



Strategies to improve outcomes in esophageal adenocarcinoma

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EXPERT
REVIEWSStrategies to improve
outcomes in esophageal
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Esophageal adenocarcinoma is one of the fastest rising cancers in Western society. Incidence has increased by 600% within the last 30 years. Rates of diagnosis and death run parallel due to the poor prognosis and a lack of effective treatments. Potentially curative treatments are followed by high rates of disease recurrence. For the majority of patients, who present with advanced disease, we have no effective treatment. We discuss the key areas of progress in this demanding field and offer our views on the direction of future research and treatment.

KEYWORDS: Barrett's esophagus • esophageal adenocarcinoma • esophageal cancer • esophageal cancer diagnosis • esophageal cancer prevention • esophageal cancer treatment • gastro esophageal reflux disease**The esophageal adenocarcinoma epidemic**

Worldwide, esophageal cancer killed 395,000 people in 2010, an increase of nearly 15% from 1990 [1]. Despite modern therapies, overall 5-year survival is less than 15% [2]. The two dominant histological subtypes are esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). The age-standardized incidence rates of EAC are rising by just under 40% every 5 years in Western countries, and EAC has become the predominant type of esophageal cancer in these areas [3]. EAC arises in Barrett's esophagus (BE), a metaplasia of the distal esophagus in response to chronic inflammation due to acid and bile exposure [4,5]. The UK has the highest incidence of EAC globally, at up to 8.7 cases/100,000 of the population [6], with Caucasian males being the most commonly affected ethnic group [7].

Historically, ESCC of the thoracic esophagus, driven by smoking and alcohol, was more common than EAC, and this remains the case outside Western populations [8]. However, countries such as Japan are beginning to observe rising rates of EAC, likely due to the 'westernization' of lifestyle risk factors.

Outcomes for EAC are poor because 60–70% of patients present with late-stage disease, too advanced for treatment with curative

intent [9]. This is partly due to the mechanically compliant esophageal anatomy, which allows symptomless tumor expansion [10]. Additionally, tumor invasion and metastasis are facilitated by the absence of an outer serosal layer and the presence of a rich lymphatic plexus, and both depth of invasion and nodal metastasis are prognostic [11]. Improving survival rates will require an increased understanding of the molecular mechanisms regulating these processes.

Even in those patients who are suitable for multimodal therapy (chemo/radiotherapy + surgery), 5-year survival is at best 35% [9], and potentially curative treatment pathways are demanding for patients, their carers and the healthcare system.

In this review, we focus on current and future developments in the diagnosis and management of EAC. We have chosen to concentrate on the nonsurgical aspects of EAC: treatment of gastroesophageal reflux disease (GERD) and prevention of EAC, early diagnosis, endoscopic therapies for early-stage disease and advances in systemic therapies, because we believe these areas offer the greatest potential to impact on outcomes for this disease. Surgery will remain central to the treatment of esophageal cancer for the foreseeable future and the many recent advances, particularly in dramatically improved mortality rates have been reviewed in detail elsewhere [12].

Heartburn cancer

EAC is predominantly a disease of middle-aged/elderly white men. EAC is caused by longstanding GERD [13], and it is unsurprising that risk factors predisposing to GERD, obesity, hiatus hernia, tobacco smoking and medications compromising lower esophageal sphincter (LES) function are associated with EAC [14]. Western diets high in fat, calories and cholesterol but low in antioxidants and fiber confer an increased risk of EAC [15]. However, in Western countries, GERD occurs in up to 40% of the population at some point [16], and it was the most common diagnosis for gastrointestinal disorders in the US outpatient clinic with almost 9 million attendances in 2009 [17], but very few of these people develop EAC. We are yet to understand why only a minority of people with GERD will ever develop EAC, but evidence from next-generation sequencing studies confirms a causal link between the two. Dulak and colleagues have performed exome sequencing of 149 EAC tumor-normal pairs and whole genome sequencing of a subset ($n = 15$), finding a mutational spectrum unique to EAC ($A > C$ transversions, predominantly in noncoding areas and less-expressed genes, especially at AAG trinucleotides), suggesting that it is attributable to GERD and possibly as a result as oxidative damage [18]. New insights, such as these, into the genetic landscape of EAC will make it possible to determine the precise carcinogens responsible for mutagenesis. For example, is gastric acid the driver of genome-wide $A > C$ transversions? Or, as has been suggested previously, are bile salts required for this effect [19] and is mutation in esophageal epithelial cells a direct effect of the refluxate or mediated by the inflammatory response in the microenvironment? *In vitro* and *in vivo* experiments to answer these questions are now required and are important when one considers the relationship between the rise in proton-pump inhibitor (PPI) use and EAC.

Chronic GERD is thought to lead to a columnar metaplasia, commonly of intestinal phenotype, of the distal esophagus – BE, and this is the only known precursor lesion for EAC with an overall association of up to 97.4% [20]. However, the majority of patients with BE will not die from EAC with the risk of progression being between 0.12–0.5% per year [21]. The association between GERD, BE and EAC is well known, and therefore the development of invasive cancer is, at least in theory, preventable.

Can we prevent EAC?

