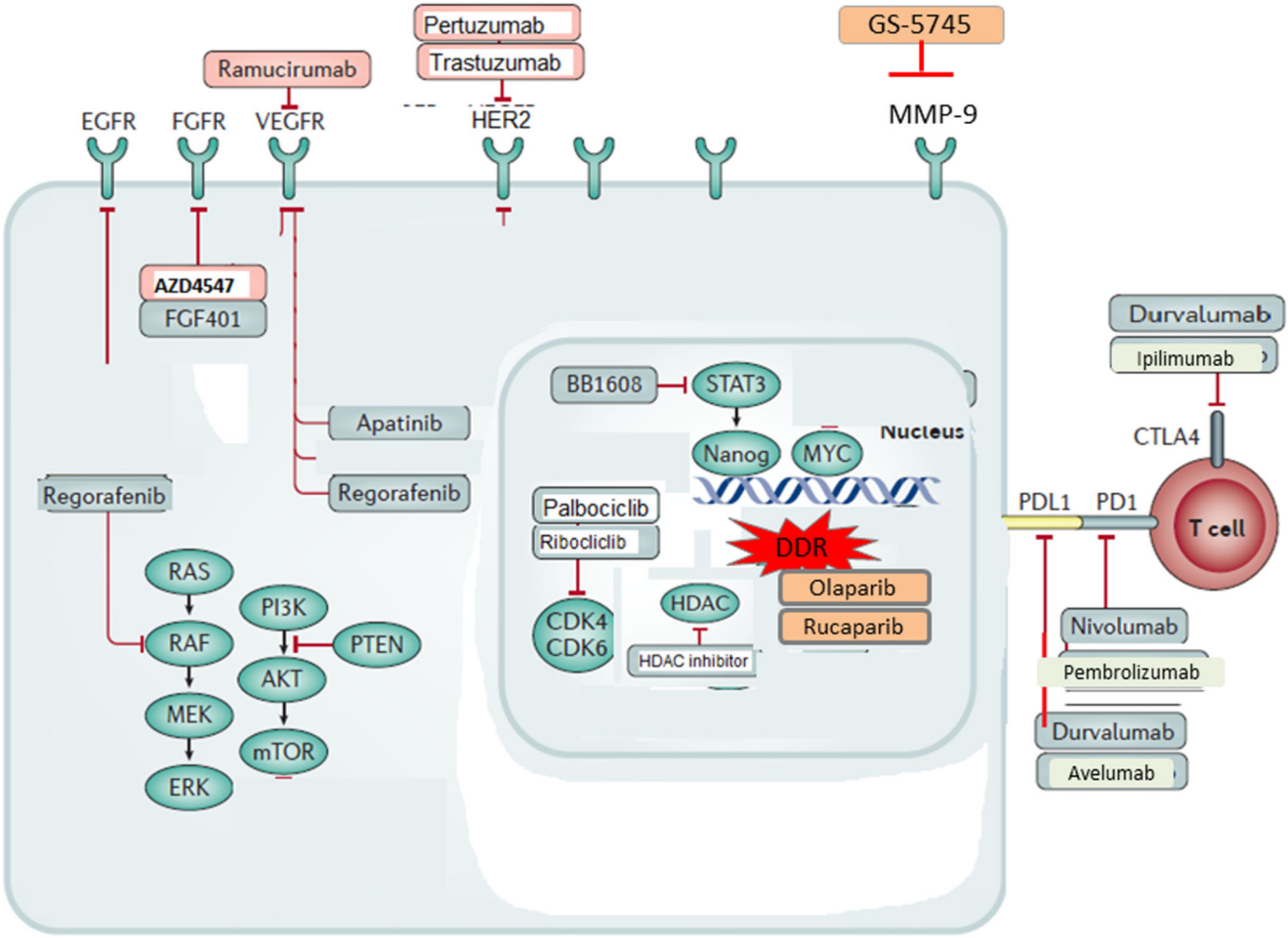

Figure 7.
Pathways of interest and available drugs in development in oesophageal cancer.

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Table 1

Key differences between oesophageal squamous cell carcinoma and adenocarcinoma

	Squamous cell carcinoma	Adenocarcinoma
Geographic distribution	Most common in East Asia, Middle East, “oesophageal cancer belt”	Most common in developed regions in Western Europe, North America, Australia”
Main risk factors	Smoking, alcohol, thermal injury, regional micronutrient deficiency	Central/visceral obesity, acid or bile reflux, Barrett’s oesophagus
Molecular characteristics	See Table 2	See Table 2
Tumour location	Throughout the oesophagus	More common in the distal oesophagus
Frequent comorbidity	Liver cirrhosis, chronic obstructive pulmonary disease, synchronous and metachronous cancer of the aero-digestive tract, arteriosclerosis	Obesity, coronary heart disease
Diagnosis and symptoms	Same as adenocarcinoma	Same as squamous cell carcinoma
Curative treatment	Definitive chemoradiotherapy Chemoradiotherapy followed by surgery	Neoadjuvant or perioperative chemotherapy followed by surgery Chemoradiotherapy followed by surgery
Palliative treatment	Chemotherapy Radiotherapy Stenting	Chemotherapy (plus trastuzumab if HER2 positive) Radiotherapy Stenting

