Advances in diagnosis and management of cancer of the esophagus

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Cite this as: *BMJ* 2024;385:e074962
http://dx.doi.org/10.1136/bmj-2023-074962

Series explanation: State of the Art Reviews are commissioned on the basis of their relevance to academics and specialists in the US and internationally. For this reason they are written predominantly by US authors.

ABSTRACT

Esophageal cancer is the seventh most common malignancy worldwide, with over 470 000 new cases diagnosed each year. Two distinct histological subtypes predominate, and should be considered biologically separate disease entities.[1] These subtypes are esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC). Outcomes remain poor regardless of subtype, with most patients presenting with late stage disease.[2] Novel strategies to improve early detection of the respective precursor lesions, squamous dysplasia, and Barrett's esophagus offer the potential to improve outcomes. The introduction of a limited number of biologic agents, as well as immune checkpoint inhibitors, is resulting in improvements in the systemic treatment of locally advanced and metastatic esophageal cancer. These developments, coupled with improvements in minimally invasive surgical and endoscopic treatment approaches, as well as adaptive and precision radiotherapy technologies, offer the potential to improve outcomes still further. This review summarizes the latest advances in the diagnosis and management of esophageal cancer, and the developments in understanding of the biology of this disease.

Introduction

Esophageal cancer is a significant global health challenge, being the seventh most common malignancy worldwide with over 470 000 new cases each year. Esophageal cancer primarily manifests in two histological subtypes: esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC), which are biologically distinct. Despite advancements, outcomes for esophageal cancer remain poor, primarily owing to late stage diagnosis in most patients. However, emerging strategies aimed at the early detection of precursor lesions such as squamous dysplasia and Barrett's esophagus hold promise for improving these outcomes. The treatment landscape for esophageal cancer is evolving, with the introduction of biologic agents and immune checkpoint inhibitors enhancing systemic treatment for locally advanced and metastatic cases. Additionally, advancements in minimally invasive surgical and endoscopic techniques, along with precision radiotherapy technologies, further contribute to improved patient prognosis. This comprehensive review explores the current state-of-the-art diagnostic and treatment approaches for esophageal cancer, highlighting recent progress in understanding the disease's biology and the implications for clinical practice.

Epidemiology

Together, EAC and ESCC impose a considerable healthcare burden; accounting for the annual loss of more than 400 000 lives and 9.8 million disease adjusted life years.[3 4] These figures reflect a 52% increase in the total number of new cases and a 40% rise in the total number of deaths between 1990 and 2017, even as the age standardized incidence and mortality fell by 22% and 29%, respectively.[3]

Around 90% of worldwide cases are ESCC, which has particularly high incidence in South America and the Asian esophageal cancer belt that extends from East Africa and sub-Saharan Africa through much of Central Asia.[3 5 6] EAC is, by contrast, more prevalent in Europe and high income North America, where its incidence has increased fourfold over the past four decades.[3 7]

These trends are reflected by the different epidemiological associations of the two subtypes. ESCC is linked with alcohol, tobacco and opium use, environmental pollution, ingestion of high temperature beverages, nutritional deficiencies, and other dietary factors such as consumption of pickled foods and high nitrosamine exposure.[5 8] In rare cases, human papillomavirus has also been linked to ESCC development, although data remain uncertain.[9 10] By contrast, EAC associates with obesity, the metabolic syndrome and gastro-esophageal reflux disease (GERD).[11]

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Sources and selection criteria

We searched PubMed in March and November 2023 using keywords such as "(o)esophageal cancer", "early-stage (o)esophageal cancer" OR "advanced (o) esophageal cancer", and "esophageal endoscopy". We considered studies published in the English language from January 2010 to November 2023. Selected publications were included before 2010 if they were relevant to the topic. We excluded articles published in non-peer reviewed journals, case reports, and case series. Additional relevant high quality references identified from articles in the original search were also reviewed and included. We also accessed the National Comprehensive Cancer Network (NCCN) guidelines.

Pathophysiology and molecular genomics

Pathophysiology

Somatic mutant clones that incorporate driver gene mutations colonize the esophageal normal squamous epithelium from infancy and increase in number and size with age.[12 13] This remodeling can be catalyzed by exogenous exposures, such as alcohol consumption and smoking, eventually reaching between 9000 and 15 000 clones per esophagus.[13] ESCC originates from one such clone, but its development, and the squamous dysplasia that precedes it, is rare in comparison with the incidence of mutation. Evidence from murine studies suggests that most newly formed ESCC is eradicated following competition with other mutant clones in adjacent normal squamous epithelium.[14 15] These data suggest treatment opportunities for disease prevention, such as through the blockade of wild type *NOTCH1*, a gene that potentially increases the aggressivity of tumor clones.[13 16]

The transformation of normal squamous epithelium to basal cell hyperplasia, which later evolves through a sequence of low grade intraepithelial neoplasia and high grade intraepithelial neoplasia to invasive carcinoma, is a multidimensional and poorly understood process. The risk of squamous dysplasia progression to carcinoma increases depending on the degree of dysplasia, although a majority will not progress. For those that do progress, progression can take many years.[17 18] Single cell analyses suggest that a slow cycling basal cell gives rise to high grade intraepithelial neoplasia.[19]

Genome-wide association studies from patients of Chinese, European, and Japanese descent have shown multiple susceptibility loci for progression to ESCC.[20] Some of these loci interact with alcohol consumption, including genes encoding alcohol dehydrogenase family proteins.[21] A rare familial disorder, tylosis, is also associated with a high risk of progression to ESCC of around 90% by age 70 because of an autosomal dominant *RHBDF2* germline mutation.[22] Other hereditary syndromes associated with ESCC include Bloom syndrome and Fanconi anemia.[23]

By contrast, the EAC precursor Barrett's esophagus arises at the gastro-esophageal junction as an adaptive response to chronic exposure to injurious acidic gastroduodenal refluxate, which is rich in bile salts. However, around 90% of people with a diagnosis of EAC have no history of Barrett's esophagus; and at the time of diagnosis, no identifiable Barrett's esophagus lesions are found in around half of EAC cases.[24-26] Despite this, population modeling and molecular analyses increasingly point to Barrett's esophagus as the sole precursor to adenocarcinoma.[27-29] Each Barrett's esophagus lesion is characterized by the metaplastic replacement of native normal squamous epithelium with a multicellular mosaic of columnar-like epithelium.[30] The two predominant subtypes are intestinal metaplasia and gastric metaplasia; the former characterized by the presence of goblet cells, the latter by their absence. The nature of the cellular milieu from which these neo-epithelial linings originate has been strongly contested.[1 27 28 31-33] Recent evidence drawn from chromatin and single cell transcriptomic profiling suggests that a transcriptional program driven by *c-MYC* and *HNF4A* causes the development of Barrett's esophagus from cells within the gastric cardia, and highlights intestinal metaplasia as a specific precursor for adenocarcinoma.[27 28] Gastric metaplasia, which is characterized by a lower mutation burden, might instead coincide with indolent atrophic gastritis.[27] Moreover, intestinal metaplasia associated with Barrett's esophagus is phenotypically indistinguishable from gastric intestinal metaplasia, the precursor to gastric adenocarcinoma.[27] This lack of distinction suggests a parallel natural history for EAC and stomach cancer, supporting existing evidence for substantial molecular similarities between these two malignancies.[1 27 34]

Once established, the initial non-dysplastic Barrett's esophagus (NDBE) lesion generally features a relatively high number of point mutations, but with intact p53 and a diploid genome that, as with the lesion itself, remain stable in most patients.[35 36] By contrast, a minority of patients with Barrett's esophagus will progress to adenocarcinoma via the development of low grade dysplasia and then high grade dysplasia. For those with NDBE, the annual risk of progression is between 0.1 and 0.5%.[37-39] A higher but less precisely defined risk of developing EAC exists following the development of dysplasia.[37 38] The rate at which dysplasia worsens is highly variable, and individual Barrett's esophagus lesions can incorporate different histopathological states, although three broad patterns of progression have been observed.[36 40] For some patients, a gradual accumulation of mutations occurs over time, with the risk of dysplastic progression conferred by the acquisition of specific deleterious mutations.[41 42] Others can have seemingly stable, low risk Barrett's esophagus that deteriorates in response to a specific catastrophic event such as chromothripsis or kataegis, whereas a third "born bad" group might have high risk Barrett's esophagus that is primed to progress from the outset even when non-dysplastic[41 42] (fig 1).

