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Carcinoma of Esophagus

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ABSTRACT

Carcinoma of esophagus is one of the most common cancer worldwide, but its epidemiology is changing. Squamous cell carcinoma is declining in the East, but adenocarcinoma is rising in the West, probably related to the pandemic of obesity and changing lifestyle. Screening of esophageal cancer (both endoscopic and nonendoscopic methods) is recommended in patients suffering from long-term acid reflux symptoms associated with high-risk factors and surveillance in patients with Barrett's esophagus. Endoscopy with virtual chromoendoscopy, endoscopic ultrasound, and CT scan is essential for diagnosis and staging of the disease. Endoscopic therapy can be used to treat early diseases. Surgery remains a mainstay treatment. Multimodality treatment strategies involving combinations of chemotherapy, radiotherapy, and more recently immunotherapy and target therapies are gaining momentum.

1 | Search Strategy and Selection Criteria

A literature search was completed in PubMed using the search term "esophageal carcinoma, ca esophagus" as well as subcategories of "squamous cell carcinoma of esophagus, adenocarcinoma of esophagus" for articles published between January 1, 2013 and June 30, 2023. For initial selection, search filters were used to identify clinical trials, meta-analyses, and systematic reviews. Articles published in the past 5 years were primarily selected, but frequently cited landmark papers were also included. We also searched the reference lists of articles identified by this search strategy and selected those that we deemed to be high-impact to the field.

2 | New Advances in Management of Carcinoma of Esophagus

- Squamous cell carcinoma is declining in the East, but adenocarcinoma is rising in the West. This is probably related to increase obesity and gastroesophageal reflux disease (GERD) in Western countries.
- Most national and international Gastroenterology Societies have guidelines for Barrett's esophagus, which are predicated on endoscopy as the screening modality.
- Nonendoscopic tests such as capsule sponge-TFF3 test and inflatable balloon capsule are increasingly used as a triage to endoscopy to confirm the diagnosis.
- Endoscopic methods (endoscopic mucosal resection [EMR] and endoscopic submucosal dissection [ESD]) to remove early (T1aN0M0) tumors are safe and effective and should be considered standard of care.
- For clinical stage T1b-2N0M0 cancers, esophagectomy without additional treatment is standard therapy. For more locally advanced T3 or node positive disease, preoperative treatment with chemotherapy or combined chemoradiotherapy is the standard of care.

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- In Asia, T2-3N0M0 squamous cell carcinoma, combined chemoradiotherapy as a potential curative treatment without surgery, is an option. For EAC, given the relatively low rate of complete response to preoperative therapy, surgery is recommended in all patients after preoperative therapy.
- Immune checkpoint inhibitors have dramatically increased anti-tumor activity administered with or without chemotherapy in MSI high or DNA mismatch repair protein-deficient cancers.
- Minimally invasive and robotic-assisted esophagectomy have gained popularity with a reduction in morbidities compared with open surgery. Long-term survival is comparable.

3 | Introduction

Esophageal cancer is the seventh most common cancer worldwide and the sixth most common cause of cancer death. It is composed of two major subtypes, namely, esophageal squamous cell carcinoma (ESC) and esophageal adenocarcinoma (EAC).

3.1 | Clinical Presentation

Dysphagia and weight loss are two cardinal symptoms of esophageal cancers. Patients usually complain of progressive painless dysphagia as food "stuck in the tube" needs to be flushed down by liquid. Swallowing of fluid is normal until the lumen of the esophagus is almost completely closed down. Dysphagia should be distinguished from the feeling of a lump in the throat (globus hystericus), which is usually related to anxiety; and painful swallowing (odynophagia), which is associated with candidiasis and gastroesophageal reflux.

ESC is more often in Asians, and EAC is more common among Caucasians who have a prolonged history of gastroesophageal reflux disease (GERD) and Barrett's esophagus (BE). Pre-existing anatomical anomalies of the esophagus such as achalasia and caustic strictures predispose patients to develop ESC. Oro-pharyngeal squamous cell cancers, previous head and neck cancer, increase the risk of synchronous or metachronous ESC. Patient who takes bisphosphonate for prolonged period developing dysphagia should alert the diagnosis of ESC.

4 | Differential Diagnosis

GERD, esophageal ulcer, and benign stricture can mimic cancer of the esophagus. With chronic acid reflux in the distal esophagus, inflammation and ulceration of the epithelial lining of the esophagus can produce symptoms suggestive of ESC/EAC. Radiation therapy or ingestion of corrosive substances increases the risk too. A careful endoscopic examination with biopsy can differentiate these benign lesions from ESC/EAC. Surveillance is generally recommended in long segment BE. Achalasia is a disorder characterized by the inability of the lower esophageal sphincter to relax allowing food to pass through. It results in dysphagia and weight loss mimicking cancer of the esophagus. Endoscopic examination of the gastroesophageal junction is mandatory because tumors arising from the cardia of the stomach may produce endoscopic feature similar to achalasia.

Between ESC and EAC, despite their differences in pathogenesis, symptoms are quite similar. EAC occurs mostly at the distal esophagus, where ESC can be in the mid or even proximal esophagus. Symptom cannot differentiate between ESC/EAC, nor is it reliable to anticipate the level of obstruction.

5 | Nature of Disease

5.1 | Epidemiology

In 2020, 604 100 (3.1%) new cases of esophageal cancer and 544 076 (5.5%) cancer deaths were reported worldwide [1]. The incidence of esophageal cancer exhibits marked regional disparities. Eastern Asia has the highest incidence and mortality rates of esophageal cancer. China alone contributes over 50% of the global burden of new cases. Males have a higher incidence and mortality rates. ESC and EAC account for 85% and 15% of new cases in 2020, respectively [2]. ESC cases mainly occur in Eastern Asia, South Central Asia, and Eastern Africa, forming the so-called "esophageal cancer belt." EAC is the dominant subtype in Northern America and Europe. In recent years, there has been a decline in ESC globally but an increasing trend of EAC reflecting a change in lifestyle and economic conditions.