Current evidence does not support prophylactic intervention at the GERD stage to prevent progression to BE and/or EAC. This is somewhat surprising, but can be explained, at least in part, by the low incidence of EAC arising in patients with GERD and the presumed length of time the distal esophagus has to be exposed to reflux for cancer to develop. Many patients with EAC have experienced GERD for several years (often decades), and trials of chemoprevention or anti-reflux surgery require large numbers and long follow-up [13]. These studies have not been performed.

Will treating GERD lower the rising rates of EAC?

If EAC is caused by acid reflux, then adequate acid suppression with medical therapy or antireflux surgery should prevent it. However, current evidence does not support this, why not?

PPI therapy is good at preventing acid reflux episodes, but weakly acidic refluxes are common in patients with BE on PPI and may account for the lack of regression of BE observed in these cohorts [22]. *In vitro* and *in vivo* data support the view that weakly acidic bile reflux may be at least as damaging to the esophageal mucosa as acid reflux [23–25], and we believe that this leaves clinicians in a dilemma about the advice they give to GERD patients who are keen to prevent BE or EAC. Observational data are contradictory, and PPIs are not without risk. After the introduction of PPI, multiple studies showed that PPI therapy did not lead to reliable regression of BE [26]. Recently, longitudinal cohort studies of patients with BE have suggested that the use of PPI may be associated with a decreased risk of dysplasia in BE patients [27]. In practice, PPIs are used in patients for both symptom control and the potential decreased risk of dysplasia despite the mechanism being unclear. Long-term PPI use has been thought to be safe, but recent concerns have been prompted over side effects such as interstitial nephritis, small intestinal bacterial overgrowth, pneumonia, osteoporosis and effects on vitamin and mineral absorption [28].

Does antireflux surgery carry an advantage over medical therapy?

Antireflux surgery offers the theoretical advantage of not only preventing acid reflux, but also establishing a physical barrier to other elements of the refluxate including bile salts. A recent large meta-analysis of studies that compared the reported incidence of EAC in subjects with BE who underwent antireflux surgery with those who had medical management showed a lower cancer incidence rate in the antireflux group (3.8 cancers/1000 patient-years vs 5.3 cancers/1000 patient-years), but this was not significant ($p = 0.29$) [29]. The authors concluded that antireflux surgery should not be recommended as an anti-neoplastic procedure. But, as the authors point out in their discussion, several potential sources of bias exist in their study, including the inclusion of cohort studies with no randomization, use of different types of antireflux surgery across studies, with some not reporting the surgery used at all, and perhaps most importantly, no reporting of the competency of the antireflux procedure to prevent reflux in the long term. This is important because observational studies suggest that the quality of the antireflux procedure is vital when considering subsequent cancer risk. In a review of 14,102 patients who received antireflux surgery in Sweden, Lofdahl and colleagues found that patients who developed EAC were three-times more likely to have recurrent reflux compared with those who did not (odds ratio: 3.1; 95% CI: 1.5–6.3) [30].

In favor of antireflux surgery, there are a small number of reports that indicate that antireflux surgery may have a protective effect on the esophageal mucosa at the cellular level compared with PPI [31,32]. A recent study by Martinez de Haro and colleagues found that at 3, 5 and 10 years after treatment, proliferation (as measured by Ki-67) and p53 expression remained stable in patients treated with antireflux surgery, whereas a significant increase was observed in patients taking PPI [32].

In general, we believe that there is a lack of good data from appropriately designed trials comparing PPI and antireflux surgery for prevention of BE or EAC. When one considers that the average follow-up from all 34 studies considered in the meta-analysis from Corey and colleagues described above is 5–6 years and that EAC occurs predominantly in the seventh and eighth decade of life, probably after many years of reflux, it is too simplistic to say that there is no place for antireflux surgery in EAC prevention.

In our opinion, the patient numbers are too small and follow-up too short in all reported studies to reliably conclude that no difference between antireflux surgery and medical therapy exists. The theoretical advantage of antireflux surgery is strong, but it is not a procedure without risk and consequence. Current evidence does not support its widespread use as an anticancer procedure. But if less invasive procedures that prevent reflux with fewer side effects were to exist, then could these be effective at preventing EAC?

A number of new interventions to treat GERD are in varying stages of development, but none has been assessed for cancer prevention. EsophyX Transoral Incisionless Fundoplication uses T tags to create an endoscopic fundoplication. Cadieri and colleagues reported 1-year results from an EsophyX Transoral Incisionless Fundoplication trial in 86 patients. GERD health-related quality of life scores improved by 50% or more in 73% of patients. Complete cessation of PPI use was reported in 81%, but importantly only 37% of patients had normalization of esophageal acid exposure [33]. This would be inadequate for the prevention or treatment of BE/EAC. The LINX[®] reflux management system has received widespread attention. It uses a bracelet of magnets encased in titanium, which is laparoscopically placed around the LES to create a ‘magnetic sphincter’. In a study of 100 patients, normalization or improvement of distal esophageal pH at 1 year was observed in 64% of patients [34]. However, the LINX device was associated with a large number of device-related consequences including dysphagia in 68% of patients, requiring endoscopic dilatation in 19 patients and a 6% explant rate. Patients with the LINX cannot undergo MRI scanning.