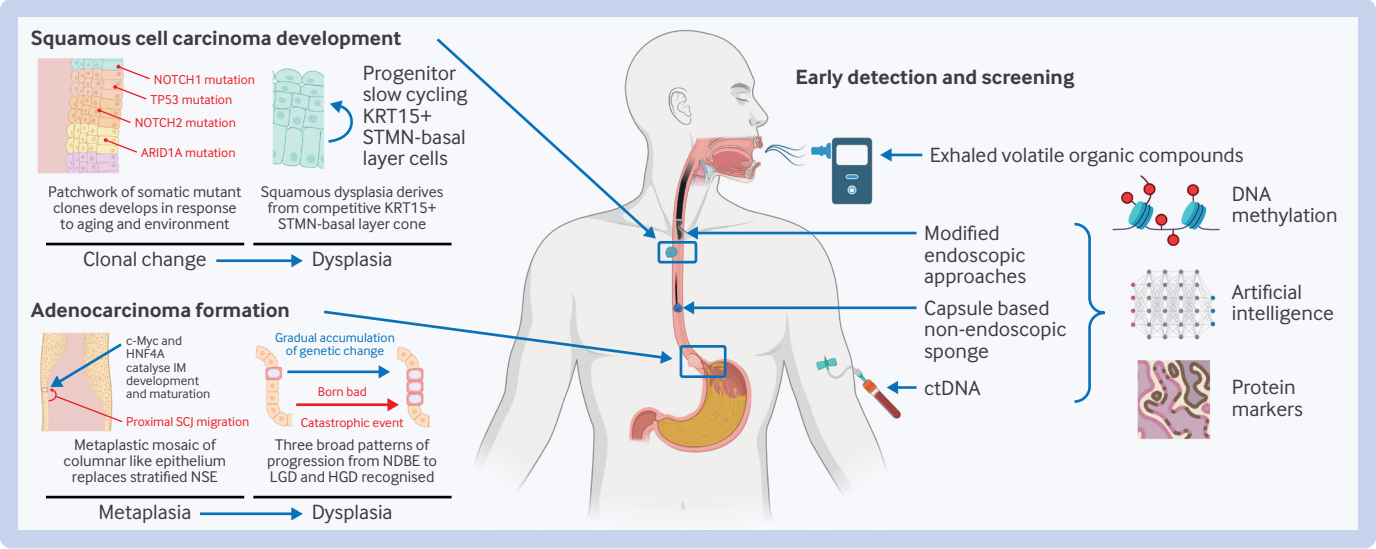

Fig 1 | An overview of the development and progression of the squamous cell carcinoma and adenocarcinoma precursor lesions, squamous dysplasia, and adenocarcinoma, alongside proposed approaches for their early detection. ctDNA=circulating tumor DNA; HGD=high grade dysplasia; IM=intestinal metaplasia; NDBE=non-dysplastic Barrett's esophagus; NSE=neosquamous epithelium; LGD=low grade dysplasia; SCJ=squamocolumnar junction.

Microenvironment in esophageal cancer and its precursors

Squamous dysplasia and squamous cell cancer

The importance of the microenvironment to squamous cell cancer development is shown by enrichment of a C:G>A:T mutational signature that is associated with tobacco exposure, as well as a difference in mutational environment between upper and lower squamous cell cancers.[1 43 44] Interestingly, recent evidence suggests that squamous dysplasia remodels its environment by reducing annexin A1 expression, and therefore signaling, via the formyl peptide receptor 2 on fibroblasts, which results in the formation of cancer associated fibroblasts.[45]

The immune microenvironment in squamous cell cancer is inflamed and enriched with immunosuppressive T regulatory, tumor associated macrophages, and exhausted or inactivated natural killer cells, CD8+ cells, and CD4+ T cells.[19 46] Unlike in adenocarcinoma, B cell infiltration is relatively low. Overall, this cellular milieu contributes to disease progression and inter-tumoral heterogeneity.[46 47] Through collaboration between tumor associated macrophages and cancer associated fibroblasts, tumor promoting CCL2, matrix metalloproteinase 9, and interleukin 6 are secreted.[48] Consequently, it has been suggested that anti-tumor immunity could be restored by targeting T regulatory cell modulation of macrophage function for treatment.[46] Relevant to the development of immunotherapies for squamous cell cancer, immune infiltrates are heterogeneous across tumors, and exert selection pressure that results in neoantigen evasion.[47]

The local microbiome is also linked to the progression of squamous dysplasia and ESCC, but its importance is yet to be fully delineated. At present, lower microbial richness is recognized with the development of squamous dysplasia, and an increase in *Fusobacterium* and *Streptococcus* is seen in ESCC compared with benign esophagus tissue.[49] A pathogenic role for *Porphyromonas gingivalis* in the formation of squamous cell cancer has also been postulated.[50]

Barrett's esophagus and adenocarcinoma

The impact of the Barrett's esophagus and EAC microenvironment is reflected by the frequent presence of signature 17, which is characterized by CTT trinucleotide repeat A:T>C:G transversions that are thought to reflect oxidative damage.[36 40 51] Cancer associated fibroblasts are another key stromal contributor to poorer outcomes in EAC, and are linked to impaired immunosurveillance, as well as chemotherapy resistance, which is alleviated in vitro by phosphodiesterase type 5 inhibitors that target cancer associated fibroblasts.[52] Activation of a similar population of cancer associated fibroblast has recently been associated with dysplastic progression of Barrett's esophagus.[27]

The immune microenvironment of Barrett's esophagus most closely resembles that of duodenal tissue than normal squamous epithelium.[53] Recent evidence suggests that epithelial metaplasia is mirrored by metaplastic changes in the stroma that are characterized by an immunosuppressive environment mediated by natural killer cells, and the appearance of fibroblasts with a cancer associated fibroblast phenotype.[54] A stromal T helper type 2 immune infiltrate, elevated infiltration of T cells, and more dendritic cells producing retinoic acid

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have also previously been described.[55 56] Progression towards adenocarcinoma from Barrett's esophagus is associated with an increase in T regulatory cells, T cell costimulatory pathway activity, and CD163+ tumor associated macrophages, as well as chemokines such as interleukin 6, CXCL8, and the CXCR1/2 chemokine receptors.[57 58] Recent immune profiling suggests that adenocarcinomas reside within one of four immune clusters; hot, suppressed, moderate, or cold.[59 60] Moreover, the importance of a favorable immune landscape to long term outcomes is increasingly recognised.[59]

As with squamous cell cancer, evidence increasingly suggests changes in the diversity and function of the oral and esophagus microbiome in patients with Barrett's esophagus and adenocarcinoma.[61 62] These changes have a role in adenocarcinoma development and progression, and are likely to come under increasing focus as potential biomarkers.

Genomic differences in esophageal cancer

Squamous cell cancer

Squamous cell cancer develops in response to the long term accumulation of somatic mutations caused by DNA damage.[12 15] Correspondingly, its genomic profile is similar to that of other ESCC not related to human papillomavirus.[1] Defective repair processes are seen early in progression to ESCC, as are mutations of *TP53* and *CDK2NA*.[63] Aberrance of p53 increases with cumulative dysplasia, and its complete inactivation is considered critical for the development of squamous cell cancer.[64] While these changes underline the similar mutations and markers of genetic instability seen between squamous dysplasia and squamous cell cancer, squamous dysplasia is nevertheless polyclonal, and heterogeneity is seen between squamous dysplasia and neighboring ESCC.[63 64]

Once formed, the genomic features of ESCC are characterized by a high frequency of somatic mutations and copy number alterations.[1 65-70] This mutational spectrum has been shown to vary spatially, with a moderate overall mutational load characterized by a burden of around 5.8 single nucleotide variants per megabase (SNVs/Mb).[44 65 71] Geographic variation in the genomic characteristics of squamous cell cancers has been observed.[64 71]

Enrichment of apolipoprotein B mRNA editing enzyme, catalytic polypeptide (APOBEC) signatures is a frequent feature of ESCC, and contributes to its mutational burden, the prognostic significance of which is uncertain.[1 44] Around a quarter of patients have mutations in DNA repair pathway genes, which appear to interact with APOBEC processes that lead to a higher mutational burden.[1 67 69] Age related changes in mutational spectra are also observed, including an increased frequency of *NOTCH1* mutation.[44] Commonly mutated genes that are relevant to treatment include those involved in cell cycle regulation (*TP53*, *CDKN2A*), the *PI3K/AKT* pathway (*PIK3CA*, *PTEN*), cell adhesion (*AJUBA*), chromatin remodeling (*MLL2*, *KDM6A*), epidermal differentiation (*ZNF750*), and *NOTCH* signaling (*NOTCH1/3*).[65-70] Structural rearrangements resulting from chromothripsis, kataegis, and breakage-fusion-bridge cycles are also observed in over half of all cases.[70] These rearrangements can result in amplification of oncogenes such as *EGFR*, *ERBB2*, and *MYC*.[70] This chromosomal instability drives intra-tumoral heterogeneity.[47] As with other ESCC, amplification of chromosome 3q, and in particular the *SOX2* locus, is frequently seen.[1] Lastly, frequent genomic amplification of *CCND1* and *TP63* is also observed in this cohort.[1]

The Cancer Genome Atlas summarized these alterations as three subgroups of ESCC that appear to show geographic variation.[1] Although these subgroups have yet to be exploited, they have potential clinical significance. The first subgroup, ESCC1, is characterized by alterations in the oxidative stress response NRF2 pathway, which is associated with radiation resistance.[1] ESCC2 is typified by high rates of *NOTCH1* and *ZNF750* mutation and shows high levels of leukocyte infiltration and cleaved caspase 7, which could be of benefit to pro-immune and pro-apoptotic treatments.[1] Recent evidence has expanded on this possibility, suggesting that loss of *NOTCH1*, *TP53*, and *CDKN2A* promote an immunosuppressive niche enriched by exhausted T cells and M2 macrophages via the *CCL2/CCR2* axis.[72] ESCC3 is characterized by activating mutations of the PI3K pathway.[1]

Barrett's esophagus and adenocarcinoma

At the genomic level, progression of Barrett's esophagus is associated at baseline with high clonal diversity that reflects varying levels of multigenerational chromosomal instability.[73 74] This association could predict EAC before malignant transformation, and is characterized by early copy number changes as well as aneuploidy and tetraploidy, which have been linked to mitotic slippage.[35 36 41 73] Accordingly, high levels of sensitivity and specificity for malignant transformation have been achieved through the measurement of genomic instability, primarily through assessment of copy number changes, including the use of flow cytometric DNA analysis, shallow whole genome arrays, and single nucleotide polymorphism arrays.[41 75] A complication of the need to evaluate clonal diversity is the requirement for a wide sampling field, which, given the potential complications of multiple biopsies, might favor the use of pan-esophagus non-endoscopic sampling modalities such as capsule delivered sponges.[36]