5.2 | Pathophysiology (Figure 1)

ESC typically derives from esophageal epithelial cells, going through intraepithelial neoplasia (IN), low-grade IN (LGIN), and high-grade IN (HGIN), transforming into carcinoma in situ, and eventually penetrating the basement membrane into the lamina propria as an invasive tumor. On the other hand, EAC arises from a columnar-lined esophagus, which is exposed to gastric reflux. BE, typically diagnosed with visible metaplastic gastric or intestinal columnar epithelium above the gastroesophageal junction (GEJ), can be a precursor of EAC as dysplasia develop. However, nondysplastic BE also has the chance to develop from LGIN and HGIN to EAC. A large proportion of EAC patients do not have BE or intestinal metaplasia (IM) when diagnosed with their cancer, and these patients often have a shorter survival time compared with EAC patients with BE, thus raising questions about the effectiveness of endoscopic surveillance. Those cancers without clear evidence of associated BE may have been overgrown by the tumor, as there is no clear molecular evidence that these are distinct entities [3].

5.3 | Risk Factors

Tobacco and alcohol consumption account for 57% and 72% of ESC in an American cohort [4]. A similar association exists in an earlier study in France [5]. A study from China shows that high-temperature beverages, high-salt diet, and contaminated drinking water increase the risk of ESC and its precancerous lesions [6]. Early-onset ESC is unique in Eastern Africa and is

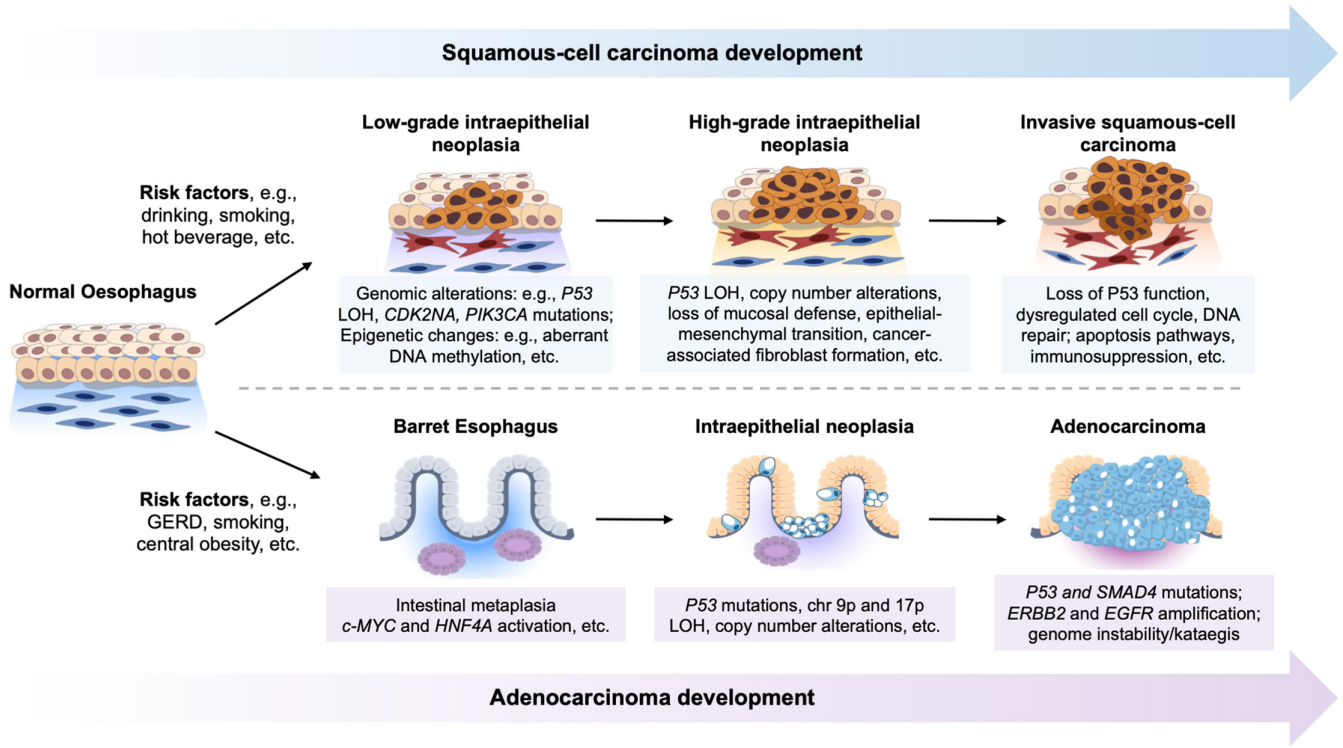

FIGURE 1 | Multiple stage development of two subtypes of esophageal cancer, ESC (squamous cell carcinoma, upper panel), and EAC (adenocarcinoma, lower panel), from normal esophagus. ESC and EAC have their specific risk factors and genomic alterations, but share some of these factors and alterations.

associated with bad dental hygiene, passive smoking, and intake of pest-infested food [7, 8]. In addition to these lifestyle factors, a case-control study in Chinese adults suggested that intake of pro-inflammatory nutrients and high level of fat increases ESC risk [9]. In Iran, thermal injury, exposure to polycyclic aromatic hydrocarbons, and poor oral health are the culprit [10]. The established risk factors for EAC are very different: GERD, central obesity, and smoking are the most likely risk factors [11]. However, heartburn caused by chronic acid reflux does not predict the development of the malignancy [12].