In our opinion, the most promising new technology is the EndoStim[™] LES stimulation system that delivers electrical stimulation to the LES. EndoStim has been shown to increase resting LES pressure without impairing LES relaxation, prevent acid reflux and eliminate GERD symptoms. Importantly, LES stimulation is not associated with any sensation or side effects and the stimulation can be tailored to the patient’s symptoms. In an open-label study, median percentage of 24-h esophageal pH <4.0 was reduced from 10.1 (7.8–13.0) to 3.3 (1.8–6.9); $p < 0.001$ [35,36]. Good quality randomized trials with appropriate follow-up are now required to determine the efficacy of these devices for GERD treatment, before considering neoplasia prevention.

Aspirin in chemoprevention

Extensive observational data show that aspirin/NSAIDs are associated with a decreased risk of EAC [37]. The exact mechanism of any chemopreventive effect is unclear, and no randomized

controlled trial has confirmed that this observed association is causative. However, given the poor prognosis associated with esophageal cancer, the potential use of chemoprevention has been suggested in patients with BE. The AspECT trial is currently assessing the benefits of esomeprazole, with or without aspirin, in preventing progression of BE to EAC.

Promoting awareness

In addition to addressing the rising obesity levels and presumed consequent GERD in Western populations that is contributing to the EAC epidemic, a widespread program of education is now required. The general public has a poor understanding of the symptoms of EAC. This has been recognized by the UK Department of Health who is shortly to launch a pilot awareness campaign that will focus on the importance of persistent heartburn and dysphagia via the ‘Be Clear on Cancer’ campaign [38]. To advance understanding of BE/EAC among the medical community, a new *British Medical Journal* online learning module is available [39].

The challenge of early diagnosis

Early diagnosis saves lives

EAC presents late as symptoms only manifest when tumors become large enough to cause dysphagia or pain. The stage at diagnosis of EAC is the key factor in determining prognosis. The depth of invasion through the esophageal wall determines the risk of lymph node (LN) metastasis, which, in keeping with other reports, in our cohort is the most prognostic pathological finding for poor outcome [40,41]. Unfortunately, in EAC, the majority of tumors have invaded through the esophageal wall at the time of diagnosis. In a cohort of 93 patients, Schlansky and colleagues showed that 79% and 10% of symptomatic new diagnoses of EAC were T3 (tumor invades adventitia) or T4 (invasion of local structures) tumors, respectively [42]. In this setting, cure is rare.

Early EAC, defined as that limited to the muscularis mucosa (T1), does not normally metastasize to LNs [43] and consequently, early-stage cancers, $\leq T1$, carry an excellent prognosis with a greater than 90% 5-year survival [44]. Unfortunately, the number of tumors detected at this stage is low (<1%) [42]. The challenge we face is how to detect EAC at an earlier stage, which would allow a better chance of survival and potentially more localized and less invasive endoscopic treatment. Intuitively, large-scale population-based screening might seem attractive.

Screening for EAC?

The diagnosis of EAC is currently made with white light endoscopy combined with biopsy for histological confirmation, and no alternative method has yet been validated. Despite high sensitivity and specificity, this is an invasive and expensive test with small but significant risk. Current endoscopy frameworks could not support national screening programs, which would be prohibitively expensive. These factors combined with the relatively low incidence of EAC do not currently justify population-based mass-screening programs. Is there justification for screening and surveying high-risk groups?



Figure 1. Cytosponge™ capsule.
Reproduced with permission from [47].

Identification & surveillance of BE

If BE is the precursor for EAC, then should we be screening for and monitoring those with BE? This may be particularly important given that the majority of patients with EAC present *de novo* with no previous history of BE.

Symptomatic GERD is common, but only 8–20% of patients with GERD have BE, and the incidence is similar in asymptomatic patients undergoing endoscopy [45]. The diagnosis of BE is made by endoscopy and subjective histological assessment. It is subject to both sampling and reporter error. Endoscopic screening of patients with GERD for BE is not recommended by worldwide gastroenterology associations.

The American Society of Gastroenterology and the British Society of Gastroenterology guidelines support the surveillance of those with histologically confirmed BE. However, there is a lack of robust evidence for this practice, and the cost-effectiveness of routine surveillance in Barrett's patients has been questioned [46]. The benefits of surveillance in BE are currently being assessed in the BE Surveillance Study, a randomized trial comparing 2 yearly endoscopy and biopsy versus endoscopy at the time of need, as determined by the patient. The not insignificant issue of interval cancers (those occurring between 2 yearly routine endoscopies) will also be captured by this study and it may shed light on the optimum time interval for surveillance.

The Benign Barrett's and Cancer Taskforce consensus group is seeking to formulate clear evidence-based factors to risk stratify BE. It is likely that a combination of patient-related factors (genetic predisposition, body mass, etc.), environmental factors and disease-specific factors (mutational burden in BE, dysplasia, etc.) will be combined to deliver more accurate risk prediction and targeting of surveillance and interventions for BE. Currently, the low risk of Barrett's progression to EAC means that Barrett's surveillance submits many patients to the psychological distress and physical discomfort of endoscopy with benefit

for only a few. Is there an alternative to endoscopic surveillance and can we utilize biomarkers to predict those at risk of progression to EAC?