By contrast, gene mutation panels are yet to yield effective biomarkers, owing to high levels of heterogeneity.[76] In Barrett's esophagus, the burden of mutations is reported at 5.6-6.8 SNVs/Mb, but whether this rate differs between dysplastic and non-dysplastic cases is uncertain.[36 40] Nevertheless, a predilection for early *CDK2NA* and somewhat later *TP53* point mutations is recognized in Barrett's esophagus.[76 77] Aberrance of p53 detected by immunohistochemistry correlates with progression

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to high grade dysplasia and EAC, and its use as an adjunct for histopathological assessment of Barrett's esophagus tissue is recommended by UK guidance.[76 78] Reflecting the importance of p53 in the pathogenesis of EAC, evidence is emerging for an association between p53 loss and the rapid accumulation of copy number heterogeneity.[74] Recent data also suggest that extrachromosomal DNA (ecDNA) arises almost exclusively in the context of *TP53* alteration in regions of high grade dysplasia, and amplifies a diversity of immunomodulatory genes and oncogenes.[79] Interestingly, a recent meta-analysis suggested a higher genetic correlation between GERD and Barrett's esophagus than between GERD and EAC.[80]

Once developed, EAC is considered a heterogeneous, structurally unstable, C type malignancy that is characterized by frequent copy number changes and complex, large scale structural rearrangements.[36 51 81] These structural rearrangements have also been seen in high grade dysplasia, and include breakage-fusion-breakage cycles, fragile site deletions, somatic mobile element insertions, and chromothripsis.[51] EAC has a high mutational burden ranging from 7.1-25.2, with an average of 9.9 SNVs/Mb.[77] Reflecting early clonal diversity, relatively little overlap is observed between the mutational patterns of EAC and adjacent Barrett's esophagus. Over 60 mutational driver genes are now recognized in EAC, with a median of five (interquartile range 3-7) driver gene events per tumor.[82] These driver genes can be promoted and exacerbated by a plethora of patient specific helper genes.[83] Among the known drivers, *SMAD4* mutation or deletion, present in around one third of EAC, is associated with a significantly poorer prognosis (hazard ratio 0.60, 95% confidence interval 0.42 to 0.84; p=0.003).[82] A similar trend is seen for *GATA4* amplification (0.54, 0.38-0.78; p<0.001), while activation of the Wnt pathway appears to be associated with well differentiated tumors.[82] Furthermore, a higher proportion of APOBEC signatures is seen in later stage disease and is associated with worsened outcomes.[59]

Broadly, these mutational signatures can be subdivided into three treatment relevant groups.[81] Around one fifth of patients have a signature of DNA damage repair impairment featuring defects in the homologous repair pathway, which could actually provide susceptibility to treatment using irradiation or other DNA damaging agents combined with poly ADP ribose polymerase (PARP) inhibition.[81] A second group enriches for a C>A/T dominant mutational pattern associated with aging, while a third group of around half of all patients have a dominant T>G mutational pattern that associates with a high mutational load.[81] Evidently, such hypermutation associates with Wnt dysregulation and the loss of immune signaling genes such as β2 microglobulin, which could explain the relatively poor sensitivity of EAC to checkpoint inhibition.[82] The immune landscape is likely to be further shaped by frequent amplification and co-amplification of targetable receptor tyrosine kinases, several of which are known to be expressed more during dysplastic progression of Barrett's esophagus.[1 81] Over half of all cases of EAC also contain sensitizing events for CDK4 and CDK6 inhibitors, the potential efficacy of which has been shown in vitro.[82]

Impact of gene regulatory mechanisms on development of esophageal cancer

Squamous cell cancer

A progressive increase in promoter hypermethylation with squamous dysplasia progression has been observed, including most reproducibly for *CDKN2A*.[84] Measurement of this increase has been exploited for the development of novel early detection tools.[85 86] Genome-wide hypomethylation is also associated with squamous dysplasia progression, and correlates with chromosomal instability.[87 88] In ESCC, abnormal methylation is centered on genes involved in DNA damage repair, cell cycle regulation, and cellular proliferation.[89] Many of these genes are prognostic or predictive of response to anticancer treatments.[90 91] Similarly, close to 100 microRNAs (miRNAs) are now considered to be dysregulated in ESCC, several of which are considered to affect chemosensitivity.[92 93]

Adenocarcinoma

The breakdown of gene regulation is of additional interest to EAC development. Marked changes in chromatin accessibility are seen during progression of Barrett's esophagus, and correlate with a transcription factor network that is centered on *HNF4A* and *GATA6*.[94] Redistribution of *KLF5* to control cell cycle genes in EAC has also been reported, and potentially contributes to its development from Barrett's esophagus.[95] Gene regulation in Barrett's esophagus and EAC is also known to be affected by CpG island methylation, for which a similar profile is seen in EAC, gastric cancer, and colon cancer.[1] This has broader relevance to the chromosomal instability that dominates Barrett's esophagus and EAC, given that commonly methylated genes include those involved in chromosomal segregation and spindle formation.[96]

Numerous methylation based subtypes of Barrett's esophagus and EAC have been proposed, and have potential prognostic and treatment relevance.[96 97] These subtypes include EAC cases in which high levels of methylation are observed, which could be more sensitive to treatment with the topoisomerase I inhibitor irinotecan, or in which susceptibility to the alkylating agent temozolomide might be conferred by high levels of *MGMT* promoter methylation.[97] Clearly also, aberrant DNA methylation holds considerable promise for the development of biomarkers, some of which have been evaluated using non-endoscopic capsule based sponge assays.[98 99] These biomarkers include detection of methylated VIM and methylated CCNA1 via the EsoCheck device.[99] In a further study, the use of a four gene digital droplet polymerase chain reaction and next generation sequencing based four marker methylation panel shown sensitivity of

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84.2%, 85.0%, and 90.8% for the detection of NDBE, high grade dysplasia, and EAC, respectively; albeit in a mixed population of biopsy and surgical resection specimens.[98] Similar to ESCC, nearly 100 miRNAs have been proposed as contributors to Barrett's esophagus progression; however, these miRNAs are supported by varying levels of evidence and often associated with conflicting data.[100] Expression changes in some of the pleiotropic group of long non-coding RNAs (lncRNAs) are also associated with EAC development and progression, but their significance is unclear.[101]

Advances in early diagnosis and prevention

Current approaches to screening and monitoring of Barrett's esophagus and squamous dysplasia

The early detection of both EAC and ESCC, or better still, their precursors Barrett's esophagus and squamous dysplasia, holds considerable promise for reducing the burden imposed by these diseases. At present, strategies for screening and surveillance of Barrett's esophagus and squamous dysplasia vary worldwide, but mostly rely on white light endoscopy.[78 102]

Most guidelines for Barrett's esophagus emphasize the importance of targeted screening at patients with symptoms of GERD, with further stratification relating to age and other known risk factors for Barrett's esophagus.[78 102] Subsequent monitoring of those with established Barrett's esophagus usually proceeds at intervals of 3-5 years based on the degree of dysplasia and length of the metaplastic segment. Endoscopic protocols that use systematic four quadrant biopsies have been shown to improve dysplasia detection for Barrett's esophagus, and are widely recommended to guide esophageal sampling.[103] No data relate to the effect of screening for Barrett's esophagus on mortality, and data relating to the efficacy of surveillance are mixed.[104]

By contrast, Lugol chromoendoscopy is used for the identification of early ESCC, and has been shown to increase identification of squamous dysplasia.[105] Evidence suggests that squamous cell screening programs reduce mortality and are cost effective when targeting endemic and high risk populations.[25 104] A cluster randomized controlled trial evaluating efficacy in non-high incidence areas is under way.[106]

Several alternative and complementary strategies aimed at improving dysplasia detection for both neoplastic subtypes are in development. Examples include the use of wide area transepithelial sampling, fluorescence aided molecular endoscopy, and capsule delivered sponges for Barrett's esophagus, the use of high resolution microendoscopy and confocal laser endomicroscopy for squamous dysplasia, and computer aided detection for both subtypes.[107-109] Detection of loss of heterozygosity in cell free DNA (cfDNA) has also been studied as a method of monitoring dysplastic progression of Barrett's esophagus, though the sensitivity appears to be limited in early disease.[110]

Future approaches to early detection

Modeling of American data suggests that up to half of all cases of EAC could be prevented through the systematic screening of individuals with symptoms of GERD who are not currently referred for investigation.[111] Unfortunately, current endoscopic approaches to diagnosis and screening are impractical, and better understanding is required to effectively stratify patients for both screening and ongoing surveillance of premalignant lesions, most importantly through further development of risk prediction models.[112]

Emerging technologies with the potential to improve early detection of esophageal cancer and their premalignant lesions include capsule endoscopy, the analysis of volatile organic compounds within exhaled breath, or the use of minimally invasive capsule delivered sponges.[99 113 114] The latter pairs cytological assessment with the detection of biomarkers such as DNA methylation status, miRNA assays, or cell surface proteins.[99 113] This includes the Cytosponge, which detects Barrett's esophagus intestinal metaplasia defining trefoil factor 3 (TFF3). In a previous trial including patients presenting to primary care with reflux symptoms, a 10.6-fold increase in detection of Barrett's esophagus was seen for those within a cohort in which the Cytosponge-TFF3 was offered compared with a cohort offered standard care alone.[113] The integration of multiplatform data, such as cytological and epidemiological data, could also be beneficial, with a recent prospective Chinese study showing favorable performance of a prediction tool that employed machine learning to enhance diagnosis of EAC and ESCC.[114] The analysis of circulating cfDNA to enable liquid biopsies of early disease has been more disappointing, with reported sensitivity of less than 20% using the Galleri and CancerSEEK tests.[115 116]

Prevention of progression to invasive disease

Interest has been shown in the use of proton pump inhibitors or non-steroidal anti-inflammatory drugs to reduce dysplastic progression of Barrett's esophagus, as was assessed in the phase 3 multicenter AspECT trial.[117] In this study, use of high dose proton pump inhibitor (esomeprazole 40 mg twice daily) (time ratio 1.27, 95% confidence interval 1.01 to 1.58; p=0.038) and combined high dose proton pump inhibitor with aspirin (300-325 mg once daily) (1.59, 1.14 to 2.23; p=0.068) resulted in prolonged time to a composite endpoint of all cause mortality, high grade dysplasia, or invasive disease, when compared with low dose proton pump inhibitor (esomeprazole 20 mg once daily) alone. Despite this result, no difference was seen between treatments in a secondary endpoint of the time to the development of EAC or high grade dysplasia. As such, the specificity of any advantage conferred by high dose proton pump inhibitor or aspirin is uncertain, and further studies are required to define their role in the chemoprevention of dysplasia.