5.4 | Genetics

GWAS studies in China have identified several common genetic variants associated with ESC [13, 14], confirmed in northern Indian and Iranian populations [15, 16]. Novel susceptible loci have been gradually elucidated and validated during these years. Most genetic variants do not contribute to the risk independently but interact with environmental factors. Drinkers with variants in both *ADH1B* encoding alcohol dehydrogenase and *ALDH2* encoding aldehyde dehydrogenase have fourfold increased ESC risk compared with drinkers without the variant genotypes [17]. Genetic susceptibility variants have also been found for EAC and BE [18]. A recent meta-analysis encompassing a large sample size of BE and EAC (16 790 cases and 32 476 controls) reported 27 risk loci [19]. Notably, this study suggests that the genetic risk factors underlying GERD have a more substantial impact on BE than on EAC. Genetic variants that contribute to EAC risk via interaction with smoking or GERD are identified [20].

During the last decades, whole-genome or whole-exome sequencing has comprehensively delineated landscapes of ESC and AC development at the genome level. Both ESC and EAC display relatively high somatic mutation and copy number alteration (CNA) burdens, probably owing to the recurrent exposure to environmental risk factors described above. ESC and EAC share a large proportion of driver mutations in genes including *TP53*, *PIK3CA*, *ARID1A*, and *CDKN2A*. These mutations frequently occur at a very early stage of cancer development. *TP53* bi-allelic loss seems to be a key event that happens before large-scale CNA and genome instability. Furthermore, copy number gain or loss is frequently seen in precursor lesions in both ESC and EAC, e.g., gain in chromosomes 3q, 8q, and 11q, loss in chromosomes 4 and 9 in ESC [21], and loss in chromosomes 9 and 17 in EAC [22, 23]. These genome alterations could be helpful markers as part of copy number assays in the early detection of esophageal cancers.

6 | Screening and Prevention

6.1 | Population for Screening

The rationale for screening is to detect cancer at an early stage when it can be treated easily in a manner that is acceptable and cost-effective. Since outcomes for esophageal cancer have a low 10-year survival of around 10%, there is a rationale for proactive detection of this disease through screening. Ideally, diagnosis is at Stage T1N0M0, because then the lesion is removable endoscopically without requiring neo-adjuvant chemotherapy and esophagectomy.

Esophageal cancer screening therefore aims to detect precursor conditions such as BE and squamous dysplasia. It is necessary to enrich the population for screening because, although these precursors are pathologically defined lesions that increase the risk for esophageal cancer, the absolute risk remains low. Furthermore, the prevalence of these cancer types is variable across the globe. Screening may not be justified for both ESC and EAC in all geographical regions. The gold standard requirement for the introduction of screening is to show a mortality reduction, though there is increasing appreciation for the importance of also measuring surrogate endpoints such as stage shift and improved quality of life. It is however essential to distinguish between the positive impact of screening and overdiagnosis [24].

To enrich the population screening, one should include a risk assessment step for the intended-to-screen population, and risk-tailored screening should be considered to maximize the benefits and minimize the harms. In a meta-analysis of 49 studies, including over 300 000 individuals, it was shown that, in order of increasing risk, GERD, age > 50 years, male gender, and family history are associated with a prevalence of BE of 3%, 6%, 7%, and 23%, respectively. Although family history is a strong risk factor, this is hard to ascertain in clinical practice and is relevant in only a small fraction of cases; therefore, it has limited utility. A combination of these risk factors is even more predictive, such that GERD in addition to one other risk factor (age > 50 years or male gender) is associated with a 12% prevalence of BE [25]. Several prediction scores have been developed for EAC developing from BE. These tools now require testing prospectively with a calculator that is easy to apply in clinical practice. For squamous dysplasia and early ESC, endoscopic screening is recommended in high prevalence areas regardless of other risk factors.

Screening for squamous dysplasia is generally recommended in countries with a high prevalence of the disease, which includes the Golestan province in Iran and the Jiangsu province in China. In lower incidence areas, there is a move towards more risk stratified approaches towards screening [26], for example, patients with a previous head and neck cancer are at an increased risk of ESC due to the field cancerization effect.

6.2 | Guidelines for Screening

Most Gastroenterology Societies have guidelines for BE, which are predicated on endoscopy as the screening modality. They all require a history of GERD, and sometimes the severity and duration of symptoms are also specified. Most societies > 3 require that risk factors are for screening of EAC, and European recommendation also specify chronic symptoms for more than 45 years [27–30] (Table 1). Swallowable capsule device with biomarker is accepted by American College of Gastroenterology for EAC screening. Surveillance should be done by high-resolution endoscopy with chromoendoscopy. Structured biopsy is generally recommended.

6.3 | Endoscopic Screening Tests

Per-oral endoscopy is the gold standard diagnostic modality for precancerous conditions of the esophagus. It is important, when performing screening, that a high-quality endoscope is used to maximize the opportunity to pick up early precancerous lesions at the index examination. Guideline has been extended to an analysis of HGD and neoplasia specific to BE, and to ensure consistent reporting.

Transnasal endoscopy is an alternative to the per-oral procedure, which is very well tolerated, with comparative effectiveness to per-oral techniques in randomized trials [31]. This technology is not widely used for screening due to the requirement of skilled operator and hardware and limited by the small biopsy size. An alternative imaging technique being developed is tethered capsule endomicroscopy. This has the advantage of being portable with the possibility of being delivered by nonexperts in an office setting. In a proof-of-concept trial across multiple sites, the swallow rate was around 80% with high quality OCT images obtained under 6 min. A blinded comparison with standard per-oral endoscopy demonstrated a high correlation in the BE segment length measured by both modalities ($r = 0.77–0.79$) [32].

6.4 | Nonendoscopic Screening Tests

There has been a huge surge in interest for nonendoscopic technologies due to the recognition that in a screening setting low-cost technologies that are highly scalable and can be made easily accessible to high risk, and disadvantaged groups are key. Nonendoscopic tests act as a triage to endoscopy to confirm the diagnosis and instigate treatment of early diseases, which is ideally localized endoscopic therapy.