Cytosponge™: a viable alternative to endoscopy?

Cytosponge™ is an ingestible capsule that has shown early promise in the primary care setting. The capsule is swallowed with water, dissolving in the stomach to expand to a sponge like mesh 3 cm in diameter. This is withdrawn, harvesting cells for analysis by immunofluorescence for trefoil factor 3. Trefoil factor 3 is a marker highly specific for cells with an intestinal phenotype. It is surprisingly well tolerated by patients and compared with gastroscopy; the sensitivity and specificity of the test were 73.3% (95% CI: 44.9–92.2%) and 93.8% (91.3–95.8%), respectively, for 1 cm or more circumferential BE, increasing to 90.0% (55.5–99.7%) and 93.5% (90.9–95.5%), respectively for clinically relevant segments of BE 2 cm or more in length [47]. It is currently undergoing further assessment in the BE Screening Trial 2. BE Screening Trial 2 is designed to compare Cytosponge™ and molecular analysis with endoscopy to determine the specificity and sensitivity of Cytosponge™, its differential sensitivity in dysplastic and non-dysplastic BE and its ability to risk stratify patients with BE. It also aims to see if high throughput and automated analysis of Cytosponge™ specimens are possible.

Cytosponge™ is an evolving technology, but one we believe has the potential to change the way we diagnose and survey those with BE and EAC (FIGURE 1).

How do we identify the patients with BE who will progress to EAC?

The ability of biomarkers to select out those at greatest risk of progression and/or early cancers is an attractive proposition. In current clinical practice, dysplasia is the biomarker for risk of EAC progression, but this is subject to sampling error and interpretation bias. It does not help in the risk stratification of the majority with nondysplastic BE. Loss of heterozygosity, DNA content abnormalities, TP53 and Cyclin-A have been used to predict the risk of EAC progression in BE [48,49]. All biomarkers that have progressed beyond Phase II studies can be linked to cellular proliferation, but none has entered clinical practice.

A possible explanation for this has recently become apparent. The traditional model of EAC development is via increasing cellular dysplasia after metaplasia in the distal esophagus (BE) in response to persistent acid reflux and inflammation. A step-wise accumulation of DNA mutations during these processes has been suggested to be required for the development of invasive cancer, akin to the adenoma–carcinoma sequence in colorectal cancer [2]. In a recent exome-sequencing study by Agrawal and colleagues, of the 11 EAC samples and 2 adjacent areas of BE, the majority of somatic mutations observed in EAC were present in histologically normal BE [50]. This discovery suggests that the mutational burden of EAC may already be established in nondysplastic BE [18,50], meaning that the

drivers for disease progression in BE–EAC lie beyond gene mutations in the epithelial cells. Suspicion must now fall on the esophageal microenvironment with the possibility that non-mutated stromal cells play a critical role in EAC development and progression, a theory that would be consistent with long-term acid and bile salt exposure leading to a proinflammatory milieu. This possibility is supported by the finding of a prognostic stromal signature identified by Saadi and colleagues in esophageal cancer patients that contained a predominance of inflammation- and TGF- β -related genes [51].

Future directions in the early diagnosis of EAC

The holy grail of translational research in screening for EAC is to be able to see and assess the patient with GERD in the primary care setting, where an easy, cost-effective test can detect the presence of abnormalities and the risk of progression to EAC. We believe that the first step will be using technologies such as the Cytosponge™ as a screening tool to target endoscopy. This will require the chosen biomarkers to be highly sensitive (it is our opinion that trefoil factor 3 alone is not sufficient in this regard), which could be at the expense of modest specificity, as long as patients with positive results could rapidly access definitive endoscopy.

In addition, if a panel of validated biomarkers can be developed that can clearly define the stage boundaries between BE, high-grade dysplasia (HGD) and EAC, then the simplicity of Cytosponge™ can be combined with the ever increasing ‘horsepower’ of next-generation sequencing to offer near patient testing and rapid diagnosis in the BE–EAC sequence. Modern information technology opens the possibility of large-scale screening for GERD patients in the primary care setting and targeted selection of those who need further investigation with endoscopy, with the potential of cancer prevention. However, this is only to be recommended if acceptable and successful treatments for HGD and early EAC are available.

Early treatment

Early treatment aims for esophageal preservation with avoidance of esophagectomy and its associated morbidity and mortality. This can be achieved by novel endoscopic therapies that may be more acceptable to patients and more inclusive of those deemed medically unfit for esophageal resection. Some of these techniques are promising, but have, as yet, no long-term data.

Endoscopic therapies

Numerous endoscopic techniques are available for HGD and early EAC including: photodynamic therapy (PDT), laser, multipolar electrocoagulation, argon plasma coagulation, radiofrequency ablation (RFA), cryotherapy, as well as endoscopic mucosal resection (EMR). We believe that EMR in combination with RFA is the current endoscopic therapy with most promise.