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Once established, dysplastic Barrett's esophagus should be eradicated using endoscopic eradication therapy. Current guidelines advocate for the subsequent ablation of any residual Barrett's esophagus as well.[78 102] In the context of low grade dysplasia, a meta-analysis has shown a relative risk of progression with radiofrequency ablation versus surveillance of 0.14 (95% confidence interval 0.04 to 0.45; p=0.001).[118] Alternative approaches include cryotherapy (via spray, carbon dioxide gas, or cryoballoon with nitrous oxide gas) and hybrid argon plasma coagulation, which have been studied as primary treatments and for salvage after failed radiofrequency ablation.[119 120]

Management of early disease

Intramuscosal (T1a) cancers are subclassified by involvement of the epithelium (m1), lamina propria (m2), or muscularis mucosae (m3). Submucosal lesions (T1b) are separated by a low (<500 µm; sm1), medium (500-1000 µm), or high (>1000 µm) depth of invasion. The Paris classification distinguishes lesions by endoscopic appearances into those that are protruding (type I), flat and superficial (type 0-II), or excavated (type 0-III).[121] Tumor depth, size, lymphovascular invasion, and poor differentiation are known prognostic features.[122]

In EAC, the risk of nodal metastases rises from less than 5% for intramucosal (pT1a) lesions to 26% for disease invading the submucosa (pT1b).[123] pT1a lesions with no adverse features can be managed definitively using either endoscopic mucosal resection or endoscopic submucosal dissection, which deliver similar outcomes.[124] pT1b lesions might necessitate an esophagectomy, though an endoscopic approach can be considered for sm1 lesions with no adverse features and no residual tumor at the deep margin.[122] Eradication of remaining Barrett's esophagus via radiofrequency ablation is mandated following endoscopic treatment, as is close surveillance. The ongoing international multicenter PREFER (NCT03222635) study is evaluating whether endoscopic follow-up might be an acceptable alternative to esophagectomy for patients with T1b N0 EAC.[125] Preliminary data indicate that this approach is feasible in patients with high risk and low risk disease.[125]

The risk of nodal metastasis is around 4% for pT1a ESCCs but higher than EAC for pT1b, at around 30%.[126] pT1a lesions can be managed endoscopically, though m3 lesions with additional risk factors will generally be considered for additional treatment.[127] Endoscopic submucosal dissection delivers more favorable local outcomes than endoscopic mucosal resection, and should be considered.[128] ESCC pT1b lesions can be managed with surgical resection or adjuvant chemoradiotherapy, both of which are associated with excellent long term outcomes.[129]

Management of locally advanced disease

Molecular testing is frequently used once a pathological diagnosis is made, particularly for microsatellite instability, but interest in HER2 and programmed death ligand 1 (PDL1) status has been growing. Recent evidence points to an emerging role for artificial intelligence in supporting pathological assessment, including for accurately assessing HER2 status.[130 131] Esophageal cancer is generally staged using positron emission tomography-computed tomography (PET-CT) and endoscopic ultrasound, although the utility of this latter assessment has been questioned.[132] Other staging modalities include diagnostic laparoscopy in selected cases to assess for occult peritoneal metastatic disease, and bronchoscopy where concern exists about airway invasion.[133-136] A multidisciplinary discussion is required to define treatment options once the stage is known, and open dialogue with patients is essential to define an individualized treatment strategy. Treatment approaches have nuances specific to regions and centers, although the focus is on ensuring that patients are treated at dedicated high volume centers, with access to highly experienced teams (table 1).[137-142 144-153]

Table 1 | The landmark clinical trials on localized treatments in esophageal and gastro-esophageal junction cancers

Trial	Trial identifier (phase)	Treatment setting	Tumor type	Treatment arm (N)	Overall survival Hazard ratio (95% CI), P value	PFS/DFS Hazard ratio (95% CI), P value	pCR, %	R0, %
MAGIC[137]	ISRCTN93793971 (3)	pCT	EAC, GEJAC, GAC	Perioperative ECF (250)	5 year OS 36% *v* 23% 0.75 (0.60 to 0.93), 0.009	Median PFS NA 0.66 (0.53 to 0.81), 0.001	31	79
				Surgery alone (253)			-	70
FLOT[138]	NCT01216644 (2/3)	pCT	GEJAC, GAC	Perioperative FLOT (356)	Median OS 50 *v* 35 months, 5 year OS 45% *v* 36% 0.77 (0.63 to 0.94), 0.012	Median DFS 30 *v* 18 months 0.75 (0.62 to 0.91), 0.0036	16	85
				Perioperative ECF/ECX (360)			6	78
FNCLCC ACCORD07[139]	NCT00002883 (3)	pCT	EAC, GEJAC, GAC	Perioperative CF (113)	5 year OS 38% *v* 24% 0.69 (0.50 to 0.95), 0.02	5 year DFS 34 *v* 19% 0.65 (0.48 to 0.89), 0.003	-	84
				Surgery alone (111)			-	74
CROSS[140]	NTR487 (3)	nCRT	ESCC, EAC, GEJ cancer	nCRT with PC (178)	Median OS 49 *v* 24 months, 5 year OS 47% *v* 44% 0.68 (0.53 to 0.88), 0.003	Median DFS NR *v* 24 months 0.498 (0.357 to 0.693), 0.001	29	92
				Surgery alone (188)			-	69

(*Continued*)

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Table 1 | Continued

Trial	Trial identifier (phase)	Treatment setting	Tumor type	Treatment arm (N)	Overall survival Hazard ratio (95% CI), P value	PFS/DFS Hazard ratio (95% CI), P value	pCR, %	R0, %
NeoCRTEC5010[141]	NCT01216527 (3)	nCRT	OSCC	nCRT with VC (224)	Median OS 100 *v* 67 months 0.71 (0.53 to 0.96), 0.025	Median DFS 100 *v* 42 months 0.58 (0.43 to 0.78), 0.001	43	98
				Surgery alone (227)			-	91
NEO-AEGIS[142]	NCT01726452 (3)	pCT, nCRT	EAC, GEJAC	CROSS regimen (178)	3 year OS 57% *v* 55% 1.03 (0.77 to 1.38), NS	Ongoing	16	95
				mMAGIC/FLOT regimen (184)			5	82
ESOPEC[143]	NCT02509286 (3)	pCT, nCRT	EAC, GEJAC	CROSS regimen	Ongoing	Ongoing		
				FLOT regimen				
OEO2[144 145]	UK MRC OE02 (3)	nCT	ESCC, EAC	nCT with CF (400)	Median OS 17 *v* 13 months, 5 year OS 23% *v* 17% 0.84 (0.72 to 0.98), 0.03	Median DFS NA 0.82 (0.71 to 0.95), 0.003	-	60
				Surgery alone (402)			-	54
RTOG 8911/ INT-113[146]	SWOG-9013/ RTOG 8911 (3)	nCT	ESCC, EAC	nCT with CF (213)	Median OS 15 *v* 16 months 1.07 (0.87 to 1.32), NS	-	-	62
				Surgery alone (227)			-	59
NeoRes[147]	NCT01362127 (2)	nCT, nCRT	ESCC, EAC, GEJ cancer	nCRT with CF (90)	3 year OS 47% vs 49% 1.09 (0.73 to 1.64), 0.77	3 year PFS 44% *v* 44% 1.0 (0.68 to 1.47), NS	28	87
				nCT with CF (91)			9	74
JCOG 1109/ NExT[148]	UMIN000009482 (3)	nCT, nCRT	OSCC	nCRT with CF (200)	Median OS 6.0 *v* NR *v* 4.6 years, 3 year OS 68% *v* 72% *v* 63% nCRT with CF; 0.84 (0.63 to 1.12), 0.12 nCT with DCF; 0.68 (0.50 to 0.92), 0.006	Median PFS 2.7 *v* NR *v* 5.3 years 3 year PFS 48% *v* 62% *v* 59% NA	39	88
				nCT with DCF (202)			20	86
				nCT with CF (199)			2	84
RTOG 85-01[149 150]	RTOG 85-01 (3)	dCRT	ESCC, EAC	dCRT with CF (134)	Median OS 14 *v* 9 months, 5 year OS 26% *v* 0% NA, NA	-	-	-
				RT alone (62)			-	-
PRODIGE5/ ACCORD17[151]	NCT00861094 (2/3)	dCRT	ESCC, EAC	dCRT with FOLFOX (134)	Median OS 20 *v* 18 months 0.94 (0.68 to 1.29), 0.70	Median PFS 9.7 *v* 9.4 months 0.93 (0.70 to 1.24), 0.64	44*	-
				dCRT with FP (133)			43*	-
FFCD9102[152]	NCT00416858 (3)	dCRT, nCRT	OSCC	nCRT with FP (129)	Median OS 18 *v* 19 months, 2 year OS 34% *v* 40% 0.90 (NA), 0.44	-	-	-
				dCRT with FP (130)			-	-
CheckMate 577[153]	NCT02743494 (3)	aIO	ESCC, EAC, GEJ cancer	Adjuvant nivolumab (532)	Ongoing	Median DFS 24 *v* 11 months 0.69 (0.56 to 0.86), 0.001	-	-
				Adjuvant placebo (262)			-	-

aIO=adjuvant immunotherapy; CF=cisplatin, fluorouracil; CI=confidence interval; DCF=docetaxel, cisplatin, fluorouracil; dCRT=definitive chemoradiation therapy; DFS=disease free survival; ECF=epirubicin, cisplatin, fluorouracil; ECX=epirubicin, cisplatin, capecitabine; FOLFOX=fluorouracil, leucovorin, oxaliplatin; FLOT=fluorouracil, leucovorin, oxaliplatin, docetaxel; FP=fluoropyrimidine, platinum; GAC=gastric adenocarcinoma; GEJ=gastro-esophageal junction; GEJAC=gastro-esophageal junction adenocarcinoma; NA=not available; nCRT=neoadjuvant chemoradiation therapy; nCT=neoadjuvant chemotherapy; NR=not reached; NS=not significant; EAC=esophageal adenocarcinoma; ESCC=esophageal squamous cell carcinoma; OS=overall survival; PC=paclitaxel, carboplatin; pCR=pathologic complete response; pCT=perioperative chemotherapy; PFS=progression free survival; R0=R0 resection rate; RT= radiotherapy; VC=vinorelbine, cisplatin.
*Clinical complete response rate.