Blood biomarkers are being investigated as multicancer early detection tests (MCED). These rely on shed DNA or proteins from cancer cells that can be measured to indicate the presence of a cancer, but also depending on the specific biomarker signature—usually an epigenetic profile—the tissue of origin can be identified. There are many different MCED tests in development, one example is the methylation-based test, which has undergone a validation study with pre-defined assay cut-offs, and this showed that while the overall sensitivity for esophageal cancer is 85%, this is highly stage specific, varying from 100% (40 cases) in Stage IV to 12.5% in Stage I (8 cases) [33]. For ESC/EAC, detection is required before Stage II for endoscopic therapy to be effective. There are a plethora of other esophageal specific biomarkers being developed including miRNAs and protein biomarkers, but none of these have been tested in large population series or randomized controlled trials.

Volatile organic compounds detected in breath are a technology that works on the premise that the metabolism of cancer cells is altered by cancer cells such that the activation of aerobic glycolysis becomes the main biosynthetic pathway, rather than the usual mitochondrial pathway—the Warburg effect [34]. The volatiles are collected through a mask onto a sensor array for mass spectroscopy analysis. In case-control studies, there is promising sensitivity [35] and specificity may be improved through the administration of a volatile organic compound with a known metabolic profile alteration as seen applied to liver disease [36].

Since the esophagus is easily accessible, an alternative approach is to collect cells directly from the esophagus with a swallowable

TABLE 1 | Comparison of guidelines in screening for Ca esophagus and surveillance of BE.

Guidelines	American College of Gastroenterology Guideline [27]	American Society for Gastrointestinal Endoscopy Guideline [29]	European Society of Gastrointestinal Endoscopy Guideline [30]	British Society of Gastroenterology Guideline [28]
Screening for BE	Screening endoscopy only in patients with 1. Chronic GERD symptoms and 2. ≥3 additional risk factors for BE (below)	Screening endoscopy only in patients with 1. Family history of EAC/BE (high risk) or 2. GERD plus at least one risk factor (moderate risk)	Screening endoscopy only in patients with 1. GERD > 5 years and 2. Multiple risk factors	Screening endoscopy only in patients with 1. Chronic GERD symptoms and 2. ≥3 risk factors (below) * Threshold of multiple risk should be lower with a family history of BE or AC
Risk factor of BE	1. Male sex, 2. Age > 50 years, 3. White race, 4. Tobacco smoking, 5. Obesity 6. First degree relatives with history of BE or EAC	1. Male sex 2. Age > 50 3. Tobacco smoking 4. Obesity (central adiposity)	1. Male sex, 2. Age > 50 years, 3. White race, 4. Tobacco smoking, 5. Obesity 6. First degree relatives with history of BE or EAC	1. Male sex, 2. Age > 50 years, 3. White race, 4. Obesity 5. First degree relatives with history of BE or EAC
Screening methods for BE	1. Endoscopy 2. Swallowable capsule device + biomarker	1. Endoscopy	1. Endoscopy	1. Endoscopy
Surveillance for BE	Recommended	Recommended	Recommended	Recommended
Surveillance method for BE	White light + chromoendoscopy With structured biopsy	White light + chromoendoscopy or virtual chromoendoscopy (no specific type) With structured (seattle protocol) biopsy	High-definition endoscopy Chromoendoscopy, virtual chromoendoscopy, or confocal laser and endomicroscopy is not advised	High-resolution white-light endoscopy Chromoendoscopy or virtual chromoendoscopy is not superior Structured biopsy

(Continues)

TABLE 1 | (Continued)

Guidelines	American College of Gastroenterology Guideline [27]	American Society for Gastrointestinal Endoscopy Guideline [29]	European Society of Gastrointestinal Endoscopy Guideline [30]	British Society of Gastroenterology Guideline [28]
Surveillance interval for BE	Surveillance interval varies according to length of BE < 3-cm longer intervals	Surveillance interval varies according to the length of BE	Surveillance interval varies according to the length of BE < 1 cm: no surveillance or routine biopsy > 1 and < 3 cm every 5 years > 3 and < 10 cm every 3 years > 10 cm refer to expert center Patients with limited life expectancy no surveillance	Surveillance interval varies according to the length of BE < 3 cm every 3–5 years > 3 cm every 2–3 years

sponge or balloon device (Figure 2). These sorts of devices have been developed in Asia for ESC screening over many decades, though their efficacy has been limited due to reliance on standard cytology. A new generation of devices is easier to swallow. The forerunner with the most evidence is an encapsulated sponge (Cytosponge) coupled with the immunohistochemical biomarker TFF3 for the diagnosis of IM. This has been tested in Phase 1 through to Phase 4 studies according to the Early Detection Research Network (EDRN) approach for biomarker development and validation. The TFF3 assay has a sensitivity that ranges 80%–94%, with a specificity of 92%. In a randomized controlled trial (RCT) for BE detection, comparing Cytosponge with the rate in GP usual care was 10.6 (95% CI 6.0–18.8), $p = 0.0004$ [37]. This has led on to an ongoing RCT (BEST4 trial) to examine whether an offer of Cytosponge in an at-risk population reduces the stage of an esophageal cancer diagnosis and in turn reduces mortality from this cancer.

The dichotomous nature of the TFF3 biomarker lends itself well to machine learning algorithms to assist the pathologist in reading the slide [38], and the automated TFF3 count correlates with segment length [39]. Methylation panels have also been shown to have a similar discriminatory power to diagnose BE when combined with Cytosponge [40]. Building on this rationale, several next-generation cell collection devices, balloons and sponge, coupled with methylation assays to screen for BE and tested with promising sensitivity (79%–100%) and specificity (92%–100%) [41–43]. Further studies in the intended to screen population are ongoing. On the strength of the published evidence to date, the latest ACG guidelines give a conditional recommendation that a swallowable, nonendoscopic capsule combined with a biomarker is an acceptable alternative to endoscopy for proactive case finding for BE in those with chronic reflux symptoms and other risk factors [27]. In high-incidence areas of China, there is recent data to show that a nonendoscopic capsule sponge test coupled with machine learning can detect squamous dysplastic lesions to serve as a useful triage to endoscopy [44]. This approach has been scaled up as a pre-endoscopy triage in a multicenter cohort study of 17498 eligible participants to develop and validate a fully automated machine learning model. The average precision was 0.482 (0.470 to 0.494) and performed similarly to cytologists, meaning that over 90% of endoscopies could be avoided, whereas those at moderate and high risk for ESC could be referred for endoscopy [45]. However, improving the precision would reduce unnecessary endoscopy for false positives.