All ablative techniques and EMR have the potential to miss occult EAC and leave behind cancer or intestinal metaplasia. This is reported after PDT in up to 51.5% [52]. The significance

is not yet determined, but EAC arising under squamous re-epithelialization has been reported in up to 4.6% of cases after PDT [53]. EMR followed by RFA (EMR/RFA) has also been compared with stepwise radical endoscopic resection (SRER). They provide complete removal of intestinal metaplasia in 96% and 92% of cases respectively. In a randomized controlled trial comparing SRER and EMR/RFA, by van Vilsteren and colleagues, SRER required a median of six sessions including dilatation for strictures in 88% of cases, whereas EMR/RFA has a median of three sessions and 14% stricture rate [54].

Despite convincing trial data and widespread uptake, it is not yet proven that ablative techniques can eliminate the risk of cancer, decrease the need for surveillance and be cost-effective. It would be sensible for ablative and mucosal resection techniques to be compared with modern series of esophagectomy for HGD or T1 cancer (including minimally invasive operative techniques) rather than using the morbidity and mortality of historical series covering all stages of disease.

Endoscopic therapy is attractive due to the presumed reduction in morbidity and mortality compared with surgery. The risk of under staging esophageal cancer and potential risk of occult EAC requires close assessment. Until robust trial data are available, it is important that the treatment for HGD and early neoplasia is discussed in a balanced fashion, and all data are entered into appropriate registries [55].

High-grade dysplasia

Up to 59% of cases of HGD progress to EAC [56]. Esophagectomy has been the treatment of choice for those fit for surgery with HGD; Williams and colleagues demonstrated a series of 38 patients, with HGD, treated with esophagectomy. There was no in-hospital or 30-day mortality, 100% disease-free survival (DFS) and 97% overall survival at 32 months [57]. Occult adenocarcinoma was found in 29% of cases of HGD following resection.

Shaheen and colleagues showed complete eradication of HGD in 81% of patients at 1 year using endoscopic RFA [58]. Three adverse events occurred in 284 treatments performed in 84 patients (mean 3.5 treatments per patient) and the stricture rate was 6%. Similar outcomes have been published from the UK National HALO RFA Registry with 81% of patients also clear of dysplasia at 1 year [55].

The consensus of the Barrett’s Dysplasia Cancer Taskforce is that endoscopic treatment should be preferred to surgical treatment in most patients with HGD in BE [59]. The high risk of EAC in HGD is an indication to stop surveillance and commence endoscopic treatment. RFA in combination with EMR, for raised or suspicious lesions, is the treatment of choice and is the current practice in our unit.

The treatment of T1 EAC

T1 tumors can be subdivided into T1a (invades lamina propria or muscularis mucosa) and T1b (invades the submucosa). Distinction is important because of the increased risk of LN involvement corresponding to the depth of tumor invasion. T1a

tumors are associated with a risk of LN metastases of 5% or less; in T1b reported rates of LN metastases varies from 23 to 40% [60,61]. This low risk of LN involvement, in combination with EUS and PET CT to improve accuracy of staging, means T1a EAC can be treated with endoscopic therapy. In the authors unit, it is our practice that, after counseling, patients with T1a EAC are offered EMR/RFA, while T1b EAC is treated with esophagectomy due to the risk of LN metastases.

In the future, it may be possible to offer EMR/RFA combined with sentinel LN biopsy (SLNB) to T1b patients. SLNB has become gold standard in surgery for breast cancer, and its use in other solid tumors remains debated. A recent study showed SLNB in esophageal cancer to have a sensitivity of 90% and specificity of 96% [62]. Such a protocol would have the theoretical benefits of allowing us to predict which patients will benefit from esophagectomy and lymphadenectomy due to occult LN metastasis. This would spare those with localized disease a morbid operation. Advances in thoracoscopic skills will make SLNB for early-stage disease a viable option. While EMR/RFA could avoid esophageal resection and its associated risks, it must not compromise long-term survival.

Advances in neoadjuvant & adjuvant therapies

Neoadjuvant therapy

Neoadjuvant therapy followed by surgery is established as the gold standard in the management of patients with locally advanced adenocarcinoma of the esophagus/EGJ. In the UK, neoadjuvant chemotherapy (NAC) in conjunction with trans-thoracic esophagogastrctomy is the current standard of care for these patients [63]. Proposed benefits of neoadjuvant therapy include: downstaging of the primary tumor [64] and LNs [65], an increase in the resectability of the tumor [66], elimination of micrometastases [67] and improved survival [68]. However, the most recent meta-analysis to compare NAC versus surgery alone in 2062 patients suggests only 5.1% survival advantage at 2 years for patients treated with NAC for adenocarcinoma [68]. NAC is demanding, may render the patient physiologically compromised and delays surgery; it does not benefit many.

It has been suggested that the UK lags behind the rest of the world in that as a medical community, we are yet to widely adopt neoadjuvant chemoradiotherapy (nCRT) in the neoadjuvant setting. In the recent Dutch CROSS trial, enrolling 368 patients, convincing evidence for the role of nCRT in esophageal cancer over surgery alone was put forward. However, the major benefit was seen for ESCC and not EAC. A direct comparison of NAC versus nCRT followed by surgery is now required for EAC. The All Ireland Cooperative Research Oncology Group is currently recruiting to a randomized clinical trial of neoadjuvant and adjuvant chemotherapy (MAGIC regimen) versus neoadjuvant chemoradiation (CROSS protocol) for patients with adenocarcinoma of the esophagus and esophagogastric junction. The trial design has received criticism because of a perception of inadequate power and the likelihood that few patients will complete the MAGIC regime; despite this, a number of UK centers are involved.