Surgery is the definitive treatment of choice for locally advanced EAC and ESCC, but evidence indicates that neoadjuvant treatment improves outcomes.[137 141 145 154] No one approach, however, is the gold standard, and the use of bimodality or trimodality treatment is subject to considerable geographic variation.

The seminal CROSS trial of 366 patients with EAC (75%) and ESCC established the superiority of neoadjuvant chemoradiotherapy (41.4 Gy in 23 fractions with concurrent carboplatin/paclitaxel) over surgery alone.[140] At 10 years, overall survival with neoadjuvant chemoradiotherapy was greater for ESCCs (46%, 95% confidence interval 33 to 64) than EAC (36%, 29 to 45).[154] However, while neoadjuvant chemoradiotherapy appeared to be beneficial for patients with squamous cell cancers, patients with EAC had similar outcomes at a follow-up of 10 years. Additionally, patients in the CROSS trials were managed predominantly with transhiatal esophagectomy, which might suggest that these patients required radiation to augment regional control. A similar advantage for neoadjuvant chemoradiotherapy versus surgery alone in ESCC was identified by the NEOCRTEC5010 trial, in which median overall survival improved from 66.5 to 100.1 months (hazard ratio 0.71, 95% confidence interval 0.53 to 0.96; p=0.25).[141]

Neoadjuvant or perioperative chemotherapy is an alternative standard of care for both subtypes.

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For ESCCs, the JCOG1109 NExT study is comparing doublet cisplatin/fluorouracil, triplet docetaxel, cisplatin, fluorouracil (DCF) and concurrent chemoradiotherapy (41.4 Gy in 23 fractions with cisplatin/fluorouracil).[148 155] Interim results have been presented, with respective three year survival of 62.6%, 72.1%, and 68.3% respectively. This result underlines previous data indicating impressive responses with DCF.[156]

For EAC, the UK MAGIC (epirubicin, cisplatin, fluorouracil (ECF)) and French ACCORD (cisplatin, fluorouracil (CF)) trials provided initial evidence for the superiority of perioperative chemotherapy over surgery alone.[137 145 154] Recently, the German FLOT-AIO trial showed a substantial overall survival advantage with a perioperative regimen of fluorouracil, leucovorin, oxaliplatin, docetaxel (FLOT) compared with the MAGIC ECF regimen (median overall survival 50 *v* 35 months, hazard ratio 0.77, 95% confidence interval 0.63 to 0.94; p=0.012).[138] As a caveat to these impressive outcomes, however, less than half of patients completed all planned treatment, and 51% experienced grade 3/4 neutropenia, in a population in which 75% of cases were gastric or Siewert type 2/3, and 25% were Siewert type 1.

Considerable uncertainty exists as to which perioperative chemotherapy or neoadjuvant chemoradiotherapy is superior for adenocarcinomas. In the recently published Neo-AEGIS trial, three year overall survival was similar for patients treated with perioperative chemotherapy (predominantly using the MAGIC regimen) and those managed using neoadjuvant chemoradiotherapy (using the CROSS regimen), at 55% versus 57% (hazard ratio 1.03, 95% confidence interval 0.77 to 1.38), respectively.[157] No significant difference was seen in pattern of recurrence though pathological complete response, and R0 rates favored neoadjuvant chemoradiotherapy. The ongoing ESOPEC (NCT02509286) and RACE (NCT0437505) studies are using a FLOT arm, which will be respectively compared with CROSS-style neoadjuvant chemoradiotherapy, or with induction FLOT followed by neoadjuvant chemoradiotherapy.[143 158]

For patients who receive chemoradiotherapy, adjuvant immune checkpoint inhibition using nivolumab for one year was shown to improve outcomes for patients with residual pathologic disease (primary, nodal, or both) in the CheckMate 577 trial.[153] An overall doubling of disease free survival compared with placebo (median disease free survival 22.4 *v* 11.0 months, hazard ratio 0.69; p<0.001) was reflected by histologic specific improvements for both EAC (median disease free survival 19.4 *v* 11.1 months, hazard ratio 0.75, 95% confidence interval 0.59 to 0.96) and ESCC (29.7 *v* 11.0 months, 0.61, 0.42 to 0.88). Overall survival results are awaited.

Patients with locoregionally advanced but unresectable cancer, or who are precluded from surgery by choice, comorbidities, or poor performance status, can be managed with definitive chemoradiotherapy.[149 150 159]

Personalized treatment

Current neoadjuvant treatment approaches remain largely empiric and an opportunity is open to define imaging, molecular, and immune tumor characteristics that associate with, and therefore allow selection of, specific treatments. The use of PET-CT to assess early metabolic response and guide ongoing treatment has been explored in the MUNICON I and II, AGITG DOCTOR, MEMORI, SCOPE-2, and CALGB80803 trials.[160-165] Broadly, PET-CT appears prognostic for outcome in EAC, but as yet no benefit of adapting perioperative chemotherapy or switching to chemoradiotherapy in patients with a poor early metabolic response has been reported. However, the CALGB80803 study suggests that a PET-CT directed switch in systemic treatment based on response to induction treatment can improve outcomes from chemoradiotherapy in patients with EAC.[161] Early metabolic response appears not to be prognostic for overall survival in ESCC.[165]

Systemic treatments

Attention has increasingly fallen on the use of immune checkpoint inhibitors in the locally advanced setting for both subtypes of esophageal cancer. Several single arm studies have reported outcomes following combinations of chemotherapy and immune checkpoint inhibitors in EAC, achieving pathological complete response rates of between 4-33%.[166-172] Larger phase 2 and 3 studies are exploring combinations of chemotherapy and immune checkpoint inhibitors in the neoadjuvant (KEYNOTE-585, MATTERHORN) and adjuvant post-neoadjuvant chemotherapy (VESTIGE, ATTRACTION-05) settings.[173-176] One unanswered question is whether treatments that increase levels of pathologic complete response will have any effect on overall survival. A smaller number of studies have focused on the use of combinations of chemotherapy and immune checkpoint inhibitors in ESCC.[161 177-179]

Radiation treatment

The advantage of concurrent chemotherapy to both local control and overall survival outcomes is long established in the context of conventionally fractionated radiotherapy to the esophagus.[150 180] Building on this advantage, several studies have attempted to define optimal drug-radiotherapy combinations.[159 181-183] Currently, most centers use a chemotherapy backbone comprising a platinum inhibitor and either a fluoropyrimidine or microtubule inhibitor.[151 181] Targeted radiosensitizers are not routinely used following a number of broadly disappointing trials of *EGFR*, HER2, and PARP inhibition; however, these trials suggested that *EGFR* inhibition might provide benefits in overexpressing patients.[182-184] More recently, the addition of immunotherapy to chemoradiotherapy has gained momentum, achieving promising rates of pathologic complete response.[185]

Radiation dose escalation has also been studied as an alternative means to improving local control

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in the context of chemoradiotherapy. The early phase 3 INT-0123 trial found no advantage with high dose radiotherapy; a finding that was repeated using intensity modulated radiation therapy (IMRT) in the ARTDECO and PRODIGE-26 (CONCORDE) studies.[186-188] A third trial examining dose escalation (SCOPE2) has yet to report.[189] Consequently, chemoradiotherapy is generally delivered to 50 Gy in 25 fractions in the definitive setting and to 41.4-50.4 Gy in the neoadjuvant setting.[159 181] Some centers advocate the use of an intraluminal brachytherapy boost, particularly in early stage disease.[190]

Alongside these developments, target volume delineation has been improved with the use of PET-CT, as well as four dimensional chemotherapy based planning. In tandem, the advent of IMRT enables a relative reduction in radiation exposure to organs at risk, including the lungs, kidneys, spleen, and heart, when compared with conventional conformal approaches. Adaptive radiotherapy technologies, including the use of magnetic resonance linear accelerators, are also under investigation for esophageal cancer, and could help spare organs from radiation.[191] These technologies are of potential importance, given recognition of the importance of radiation related cardiac and pulmonary toxicity to surgical and long term outcomes, in addition to evidence for sequalae, such as functional hyposplenism.[192 193]