6.5 | Prevention

Primary prevention aims to reduce the incidence of disease by reducing the risk factors. It has been shown that smoking and drinking cessation can reduce the relative risks for esophageal cancer, but data on dietary modification are weak.

Secondary prevention aims to reduce risks from premalignant lesions. This can be achieved by monitoring or surveillance coupled with endoscopic therapy to remove dysplastic and T1 lesions. The yield for identifying dysplasia is greatest at index diagnosis of BE, and so this may be the most important area to focus on to achieve maximal population impact [46]. This is

especially important for longer segments BE where the cancer risk is higher [47]. The evidence for the efficacy of endoscopic surveillance in reducing cancer incidence is mixed due to variation in endoscopy quality and the challenges of overcoming sampling bias, and this can be augmented using advanced imaging modalities such as narrow band imaging and applied dyes such as acetic acid for BE and Luogol's iodine for squamous dysplasia [48].

The use of medical therapies such as proton pump inhibitors (PPIs), statins, NSAID, aspirin, and metformin to prevent esophageal cancers has been tested. Meta-analyses suggest a significant reduction in the risk of esophageal cancer in statin users, which is more marked in BE patients with up to a 41% decrease in the risk of adenocarcinoma [49]. The effect is even greater among statin and aspirin users [50]. Meta-analyses suggest a benefit for PPIs and NSAIDs/aspirin with greatest protection from aspirin in both EAC (OR 0.67) and ESC (OR 0.58) [51]. The AspECT trial was a large randomized controlled trial of low- versus high-dose PPI with or without aspirin. The results suggested an overall mortality benefit after 8–9 years, though compliance was challenging [52]. Overall, when weighing the risks and benefits, PPI may have some additional chemopreventive benefit. NSAIDs and aspirin are not routinely recommended as chemopreventive agents, and further evidence is required to evaluate statins and metformin. Anti-reflux surgery may also reduce the reflux burden, and there is some evidence from the more recent literature that anti-reflux surgery reduces the adenocarcinoma of esophagus [53].

Overall, nonendoscopic cell collection devices coupled with analytical biomarkers or machine learning approaches offer a major advance towards targeted screening for individuals at risk for esophageal cancer. When coupled with highly effective endoscopic therapies for early lesions, there is potential to reduce the mortality from this poor prognosis cancer.

7 | Diagnosis and Staging

The gold standard for confirming the diagnosis of esophageal cancer is upper endoscopy, which allows for both direct visualization of the lesion and the ability to biopsy the tissue for evaluation by pathology (Figure 3).

High-definition endoscopy, virtual chromoendoscopy, such as narrow band imaging (Figure 4), dye spray endoscopy, and

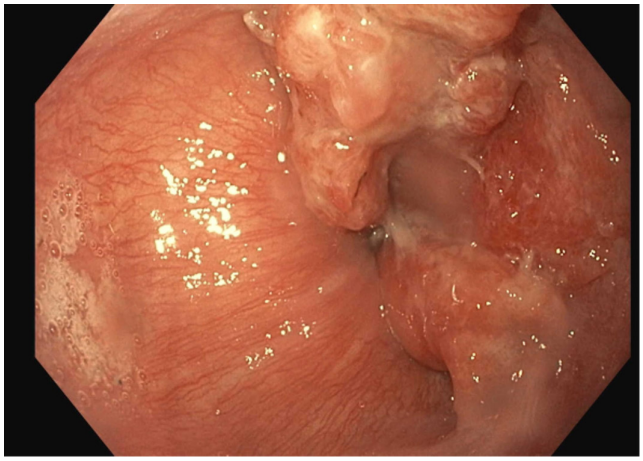

FIGURE 3 | Esophagogastroduodenoscopy (EGD) image that shows a large exophytic, ulcerated lesion at 44 cm from the incisors measuring 2.5 cm extending to the gastroesophageal junction (GEJ).