No matter what type of treatment is given, patients who have a significant pathological response to neoadjuvant therapy have consistently been shown to have an improved survival compared with poor responders [69]. We have recently identified a hitherto unrecognized group of patients who derive benefit from NAC by virtue of LN downstaging despite little or no pathological response in the primary tumor. In this group, disease free survival (DFS) is increased from 1.114 years (95% CI: 0.961–1.2675) to 5.533 years (95% CI: 3.558–7.531); $p < 0.0001$ [41].

But, for patients without a significant pathological or nodal response, the delay to surgery may outweigh the benefits of neoadjuvant therapy and these patients may be needlessly exposed to toxic treatments. Both NAC and surgery are associated with considerable morbidity and mortality [70]. We urgently need mechanisms to predict response to neoadjuvant therapies at the patient level to allow optimal tailored treatment.

Predicting response to neoadjuvant therapy

We have proposed predictive markers of response to chemotherapy, and like many other groups have shown potential biomarkers [40]. Serum albumin was shown to be the only predictor of pathological response to chemotherapy. Neutrophil-lymphocyte ratio is predictive of overall and DFS in EAC but not response to NAC. No biomarker has been robustly validated or has reached sufficient sensitivity or specificity to be of clinical value [71].

The most promising method to assess response has been PET-CT. The Metabolic response evalUatioN for Individualization of neoadjuvant Chemotherapy in Esophageal and esophagogastric adenocarcinoma II trial looked at tumor glucose uptake with 18F-FDG PET CT before and 14 days after initiation of chemotherapy [72]. A subgroup of PET nonresponders was identified whose prognosis was poor. Salvage chemoradiotherapy was used in those where PET predicted a lack of response and this yielded an increased histological response but not an increased RO resection rate which formed the primary endpoint of this trial. Metabolic response evalUatioN for Individualization of neoadjuvant Chemotherapy in Esophageal and esophagogastric adenocarcinoma looks at PET-CT response following NAC. Worldwide nCRT reflects the standard pattern of care, and there is no evidence yet to support PET-CT in predicting response to nCRT. We await the results of the Dutch NEOadjuvant therapy monitoring with PET and CT in Esophageal Cancer trial specifically powered and designed to answer this question [73].

Other solid tumors lead the way in predicting the benefit of neoadjuvant therapy, and it is likely that a panel of markers will be required to predict the benefit for EAC patients. The search remains to identify a robust predictor of response to neoadjuvant therapy as a first step to truly personalized therapy.

Adjuvant therapies

The role of adjuvant therapy in esophageal cancer is controversial. There are concerns over the additional risk, versus benefit, of postoperative treatment over neoadjuvant therapy alone [70]. This has resulted in a lack of adoption in the UK [63]. In

addition, the reclassification of junctional tumors that invade the esophagus as esophageal tumors in the TNM 7 staging system makes decision making regarding adjuvant therapy for these patients difficult, and recent evidence suggests that the site of the tumor relative to the gastroesophageal junction is important for outcomes in current cohorts [74].

The MRC ST02 (MAGIC) trial, evaluating Epirubicin, Cisplatin and 5-Fluorouracil perioperatively (pre- and post-surgery), was originally designed to study gastric cancer. However, a significant number of patients with distal esophageal and junctional cancers were recruited. When compared with surgery alone, patients who received perioperative chemotherapy had a better overall survival (5-year survival 36 vs 23%) and progression-free survival [70]. The contribution of the postoperative component of chemotherapy was difficult to assess because a significant proportion of the group failed to complete the chemotherapy regimen.

It makes sense that patients who have a partial response to NAC may be the most appropriate to be considered for trials of adjuvant treatment. Data from other disease sites suggest only patients responding to neoadjuvant treatment benefit from further treatment [75].

Additional adjuvant therapies in esophageal cancer are scarce, but therapies are being suggested and assessed following their routine clinical use in other solid tumors. The AddAspirin trial is looking at the benefit of aspirin to improve survival after standard primary therapy in common early stage solid tumours, including EAC. The use of agents, such as trastuzumab and lapatinib, which inhibit the growth cascade of human EGF 2 (HER2), in breast cancers that overexpress HER2 is well established. HER2 overexpression is linked to poor prognosis in breast and ovarian cancer [76]. Over expression of HER2 is seen in other cancers including esophageal cancer. HER2 overexpression is reported in 17–32% of esophageal junctional adenocarcinomas, and this would suggest a potential role for HER2 inhibitors in EAC [77]. Supportive evidence comes from the trastuzumab for gastric cancer study, a Phase III randomized controlled trial in patients over expressing HER2, which randomized patients to receive capecitabine and cisplatin or fluorouracil (5-FU) with cisplatin (given every 3 weeks for six cycles) or chemotherapy in combination with intravenous trastuzumab. Intention-to-treat analysis showed improved median survival of 2.7 months with trastuzumab. Pathological response rate, time to tumor progression and duration of response were significantly higher in the trastuzumab-plus-chemotherapy group [78]. Lapatinib, a small molecule dual tyrosine kinase inhibitor of EGF receptor and HER2, is used in breast cancer resistant to trastuzumab. A Phase II study with lapatinib monotherapy in EGF receptor \pm HER2 positive EAC on patients with disease progressing on previous therapies showed no objective response [79].