Table 2

Frequently dysregulated genes in OSCC and OAC as per Oesophageal Cancer Genome Atlas and International Cancer Genome Consortium79,84

		OSCC	OAC
Receptor Tyrosine Kinases			
ERBB2	MAPK signalling pathway	3%	15-32%
EGFR	MAPK signalling pathway	19%	8-15%
VEGFA	Angiogenesis pathway	3%	5-28%
IGF1R	MAPK/AKT signalling pathways	2%	1-10%
KRAS	MAPK signalling pathway	7%	13-14%
PIK3CA	PI3K-AKT signalling pathway	13%	3-5%
FGFR1	MAPK/PI3K-AKT signalling pathways	12%	2-4%
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%
RB	Regulator of cell cycle progression	9%	0%
Proliferation and differentiation			
MYC	Regulator of proliferation and differentiation	23%	16-32%
SMAD4	Regulator of TGFβ and BMP pathways	8%	24-59%
GATA4	Transcription factor	1%	15-19%
GATA6	Transcription factor	3%	18-21%
TP63/SOX2	Transcription factors	48%	7-12%
Chromatin remodelling			
KDM6A	Histone demethylase	19%	4%
KMT2D	Histone methyltransferase	14%	1%

Red shading indicates degree of pathway upregulation, blue shading degree of pathway inhibition

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Table 3

Landmark studies including meta-analysis of neoadjuvant/perioperative or definitive treatment localised oesophageal and OGJ cancer (*proportion of gastric and oesophageal patients specified per trial)

Trial	Arms	N	OAC/OSCC	Site of primary (n) (%)	Survival rate %	HR (95% CI)	p
Neoadjuvant chemotherapy							
OE02177	Surgery CF[a] x2 + surgery	402 400	533/247	Oesophagus n=720 (90%) Cardia n=82 (10%)	5y: 17% vs. 23%	0.84 (0.72-0.98)	0.03
OE05165	CF x 2 + surgery ECX[b] x 4 + surgery	451 446	897/0	Not available	3y; 39% vs 42%	0.92 (0.79, 1.08)	0.8582
Perioperative chemotherapy							
MAGIC*182	Surgery ECF[b] (3 pre-op + post-op.) + surgery	253 250	503/0	Oesophagus n= 73 (14%) OG Junction n= 58 (12%) Gastric n=372 (74%)	5y: 23% vs. 36%	0.75 (0.60-0.93)	0.009
FFCD*183	Surgery CF (3 pre-op and post op.) + surgery	111 113	224/0	Oesophagus n=25 (11%) OGJ n= 144 (64%) Gastric n= 55 (25%)	5y: 24% vs. 38%	0.69 (0.50-0.95)	0.02
FLOT4-AIO	ECF/X – surgery – ECF/X FLOT – surgery – FLOT	350 356	100/0	Oes/GEJ 56% Gastric 44%	3y 48% vs. 57%	HR 0.77 [(0.63 - 0.94)	p = 0.012
Neoadjuvant chemoradiotherapy							
CALGB 9781264	Surgery CF+ RT (50.4Gy) + surgery	26 30	42/14	Not available	5y: 16% vs. 39%	na (1.46-5.69)	0.002
CROSS186	Surgery Carbo-Pac[c] + 41.1Gy + surgery	188 178	275/84	Oesophagus (73%) Upper/middle n=57 (15%) Lower n=211 (58%) OG Junction (24%)	5y: 34% vs. 47%	0.657 (0.495-0.871)	0.003
Definitive chemoradiotherapy							
Herskovic et al265	RT (64Gy) CF + RT (50Gy)	60 61	16/ 106	Upper oes=24(19%) Mid oes n= 58 (51%) Lower oes n=39 (30%)	2y: 10%vs.38%	na	<0.001
PRODIGE5/ACCORD17194	CF-RT (50Gy). FOLFOX[d] + RT (50Gy)	133 134	129/37	Upper oes n=87 (33%) Mid oes n= 113 (42%) Lower oesn=67 (25%)	3y: 27%vs.20%	0·94 (0·68 -1·29)	0·70

[a] CF: cisplatin and 5-fluorouracil (exact regimen may vary in trials);

[b] ECF/X: epirubicin, cisplatin and 5-fluorouracil (F) or capecitabine (X);

[c] Carbo-Pac: carboplatin and paclitaxel;

[d] FOLFOX: oxaliplatin, 5-fluorouracil, leucovorin; OAC; oesophageal adenocarcinoma; OSCC, oesophageal squamous cell carcinoma

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Table 4

To support oesophageal cancer patients' survivorship

Core information set to improve shared decision-making and informed consent.
Primary contact nurse throughout the care pathway
Dietitian throughout the care pathway
Psychosocial support
Tailored, but structured follow-up depending on patients' needs