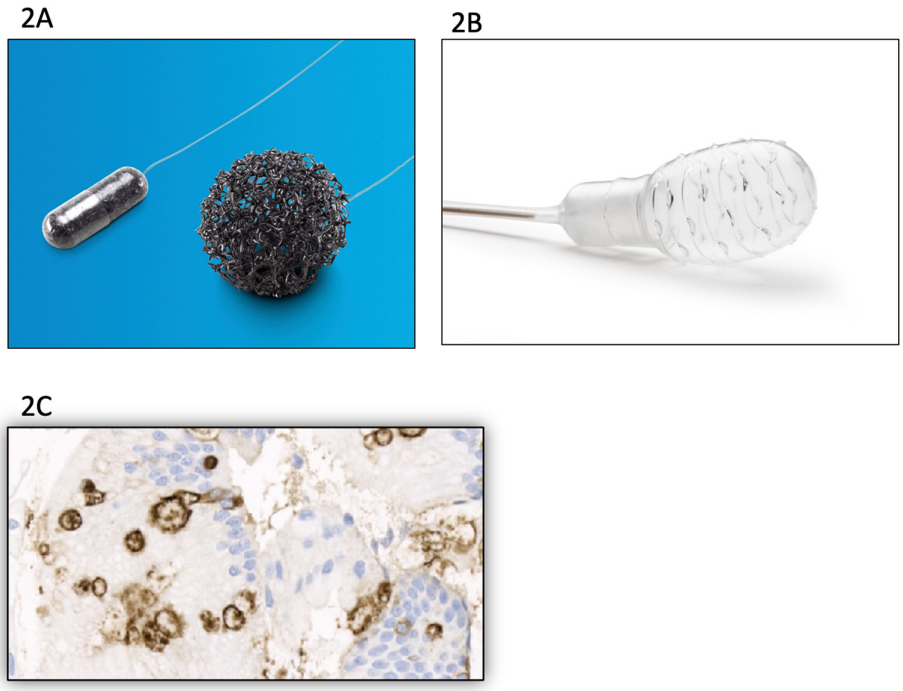

FIGURE 2 | Nonendoscopic capsule sponge-TFF3 test and inflatable balloon capsule for Barrett's esophagus. (A) Capsule on a thread is swallowed; after 7–8 min in the stomach, the capsule dissolves and the sponge is released, which can be drawn back out through the mouth. (B) Inflated balloon capsule. (C) Cells from the retrieved sponge are processed to a pseudo-biopsy and stained for TFF3 a specific IM marker.

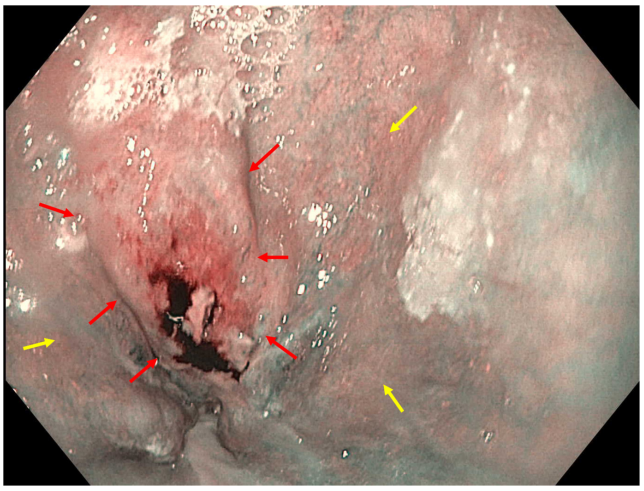

FIGURE 4 | This image depicts a narrow band imaging (NBI) of the distal esophagus, which shows a 2-cm lesion (red arrows) arising within a background of Barrett's mucosa (yellow arrows). The histological analysis revealed poorly differentiated adenocarcinoma.

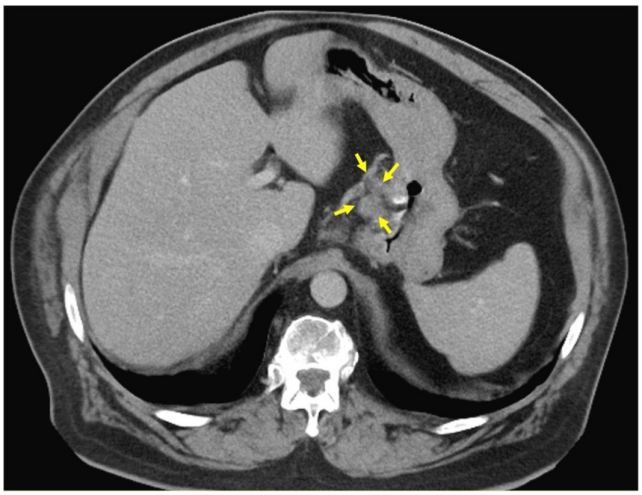

FIGURE 5 | Cross-sectional imaging (CT scan) showing large peri gastric lymph nodes measuring 2–2.5 cm in the setting of esophageal cancer.

high-resolution microendoscopy improve the detection of early-stage disease. Artificial intelligence (AI) is increasingly being evaluated for use during endoscopy as well as for diagnosing, characterizing, and even evaluating the depth of invasion of esophageal cancer. There are both computer-aided detection (CADe) and computer-aided diagnosis (CADx) systems. While CADe assists with detecting abnormal areas during endoscopy, CADx assists with diagnostics, such as the differentiation of benign versus malignant lesions [54]. These AI systems have demonstrated high accuracy when tested on videos and real patients. In a study evaluating the use of AI to detect T1 esophageal squamous cell carcinoma, the AI system correctly diagnosed 100% of ESC, while endoscopists only detected 45% [55]. A multicenter study for real-time detection of upper gastrointestinal cancer demonstrated that AI had a sensitivity similar to the expert endoscopist (0.94 vs. 0.91, $p = 0.0692$), and superior competent and trainee endoscopists (0.85, $p < 0.0001$; 0.72, $p < 0.0001$, respectively) [56].

7.1 | Staging

Current guidelines suggest initial staging to be completed through computed tomography (CT) with intravenous contrast of the chest and abdomen, and possibly the pelvis, depending on tumor margins (Figure 5). CT scans alone have low sensitivity and specificity, with some studies demonstrating a sensitivity and specificity of 66% and 61%, respectively [57]. Positron emission tomography (PET) may also be ordered, followed by an endoscopic ultrasound (EUS). EUS assists during the staging process by providing high-quality images of the malignancy and nearby tissue [58]. (Figure 6) The use of EUS helps to examine tumor depth and evaluate regional lymph nodes, in turn assisting the staging process and the treatment development plan. The accuracy of EUS to staging can vary, ranging between 74% and 93% depending on tumor stage [59]. In a meta-analysis of 19 studies, the pooled sensitivity and specificity for EUS staging for T1a cancer was 0.85 (95% CI, 0.82–0.88) and 0.87 (95% CI, 0.84–0.90), respectively [60].