Proton beam therapy is a potential alternative to photon based treatment strategies. Protons benefit from a Bragg peak, at which dose rises sharply and then falls off. This in theory allows for the radiation dose to be deposited in the target volume while limiting the exposure of surrounding tissues.[194 195] In a phase 2b trial, patients with esophageal cancer were randomized to receive proton beam therapy or IMRT, resulting in a reduction in total toxicity burden for patients managed with proton beam therapy.[196] A number of studies are ongoing to define the role of protons in esophageal cancer, including the HI-SIRI, NRG-GI006 (NCT03801876), and PROTECT trials.[197 198]

Surgical management of esophageal cancer

Esophagectomy can be achieved via two transthoracic approaches: the Ivor Lewis approach, which entails accessing the abdominal cavity and right chest, or the McKeown approach, which entails accessing the abdominal cavity, right chest, and left neck. Alternatively, a transhiatal approach can be employed, in which only the abdominal cavity and left neck are operated on, avoiding a thoracic incision. Randomized controlled trials and comparative studies between transthoracic esophagectomy and transhiatal esophagectomy have revealed that accessing the thoracic cavity during transthoracic esophagectomy has higher nodal resection counts and more complete resections (R0), but in some studies was associated with higher morbidity rates owing to increased pulmonary complications, without significant differences in quality of life or overall survival rates.[199-202] Notably, the Ivor Lewis and McKeown procedures can also be accomplished using minimally invasive techniques, including fully video assisted minimally invasive esophagectomy, hybrid minimally invasive esophagectomy (HMIE) involving laparoscopy and thoracotomy, or a robotic assisted minimally invasive esophagectomy (RAMIE). A complete lymphadenectomy, appropriate for location of tumor, is preferred.

The implementation of enhanced recovery after thoracoscopic surgery (ERATS) pathways has become an increasingly common buzz term in recent years, but have probably existed as quality improvement projects since Torek's first esophagectomy. ERATS incorporates various preoperative and in-hospital strategies to improve postoperative outcomes. These strategies include preoperative measures such as nutritional optimization, physical prehabilitation, and smoking cessation, as well as in-hospital recommendations such as minimized use of chest tubes and drains, multimodal analgesia, early oral nutrition and mobilization, and targeted timeline to discharge.[203-206] Studies have also shown that a fast track esophagectomy protocol, which requires transferring patients to telemetry instead of intensive care units, can safely reduce hospital length of stay, perioperative morbidity, and hospital charges.[207 208]

Evolution towards minimally invasive surgery

TIME is a randomized controlled trial that included five centers across three countries evaluating patient reported outcome measures (PROMs), and clinical and operative characteristics between open transthoracic esophagectomy (Ivor Lewis, n=56) and minimally invasive esophagectomy (McKeown, n=59).[209] While the authors noted that patients managed with minimally invasive esophagectomy benefited from a lower rate of in-hospital pulmonary infections (12% *v* 34% in open group, risk ratio 0.35, 95% confidence interval 0.16 to 0.78; p=0.005), the rate of pneumonia in patients undergoing transthoracic esophagectomy was abnormally high. Additionally, minimally invasive esophagectomy was shown to have lower intraoperative blood loss (200 *v* 475 mL, p<0.001), shorter hospital length of stay (11 *v* 14 days, p=0.044), and better physical quality of life (p=0.007). A similar number of lymph nodes were resected in both groups. In an updated analysis, the authors reported no difference in oncologic outcomes (both overall survival and disease free survival) between the groups.[210] De Groot and colleagues surveyed an international group of thoracic surgeons to assess current trends in preferred approaches, and noted a majority of surgeons preferring minimally invasive surgery followed by hybrid and total open esophagectomy.[211]

The MIRO trial assessed major complications in patients undergoing open transthoracic esophagectomy (n=103) compared with HMIE (n=104) where the abdominal portion of the case was minimally invasive.[212] The authors defined major complications as patients with an event

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requiring pharmacotherapy or more (Clavien-Dindo grade 2 and above). The incidence of major complications in HMIE was 36% compared with 64% in transthoracic esophagectomy, major pulmonary complications occurred at a rate of 18% in the transhiatal esophagectomy, and 30% in the transthoracic esophagectomy group. An important distinction to be made, however, is that the rate of clinically relevant complications requiring an invasive intervention (Clavien-Dindo grade 3) was similar across both open and HMIE cohorts. Furthermore, there appeared to be more events requiring deviation from standard treatment (Clavien-Dindo grade 1) in the HMIE cohort. Lastly, while no significant difference was observed in overall survival between the groups, perhaps because the trial was underpowered, patients who underwent HMIE trended toward a survival advantage (hazard ratio 0.67, 95% confidence interval 0.44 to 1.01) that appeared stable after five years, with updated reporting on overall survival favoring HMIE (0.71, 0.48 to 1.06).[213] The authors reported no significant difference in recurrence rate or recurrence location between the cohorts.

Robotic assisted minimally invasive esophagectomy

The ROBOT trial conducted a comparative evaluation between the use of robotic and open transthoracic esophagectomy (McKeown) and has concluded that the use of a robotic approach is associated with a reduction in total complications (Clavien-Dindo grade 2) compared with transthoracic esophagectomy (59% *v* 80%, risk ratio 0.74, 95% confidence interval 0.57 to 0.96) and pulmonary complications (0.54, 0.34 to 0.85).[214] In addition, patients who underwent robotic esophagectomy experienced enhanced functional recovery, as well as improved quality of life at discharge and six weeks post-resection. A recent update of the trial's survival data showed comparable overall survival and disease free survival between the two groups, with no differences observed in recurrence patterns.[215] Furthermore, a multicenter international registry has recently highlighted current techniques and self-reported outcomes from over 800 patients across 20 centers, and indicated high surgical quality associated with robotic esophagectomy.[216]

RAMIE is a randomized controlled trial that compared outcomes between RAMIE (n=181) and minimally invasive esophagectomy (n=177) in patients with squamous esophageal cancer. The study found that robotic assisted resections led to a larger number of lymph nodes being evaluated (15 *v* 12 lymph nodes, p=0.016), a lower operative time, no difference in estimated blood loss or conversion rates, and similar rates of complications (Clavien-Dindo grade 3) or anastomotic leaks.[217]

While randomized controlled trials can provide the highest level of evidence, carefully defining and interpreting the outcomes used to evaluate different surgical approaches is important. Meaningful metrics are essential for accurately establishing superiority between approaches and guiding clinical decision making. Considering the potential limitations of randomized controlled trials, such as generalizability to patient populations managed at smaller centers or the possibility of confounding variables, is also important.

Ongoing surgical trials

Several ongoing clinical trials could provide further clarity on the benefits of minimally invasive surgery for esophageal cancer. The ROMIO trial will compare minimally invasive esophagectomy, HMIE, and transthoracic esophagectomy, with primary outcome measures including patient reported physical status at three and six weeks post-resection, as well as three months following esophagectomy.[218] Secondary outcomes will include various patient reported outcomes, oncologic outcomes, operative outcomes (including complications), and cost. REVATE will evaluate RAMIE versus minimally invasive esophagectomy for squamous esophageal cancer, with the primary outcome measure being the rate of unsuccessful lymph node dissection specifically along the left recurrent laryngeal nerve.[219] ROBOT-2 will compare RAMIE with minimally invasive esophagectomy for OAC, with the primary outcome measure being the number of lymph nodes resected.[220] Finally, MIVATE aims to evaluate postoperative morbidity using the comprehensive complication index in patients with esophageal cancer managed with minimally invasive esophagectomy and linear stapled anastomosis, compared with transthoracic esophagectomy (Ivor Lewis) and circular stapled anastomosis.[221]

Definitive local regional treatment without surgery: organ preservation

Given the long term impact of esophagectomy on health related quality of life, interest has arisen in the development of organ preservation strategies for patients who show a complete clinical response to chemoradiation.[222-224] In this paradigm, surgery is only performed after a period of observation in the instance that tumor recurs locoregionally (salvage resection). This approach is under evaluation for ESCC within the international NEEDS trial, in which the non-inferiority of definitive chemoradiotherapy with surgery as needed is compared with neoadjuvant chemoradiotherapy and surgery.[225] The SANO trial is also seeking to compare active surveillance with planned esophagectomy, but in patients with both EACs and ESCCs, using overall survival as the primary endpoint.[226] Preliminary data indicate no overall survival difference when patients who achieved a complete clinical response were either operated on quickly or delayed until persistence/recurrence of disease was documented.

The accurate identification of residual or recurrent disease is central to these trials, but concerns have been raised regarding the sensitivity of conventional response assessments.[227-229] A recent study showed that the use of bite-on-bite biopsies delivers a 20%

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improvement in the detection of residual esophageal cancer.[230] A separate study (preSINO) is ongoing, and will determine the accuracy of radiographic and endoscopic evaluation of clinical complete response in squamous cell esophageal cancer.[231] Alternative and augmentative approaches have also been studied, including through the use of a non-endoscopic sponge and endoscopic response evaluation guided by artificial intelligence.[232 233]

Management of advanced esophageal cancer

Oligometastatic disease

Recent evidence suggests that the addition of local treatment to metastases improves progression free survival in patients with oligometastatic ESCC.[234] Further trials are awaited to establish the impact of metastasis directed treatment in both major esophageal cancer subtypes. In the absence of these data, the European OligoMetastatic Esophagogastric Cancer consortium has identified significant variation among multidisciplinary teams in the management of oligometastatic disease, which most teams define as 1-2 stable metastases in the liver, lung, soft tissue, bone, retroperitoneal lymph nodes, or adrenal gland.[235 236]

Metastatic disease

Systemic treatment can relieve symptoms, delay cancer progression, and prolong overall survival of patients with stage IV (M1) esophageal cancer.[237 238] Platinum-fluoropyrimidine doublet has been recommended for treatment naive patients. In older or frail patients, the UK GO2 trial showed that when compared with standard dose treatment, reduced intensity chemotherapy improved patient experience without significant detriment to cancer control.[239]

Only recently, several studies have shown the benefit of the addition of immune checkpoint blockade (table 2).[242-245] For patients with HER2 positive EAC, the addition of trastuzumab (monoclonal antibody (mAb) targeting HER2) has produced modest overall survival advantage.[240] An interim analysis in the KEYNOTE-811 trial showed a higher objective response rate when pembrolizumab (mAb targeting programmed cell death protein 1 (PD1)) was added to trastuzumab plus chemotherapy (pembrolizumab 74.4 *v* placebo 51.9%; p=0.0001).[241] In patients with HER2 negative EAC, nivolumab (mAb targeting PD1) plus platinum-fluoropyrimidine doublet resulted in considerable overall survival benefit for those who exhibited high tumoral expression of PDL1 (combined positive score ≥5).[242] Thus, combination of nivolumab and chemotherapy for the PDL1 high population has been approved as first line treatment in many regions.