Further clinical trials assessing adjuvant treatments will continue to report, and the hope is that they will show some marginal benefits to prolong survival. New agents are urgently needed that improve the outlook for patients with unresectable EAC.

The tumor microenvironment in EAC

The major focus of cancer research over the past three decades has been the cancer cells themselves. However, tumor cells do not exist in isolation, and attention is increasingly being paid to the tumor microenvironment (stroma). Early data from whole-genome sequencing studies suggest that the mutational burden of EAC may already exist at the time of metaplastic transformation, and the relationship with the stroma may provide the impetus for malignant transformation [18,50]. Convincing evidence exists that supports the role of the stroma in cancer progression.

Cancer-associated fibroblasts (CAF) form the major cellular component of the tumor stroma. CAF are a complex heterogeneous group of cells, and they are shown to derive from resident fibroblasts as well as other mesenchymal cell types (endothelial, pericytes, stellate cells, preadipocytes) and bone marrow-derived cells (fibrocytes, mesenchymal stem cells). Activated CAF have a contractile, myofibroblastic phenotype and express alpha-smooth muscle actin (α -SMA), they promote tumor cell growth, invasion and metastasis [80].

High levels of α -SMA expression predict poor outcome in several cancer types [81]. We have validated this in our own EAC cohort showing α -SMA expression to be more accurate than T, N, M or R status in predicting survival (FIGURE 2) [UNDERWOOD *ET AL.*, UNPUBLISHED DATA].

TGF- β is a key, and well documented [82], player in CAF recruitment and function. It represents an appealing target and several TGF- β inhibitors, such as Lerdelimumab and Metelimumab, have been developed and are in early phase trials [83]. However, the role of TGF- β is complex, and it is clearly tumor suppressive at defined points in EAC development. Therefore, strategic targeting of TGF- β inhibitors is required if we are to maximize it as a therapy.

CAF have also been shown to influence the local immune system in the microenvironment through their secreted cytokines, chemokines and extracellular matrix proteins. These influence the recruitment, functional status and retention of myeloid and lymphoid cells. CAF have been immunotherapeutic targets through the use of fibroblast-activating protein vaccinations, prolonging survival when used in combination with chemotherapy in murine models of breast and colorectal cancer [84]. Novel targeting of CAF is likely to be either via decreasing the CAF population through targeting of expansion, recruitment or transdifferentiation or alternatively blockade of tumor promoting secretions from CAF.

In addition to the potential to develop treatments, it would also seem logical to include biomarkers from the tumor microenvironment in the staging of cancer to more accurately reflect the aggressiveness of tumors. The classification of cancer may therefore be better served by not only information of the tumor and its cells but also utilizing the tumor microenvironment and the host. There are now increasing calls to adopt this strategy with particular focus on the local immune infiltrate and the host inflammatory response [85].