8 | Treatment of Early Disease

During the early stages of disease (mucosal and superficial submucosal invasion), endoscopic therapies offer alternatives to

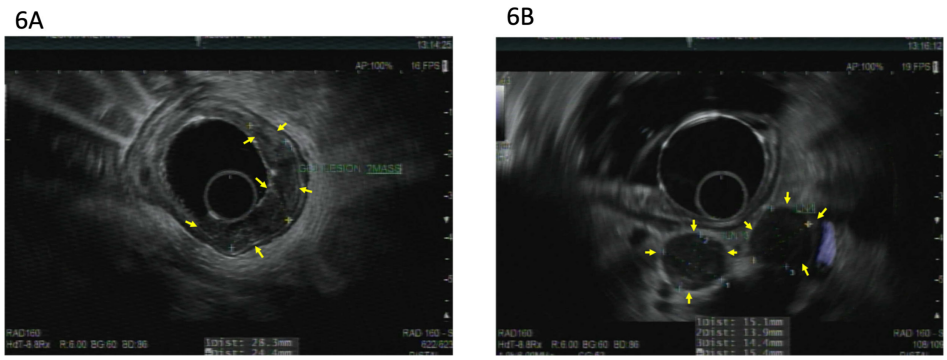

FIGURE 6 | Endoscopic ultrasound (EUS) for esophageal cancers. (A) Image showing a 2.8 × 2.4-cm hypoechoic mass (yellow arrows) arising from mucosa and extending to the submucosa (layer 3) without extension to muscularis propria (layer 4). (B) EUS image with lymph nodes—this image shows two lesions that are hypoechoic, with sharply demarcated borders and rounded contours (yellow arrows). These lesions were consistent with malignant-appearing lymph nodes per EUS criteria.

surgery that are less invasive, cost-effective, and can lead to a better quality of life for the patient. EMR and ESD are often used in combination with ablation therapy. EMR is recommended for lesions <20 mm, while ESD is recommended when lesions are larger and submucosal invasion is suspected.

Studies have demonstrated for ESC the curative resection rate was higher for those who underwent ESD (92.3%) versus EMR (52.7%) (OR = 143.9; 95% CI: 4.83–39.05; $p<0.001$) [61]. Long-term outcomes of ESD are also favorable. A study from Japan showed that those with circumferential OSC who underwent ESD had a 4-year overall survival rate of 86.2% (95% CI, 71.6–93.6), disease-specific survival rate of 95.5% (95% CI 83.1–98.9), and cumulative recurrence rate of 11.5% (95% CI, 4.1–23.1) [62]. Tunnel ESD (T-ESD) involves the creation of a tunnel adjacent to the lesion to access the lesion is also used. In a multicenter trial, T-ESD was proven to require shorter procedure time (40.0 vs. 47.3 min), had better safety outcomes, and showed improved healing of the esophageal mucosa [63].

For EAC, complete resection rates between EMR and ESD are similar. In one randomized trial, while ESD achieved clear margins more than EMR (10/17 vs. 2/17, $p=0.001$), there were no differences in complete remission at 3-months postprocedure (ESD 15/16, EMR 16/17, $p=1.0$) [64]. For patients with EAC in the setting of BE, ablation of the BE segment immediately following EMR is recommended. Commonly used ablation techniques include radiofrequency ablation (RFA), cryotherapy, and hybrid APC. Eradication of BE postprocedure achieves high complete eradication of neoplasia and eradication of IM [65]. Recurrence rates of EAC and high-grade dysplasia post-EMR are 1.4% and 2.5%, respectively [65].

9 | Treatment of Locally Advanced Disease

In disease that has progressed beyond clinical stage T1aN0, surgery is the mainstay of curative treatment. The optimal surgical approach remains controversial. One randomized trial from the Netherlands compared transhiatal to transthoracic esophagectomy in EAC or GEJ [66] showed no difference in survival, but with increased pulmonary complications in the more invasive transthoracic group. Transhiatal resections have largely been replaced by minimally invasive techniques, with combinations of video-assisted thoracoscopy (VATS) and laparoscopy—totally minimally invasive (MIE) or hybrid approaches. Both MIE and hybrid esophagectomies have been shown in randomized trials to fare better than open surgery in short-term outcomes [67, 68]. Robotic-assisted approach (RAMIE) is again superior to open surgery [69]. There is as yet no evidence to show that RAMIE is better than MIE [70]. In all published trials so far, long-term survival is not compromised with less invasive methods compared to open esophagectomy.

The optimal extent of lymphadenectomy is controversial regardless of the surgical approach. Some argue for three-field lymph node dissection (whereby lymphadenectomy is carried out for nodes in the mediastinum, around the coeliac axis as well as the neck), especially for squamous cell cancer, while others are more selective. Limited randomized trials could not demonstrate the superiority of survival versus more limited two-field lymphadenectomy (when neck dissection is omitted) [71]. For EAC, most would opt for a middle and lower mediastinal nodal dissection only. Esophagectomy remains a surgical oncologic operation with substantial morbidity rates [72]. Much work has been explored to improve complication rate and shorten hospital stay, such as Enhanced Recovery After Surgery Programs (ERAS), and refinement in surgical techniques [73, 74]. Given the complexity of surgical and postsurgical management, treatment at high-volume tertiary referral centers is recommended.

For clinical stage T1b-2N0M0 cancers, esophagectomy without additional treatment is standard therapy.

For more locally advanced T3 or node positive disease, preoperative treatment with chemotherapy or combined chemoradiotherapy is the standard of care. For SC, in the West, combined chemoradiotherapy is used with the potential for nonoperative management without surgery in patients achieving a clinical complete response. A landmark trial treating largely esophageal squamous cancers established combined chemoradiotherapy as a potential curative, nonsurgical option [75]. This trial showed superior survival for the combination of continuous infusion 5-FU/cisplatin chemotherapy and radiotherapy over radiotherapy alone. The optimal chemotherapy regimen to use with radiotherapy has evolved. A recent randomized trial in patients treated with primary nonoperative chemoradiotherapy indicated equivalent outcomes with continuous infusion 5-FU combined with either cisplatin or oxaliplatin [76]. With the high pathologic complete response observed at surgery for preoperative weekly carboplatin/paclitaxel and radiotherapy for esophageal squamous cancer, in the CROSS Dutch trial discussed below, this regimen has also been endorsed to combine with radiotherapy in the nonoperative setting [77]. The therapy tolerance and ease of administration of this therapy further support its use (Figure 7).