As with EAC, platinum-fluoropyrimidine doublet has been the standard first line treatment for metastatic squamous cell cancer. Recently, combination treatment of pembrolizumab and platinum-fluoropyrimidine doublet has emerged based on the phase 3 KEYNOTE-590 trial for advanced esophageal cancer.[243] This trial included

Table 2 | Landmark clinical trials on systemic treatments in esophageal cancer and gastro-esophageal junction cancers

Trial	Trial identifier (phase)	Treatment setting	Tumor type	Treatment arm (N)	Overall survival Hazard ratio (95% CI), P value	Progression free survival Hazard ratio (95% CI), P value	ORR, %
ToGA[240]	NCT01041404 (3)	First line	GEJAC, GAC (HER2+)	Trastuzumab + chemotherapy (294)	Median OS: 13.8 *v* 11.1 months 0.74 (0.60 to 0.91), 0.0046	Median PFS: 6.7 *v* 5.5 months 0.71 (0.59 to 0.85), 0.0003	47
				Chemotherapy alone (290)			35
KEYNOTE-811*[241]	NCT03615326 (3)	First line	GEJAC, GAC (HER2+)	Pembrolizumab + trastuzumab + chemotherapy (133)			74
				Placebo + trastuzumab + chemotherapy (131)			52
CheckMate 649[242]	NCT02872116 (3)	First line	EAC, GEJAC, GAC	Nivolumab + chemotherapy (789)	CPS ≥5: 14.4 *v* 11.1 months 0.71 (0.59 to 0.86), <0.0001 CPS ≥1: 14.0 *v* 11.3 months 0.77 (0.64 to 0.92), <0.0001 All: 13.8 *v* 11.6 months 0.80 (0.68 to 0.94), 0.0002 CPS ≥5: 60 All: 58	CPS ≥5: 7.7 *v* 6.0 months 0.68 (0.56 to 0.81), <0.0001 CPS ≥1: 7.5 *v* 6.9 months 0.74 (0.65 to 0.85), NA All: 7.7 *v* 6.9 months 0.77 (0.68 to 0.87), NA CPS ≥5: 45 All: 46	
				Chemotherapy alone (792)			
KEYNOTE-590[243]	NCT03189719 (3)	First line	ESCC, EAC, GEJAC	Pembrolizumab + chemotherapy (373)	ESCC with CPS ≥10: 13.9 *v* 8.8 months 0.57 (0.43 to 0.75), <0.0001 ESCC: 12.6 *v* 9.8 months 0.72 (0.60 to 0.88), 0.0006 CPS ≥10: 13.5 *v* 9.4 months 0.62 (0.49 to 0.78), <0.0001 All: 12.4 *v* 9.8 months 0.73 (0.62 to 0.86), <0.0001	ESCC: 6.3 *v* 5.8 months 0.65 (0.54-0.78), <0.0001 CPS ≥10: 7.5 *v* 5.5 months 0.51 (0.41 to 0.65), <0.0001 All: 6.3 *v* 5.8 months 0.65 (0.55 to 0.76), <0.0001	45
				Placebo + chemotherapy (376)			29
KEYNOTE-859[244]	NCT03675737 (3)	First line	GEJAC, GAC	Pembrolizumab + chemotherapy (790)	Median OS: 12.9 *v* 11.5 months 0.78 (0.70 to 0.87), <0.0001	Median PFS: 6.9 *v* 5.6 months 0.76 (0.67 to 0.85), <0.0001	51
				Placebo + chemotherapy (789)			42

(*Continued*)

doi: 10.1136/bmj-2023-074962 | *BMJ* 2024;385:e074962 | the bmj

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Table 2 | Continued

Trial	Trial identifier (phase)	Treatment setting	Tumor type	Treatment arm (N)	Overall survival Hazard ratio (95% CI), P value	Progression free survival Hazard ratio (95% CI), P value	ORR, %
CheckMate 648[245]	NCT03143153 (3)	First line	ESCC	Nivolumab + chemotherapy (321)	(Nivolumab + chemotherapy *v* chemotherapy alone) TPS ≥1%: 15.4 *v* 9.1 months 0.54 (0.37 to 0.80), <0.001 All: 13.2 *v* 10.7 months 0.74 (0.58 to 0.96), 0.002 (Nivolumab + ipilimumab *v* chemotherapy alone) TPS ≥1%: 13.7 *v* 9.1 months 0.64 (0.46 to 0.90), 0.001 All: 12.7 *v* 10.7 months 0.78 (0.62 to 0.98), 0.01 TPS ≥1: 53 All: 47	(Nivolumab + chemotherapy *v* chemotherapy alone) TPS ≥1%: 6.9 *v* 4.4 months 0.65 (0.46 to 0.92), 0.002 All: 5.8 *v* 5.6 months 0.81 (0.64 to 1.04), 0.04 (Nivolumab + ipilimumab *v* chemotherapy alone) TPS ≥1%: 4.0 *v* 4.4 months 1.02 (0.73 to 1.43), 0.90 All: 2.9 *v* 5.6 months 1.26 (1.04 to 1.52), NA	
				Nivolumab + ipilimumab (325)	TPS ≥1: 35 All: 28		
				Chemotherapy alone (324)	TPS ≥1: 20 All: 27		
SPOTLIGHT[246]	NCT03504397 (3)	First line	GEJAC, GAC (CLDN18.2+)	Zolbetuximab + mFOLFOX6 (283)	Median OS: 18.23 *v* 15.54 months 0.75 (0.601 to 0.936), 0.0053	Median PFS: 10.61 *v* 8.67 months 0.751 (0.598 to 0.942), 0.0066	48
				Placebo + mFLOFOX6 (282)			48
GLOW[247]	NCT03653507 (3)	First line	GEJAC, GAC (CLDN18.2+)	Zolbetuximab + CAPOX (254)	Median OS: 14.39 *v* 12.16 months 0.771 (0.615 to 0.965), 0.0118	Median PFS: 8.21 *v* 6.80 months 0.687 (0.544 to 0.866), 0.0007	54
				Placebo + CAPOX (253)			49
FIGHT[248]	NCT03694522 (2)	First line	GEJAC, GAC (FGFR2b+)	Bemarituzumab + mFOLFOX6 (77)	Median OS: 19.2 *v* 13.5 months 0.60 (0.38 to 0.94), NA	Median PFS: 9.5 *v* 7.4 months 0.68 (0.44 to 1.04), 0.073	47
				Placebo + mFLOFOX6 (78)			33
DisTinGuish*[249]	NCT04363801 (2)	First line	GEJAC, GAC	DKN-01 + tislelizumab + CAPOX (25)			71
ATTRACTION-3[250]	NCT02569242 (3)	Second line or later	ESCC	Nivolumab (210)	Median OS: 10.9 *v* 8.4 months 0.77 (0.62 to 0.96). 0.019	Median PFS: 1.7 *v* 3.4 months 1.08 (0.87 to 1.34), NA	19
				Chemotherapy (209)			22
KEYNOTE-181[251]	NCT02564263 (2)	Second line or later	ESCC, EAC	Pembrolizumab (314)	CPS >10 : 9.3 *v* 6.7 months 0.69 (0.52 to 0.93), 0.0074 ESCC: 8.2 *v* 7.1 months 0.78 (0.63 to 0.96), 0.0095 All: 7.1 *v* 7.1 months 0.89 (0.75 to 1.05), 0.0560	CPS >10 : 2.6 *v* 3.0 months 0.73 (0.54 to 0.97), NA ESCC: 2.2 *v* 3.1 months 0.92 (0.75 to 1.13), NA All: 2.1 *v* 3.4 months 1.11 (0.94 to 1.31), NA CPS >10: 22 All: 13	
				Chemotherapy (314)		CPS >10: 6 All: 7	
REGARD[252]	NCT00917384 (3)	Second line or later	GEJAC, GAC	Ramcirumab (238)	Median OS: 5.2 *v* 3.8 months 0.776 (0.603 to 0.998), 0.047	Median PFS: 2.1 *v* 1.3 months 0.483 (0.376 to 0.620), <0.0001	3
				Placebo (117)			3
RAINBOW[253]	NCT01170663 (3)	Second line or later	GEJAC, GAC	Ramcirumab + paclitaxel (330)	Median OS: 9.6 *v* 7.4 months 0.807 (0.678 to 0.962), 0.017	Median PFS: 4.4 *v* 2.9 months 0.635 (0.536 to 0.752), <0.0001	28
				Placebo + paclitaxel (335)			18
AdvanTIG-203[254]	NCT04732494 (3)	Second line or later	ESCC (PD-L1 CPS ≥10)	Tislelizumab + ociperlimab	Recruiting		
				Placebo + ociperlimab			
DESTINY-Gastric01[255]	NCT03329690 (3)	Third line or later	GEJAC, GAC (HER2+)	Trastuzumab Deruxtecan (125)	Median OS: 12.5 *v* 8.4 months 0.59 (0.39 to 0.88), 0.01	Median PFS: 5.6 *v* 3.5 months 0.47 (0.31 to 0.71), NA	51
				Chemotherapy (62)			14