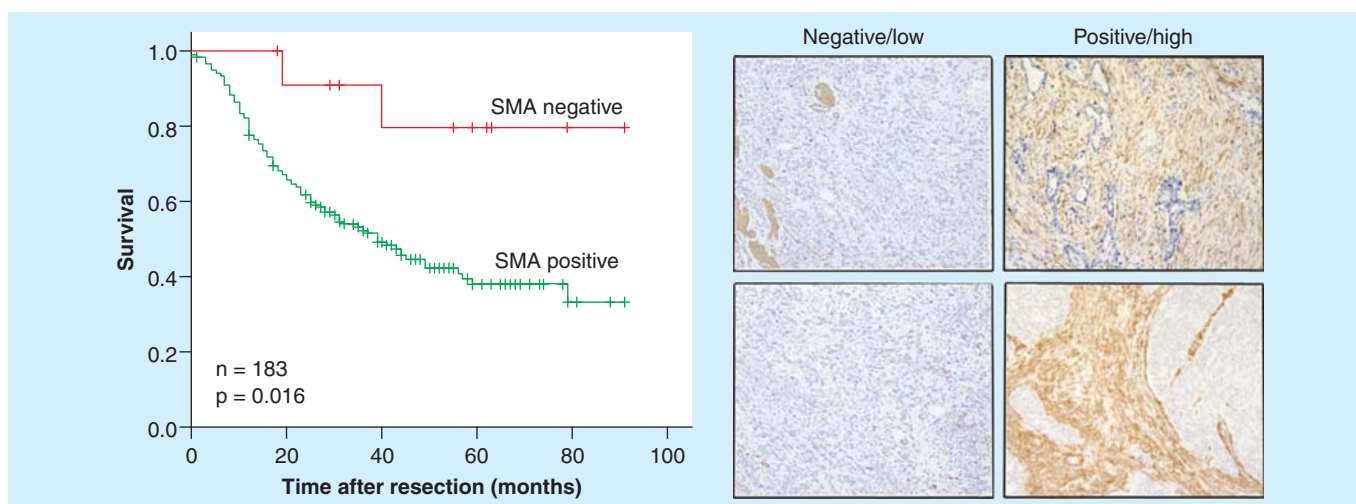


Figure 2. CAF in the tumor microenvironment predict survival in EAC. Left panel – Kaplan-Meier survival curve following esophagectomy in α -SMA positive and negative tumors. Median survival α -SMA positive tumors = 39 months. Hazard ratio: 7.1 (1.7–29.4; $p = 0.007$). More predictive than T, N, M or R status. Right panel – representative immunohistochemistry. CAF: Cancer-associated fibroblasts; EAC: Esophageal adenocarcinoma; SMA: Smooth muscle actin.

Expert commentary & five-year view

Esophageal cancer is a significant global health burden. It is diagnosed late, and overall survival remains stubbornly poor. We are witnessing a silent epidemic of adenocarcinoma of the distal esophagus and gastroesophageal junction that is only now being given the attention that it deserves. It is clear that western lifestyles are driving the rapid increase in EAC, with obesity and GERD the most convincing causative factors. We are likely to see a continued increase in the incidence of EAC as Western populations continue to become more obese.

So if we are unable to easily turn back the tide of obesity what can be done to improve outcomes for EAC patients? We and others believe that early diagnosis is vital for the future. Mass screening of symptomatic GERD patients with endoscopy is not feasible, and novel techniques that are inexpensive, minimally invasive and applicable to primary care will be required. The Cytosponge™ shows promise in this arena. Public awareness of the symptoms of EAC is equally important.

There is developing evidence that medical therapies for the treatment of GERD, PPI in particular, are not as safe in the long term as first thought, and it is likely that a growing number of GERD patients will demand alternative therapies. Antireflux surgery is effective and theoretically offers the advantage of preventing bile reflux. If we are to prove that antireflux surgery prevents BE/EAC, then we will need well-constructed studies that incorporate assessment of the efficacy of the antireflux procedure in the long term. Such studies are likely to be expensive and difficult to manage. They will require national/international recruitment and standardization of surgery, but this has been proven possible by the LOTUS trial collaborators [86].

Endoscopic therapies already exist for premalignant and early-stage EAC, and we are likely to see a substantial increase in their application as and when diagnosis moves away from

patients with dysphagia and advanced incurable disease. It is important to remember that some patients will still be better served (and may desire) definitive surgery and our efforts to make esophagectomy safe and efficient must continue.

But what of new treatments for established disease? We are currently limited to the blunt tools of conventional chemotherapy, radiotherapy and surgery. Understanding the fundamental biology of EAC is critical to the development of new therapies. Current efforts to define the genetic landscape of EAC and understand what determines germ-line susceptibility to BE and EAC are beginning this process. The clinical utility of whole-genome sequencing projects will be the development of molecular–phenotype therapeutics. To achieve this, model systems that faithfully represent the tumor of origin are required. Our group has developed the first such system to come from the Esophageal International Cancer Genome Consortium project, a novel EAC tumor cell line derived from 55-year-old male (pT4N3M0) who died from disease recurrence 7 months after NAC and esophagectomy [UNDERWOOD *ET AL.*, UNPUBLISHED DATA]. Authentication of this cell line using whole-genome sequencing, genome-wide microarrays and *in vitro* and *in vivo* functional studies confirms that it is a representative invasive tumor model and contains somatic deletions/mutations in the most commonly mutated genes in EAC (p16, SMAD4 & TP53). Models such as this will become a test bed for new targeted therapies that will be included into adaptive trials of combinations of existing therapies determined by the patient's own DNA and their tumors' molecular phenotype. This genetic information will be used to prevent patients receiving toxic treatments that will have no benefit; for instance, if we can find reliable markers of tumor resistance to platinum compounds from pretreatment biopsies in real time, then we will be able to reasonably withhold this treatment. It is also vital

that we deepen our understanding of the relationship between EAC and the host environment; our group and others are leading efforts in this regard.

Once a bastion of nihilism, we believe the future to be much more optimistic for patients diagnosed with EAC. It is not unreasonable to think that in addition to the aggregation of marginal gains observed in the recent past, a 'game-changing' development in the management of EAC might be around the corner.

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Key issues

- The incidence of esophageal adenocarcinoma is rising worldwide but most rapidly in the west.
- Trials assessing screening, surveillance and chemoprevention near their conclusion.
- New endoscopic therapies seem promising, but lack long-term efficacy, cost-effectiveness and comparison with established treatment modalities.
- Neoadjuvant therapy is now established in treating patients with locoregional esophageal cancer, but as yet the optimum treatment algorithm is undefined.
- There are no clinically useful predictors of response to neoadjuvant therapy.
- Morbidity and mortality continue to fall, following surgery with continued innovation in the perioperative treatment pathway.
- The International Cancer Genome Consortium and similar consortia are defining the genetic landscape of esophageal adenocarcinoma providing the potential to develop personalized medicine as well as novel therapies.

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