CI=confidence interval; CLDN18.2=Claudin18.2; CPS=combined positive score; GAC=gastric adenocarcinoma; GEJAC=gastro-esophageal junction adenocarcinoma; mFOLFOX6=5-fluorouracil, leucovorin, oxaliplatin; NA=not available; EAC=esophageal adenocarcinoma; ORR=overall/objective response rate; OS=overall survival; ESCC=esophageal squamous cell carcinoma; PFS=progression free survival; TPS=tumor proportion score.
*The primary endpoints of overall survival and progression free survival will be assessed later in accordance with the statistical analysis plan.

more than 70% squamous cell cancer in each cohort, and the results showed superior overall survival and progression free survival for pembrolizumab plus chemotherapy compared with placebo plus chemotherapy in patients with ESCC, and combined positive score ≥10 (median overall survival 12.6 *v* 9.8 months; median progression free survival 6.3 *v* 5.8 months). More recently, the phase 3 CheckMate 648 trial evaluated patients with advanced ESCC and showed that both first line treatment with

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nivolumab plus chemotherapy and nivolumab plus ipilimumab, an anti-CTLA4 mAb, resulted in survival advantage over chemotherapy alone (median overall survival: nivolumab plus chemotherapy 13.2 months; nivolumab plus ipilimumab 12.7 months; chemotherapy alone 10.7 months).[245]

Second line treatment varies by disease type and consists of nivolumab or pembrolizumab for patients with squamous cell cancer patients who are immune checkpoint blockade naive.[250 251] In the event of PD1 blockade resistance, paclitaxel or irinotecan can be used.[256-258] For patients with EAC, the preferred second line treatment is ramucirumab plus paclitaxel.[252 253] For patients with EAC who have HER2 positivity, trastuzumab-deruxitecan is available in some regions, and might offer a survival benefit.[255]

Claudin18.2 is a novel biomarker targeted by zolbetuximab (mAb targeting Claudin18), which has shown benefit in untreated advanced patients with EAC. In the phase 3 SPOTLIGHT trial, the addition of zolbetuximab to 5-fluorouracil, leucovorin, oxaliplatin (mFOLFOX6) prolonged overall survival and progression free survival over placebo (median overall survival 18.23 *v* 15.54 months; median progression free survival 10.61 *v* 8.67 months).[246] Another phase 3 trial (GLOW) also showed prolonged overall survival and progression free survival of zolbetuximab plus capecitabine and oxaliplatin over placebo (median overall survival 14.39 *v* 12.16 months; median progression free survival 8.21 *v* 6.80 months).[247] Many new treatment targets are also being explored in the clinic, such as *FGFR2b*, *KRAS* amplification, *TIGIT*, and *DKK-1* (table 2).[248 249 254]

Outside of systemic treatment, options for symptom control include esophageal stenting, typically using self-expanding metal stents (SEMS), as well as external beam radiotherapy and endoluminal brachytherapy. An international multicenter randomized controlled trial showed that the addition of concurrent chemotherapy (cisplatin/5-fluorouracil) to radiotherapy (30-35 Gy in 10-15 fractions) achieved minimal added symptom benefit compared with radiotherapy alone, but caused significantly more toxicity.[259] Furthermore, data from the ROCS study suggest no benefit to maintaining swallow function from the use of radiotherapy in patients who have had SEMS inserted.[260]

Emerging areas

Insights into the disease

Unlike traditional approaches that analyze bulk cell populations, single cell RNA analysis provided new insights into tumor heterogeneity.[261 262] Small endoscopic biopsies impose many challenges. Spatial transcriptomic platforms provide spatial and single cell analyses.[263 264] Emerging multiplex technologies that include transcriptome and proteomics are likely to provide a higher level of understanding of esophageal cancer.

Biomarkers

Assessment of biomarkers has improved treatment selection for patients with esophageal cancer. For patients with EAC, it might be appropriate to assess HER2, PDL1, *MSI/MMR* status, *TMB-H* status, *RET* fusion, *BRAF* mutation, and *NTRK* gene fusions. We expect this list to expand in the future. Early detection and intervention requires proactive measures, and remains a promising area. Use of minimally invasive tests (tissue based or blood based) is promising, with biotechnology improving.

Liquid biopsy

Liquid biopsy based analyses of circulating cell free RNA/circulating tumor DNA (cfRNA/ctDNA) and miRNAs hold additional promise in both EAC and squamous cell cancer, predominantly for monitoring response to treatment, and occasionally for identifying targetable drivers.[85 100 265] This approach assesses ctDNA, circulating tumor cells, circulating cfRNA, extracellular vehicles, or tumor educated platelets, and will undoubtedly continue to expand.[266-269]

Treatments

Novel targeted treatments include antibody-drug conjugates, bispecific or trispecific antibody, and bispecific T cell engager.[270-272] Fam-trastuzumab deruxtecan-nxki is an antibody-drug conjugate consisting of trastuzumab and a topoisomerase I inhibitor joined by a cleavable tetrapeptide based linker.[255] Vaccines and cell treatments, with further refinements, hold considerable promise. Future strategies should include targeting of oncoprotein and immune components simultaneously.

Guidelines

Throughout this review, society guidelines that reflect the current standard of care are discussed. NCCN has published evidence based guidelines encompassing diagnostics and treatments for the management of dysplasia, early stage esophageal cancer, and advanced stage esophageal cancer.[273]

Conclusion

Esophageal cancer, a common illness globally, remains a challenge for patients, caregivers, and treatment teams alike. Many opportunities exist for its early detection, which could allow elimination of cancer and premalignant lesions endoscopically. Improving knowledge of molecular and immune underpinnings of both ESCC and EAC has allowed us to focus on biomarkers, next generation sequencing, and liquid biopsy to manage these cancers more rationally and effectively. A lack of uniform specialized centers to treat esophageal cancer has also led to diverse outcomes.[274] A multidisciplinary approach in developing a consensus on initial treatment approach might have improved recommendation of effective treatment in many large centers, as might the availability of newly developed drugs to prolong survival. However, access to such resources

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is not uniform and needs to improve. Outcomes are poor for most patients with esophageal cancer, and much remains to be accomplished. Particularly, we should avoid empiric approaches that assume that all patients are alike and have disease that behaves similarly.

Continued emphasis on detailed molecular and immunologic interrogations will improve our understanding of esophageal cancer, and novel but rational treatments are likely to emerge.

RESEARCH QUESTIONS

- What novel approaches can be developed and implemented for the early detection of precursor lesions, such as squamous dysplasia and Barrett's esophagus, considering their pivotal role in the progression to esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC)?
- What specific molecular mechanisms underlie the distinct pathophysiology of ESCC, particularly regarding the interplay among somatic mutant clones? How can this knowledge be leveraged to identify treatment targets?
- Given the associations of ESCC with alcohol use and tylosis, and those of EAC with obesity and gastro-esophageal reflux, what targeted prevention and chemoprevention strategies, including the use of proton pump inhibitors and non-steroidal anti-inflammatory drugs, can be developed to mitigate the risk and progression of these subtypes?
- In the context of locally advanced esophageal cancer, how can the current treatment modalities, including neoadjuvant chemotherapy, chemoradiotherapy, and immunotherapy, be optimized for improved outcomes?

GLOSSARY OF ABBREVIATIONS

- EAC: esophageal adenocarcinoma
- ESCC: esophageal squamous cell carcinoma
- GERD: gastro-esophageal reflux disease
- NCCN: National Comprehensive Cancer Network
- NDBE: non-dysplastic Barrett's esophagus
- SNVs/Mb: single nucleotide variants per megabase
- APOBEC: apolipoprotein B mRNA editing enzyme, catalytic polypeptide
- ecDNA: extrachromosomal DNA
- PARP: poly ADP ribose polymerase
- miRNA: microRNA
- lncRNA: long non-coding RNA
- cfDNA: cell free DNA
- TFF3: trefoil factor 3
- PDL1: programmed death ligand 1
- PET-CT: positron emission tomography-computed tomography
- DCF: docetaxel, cisplatin, fluorouracil
- ECF: epirubicin, cisplatin, fluorouracil
- CF: cisplatin, fluorouracil
- FLOT: fluorouracil, leucovorin, oxaliplatin, docetaxel
- IMRT: intensity modulated radiation therapy
- HMIE: hybrid minimally invasive esophagectomy
- RAMIE: robotic assisted minimally invasive esophagectomy
- ERATS: enhanced recovery after thoracoscopic surgery
- PROM: patient reported outcome measure
- mAb: monoclonal antibody
- PD1: programmed cell death protein 1
- mFOLFOX6: 5-fluorouracil, leucovorin, oxaliplatin
- SEMS: self-expanding metal stents
- cfRNA: circulating cell free RNA
- ctDNA: circulating tumor DNA

JAA and WH are joint corresponding authors on this paper.

We thank Rebecca Fitzgerald for her review of and helpful comments on an earlier draft of this manuscript.

Patient involvement: No patients were involved in the writing of this article.

Competing interests: We have read and understood the BMJ policy on declaration of interests and declare the following interests: CMJ is supported by a clinical lectureship part funded by Cancer Research UK RadNet Cambridge. All other authors have no conflicts of interest to declare. WH is the guarantor.

Contributors: All authors contributed equally to the design, development, and writing of this manuscript. All authors contributed to the editing process as well as the collation and examination of the data. All authors attest and are accountable for the accuracy of the data that are presented and gave final approval of the work.

Provenance and peer review: commissioned; externally peer reviewed.

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