In some Asian centers, preoperative chemotherapy alone without radiation therapy is employed in ESC. A recent trial from Japan favored the addition of docetaxel to fluorinated pyrimidine/platinum as the most effective preoperative chemotherapy [78]. For EAC, given the relatively low rate of complete response to preoperative therapy, surgery is recommended in all patients after preoperative therapy. The FLOT (5-FU, leucovorin, oxaliplatin, and docetaxel) continuous infusion regimen is the most active preoperative chemotherapy regimen in EAC. In a randomized trial comparing FLOT to the older regimen of epirubicin, continuous infusion 5-FU, and cisplatin (ECF), FLOT achieved superior surgical outcomes and superior disease-free and overall survival [79].

For the combination of chemotherapy and radiotherapy followed by surgery, weekly carboplatin/paclitaxel plus concurrent radiation followed by surgery is used, based on the CROSS Dutch trial [80]. CROSS indicated a significant rate of pathologic complete response as well as improved surgical outcomes and survival over surgery alone in both EAC and ESC, with good safety and tolerance. The higher rate of pathologic complete response in ESC (49%) compared to EAC (23%), as noted above, also established this regimen as an option for ESC in the non-operative setting. The recent NEO-AEGIS Irish trial reported equivalent outcomes comparing

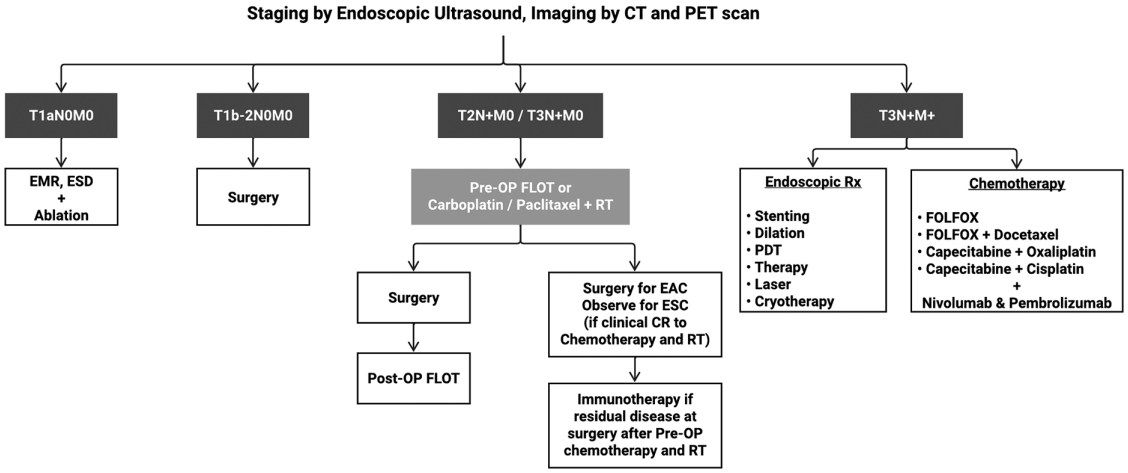

FIGURE 7 | Management for locally advanced esophageal cancer.

preoperative chemotherapy with chemoradiotherapy in EAC [81]. Chemotherapy with ECF was compared to weekly carboplatin, paclitaxel, and radiotherapy, followed by surgery. Pathologic endpoints favored combined chemoradiotherapy over chemotherapy alone, including higher rates of curative resection, pathologic complete response, and pathologic node negative status for combined chemoradiotherapy over chemotherapy alone, factors which usually correlate with a superior survival outcome. However, the trial showed no difference in 3-year overall survival for either approach. The trial argues equipoise for preoperative chemotherapy versus chemoradiotherapy. Randomized trials are ongoing comparing chemotherapy alone versus combined chemoradiotherapy in esophageal and GEJ adenocarcinoma.

After chemoradiotherapy and surgery in both ESC and EAC, the risk of recurrence is high in patients not achieving pathologic complete response with residual disease remaining in the primary or lymph nodes. A recent randomized trial indicated that adjuvant therapy with 1 year of nivolumab significantly improves disease-free survival over observation alone in both EAC and ESC [82]. Adjuvant nivolumab led to a doubling of disease-free survival when given as adjuvant therapy in patients with residual disease resected. Trials are ongoing to assess whether adding immune checkpoint inhibitors to definitive chemoradiotherapy (without surgery) or combined with preoperative and postoperative chemotherapy in the adjuvant setting, improves survival.

10 | Palliation of Advanced Disease

An esophageal stent can be inserted to widen the area near the tumor to allow the passage of soft food and liquids. A study focusing on the quality of life for those with inoperable cancer had shown an increase in functional scores for patients 8-weeks post-stent placement. They demonstrated significant improvement in swallowing and eating [83]. Although symptoms do improve, the placement of esophageal stents can be associated with side effects. Early side effects include chest pain and bleeding, and late side effects include GERD, stent migration, and fistula formation.

Esophageal dilation only provides temporary symptom relief. Additional endoscopic therapies include laser and photodynamic therapy (PDT) and cryotherapy can ablate the cancerous cells, relieve obstruction, and reduce tumor bleeding. However, all these endoscopic ablative techniques may require multiple sessions.

11 | Palliation of Metastatic Disease

For metastatic esophageal cancer, systemic chemotherapy leads to symptom palliation as well as improvement in survival. Treatment guidelines included the modified FOLFOX regimen combining continuous infusion 5-FU [77] and oxaliplatin, oral capecitabine combined with oxaliplatin, the potential substitution of cisplatin for oxaliplatin, and in Asia use of the oral agent S-1 in place of 5-FU. Triplet regimens adding either epirubicin or docetaxel to fluorinated pyrimidine/platinum-based therapy have not consistently improved survival over two-drug therapy and are more toxic [84]. Palliation of dysphagia may be achieved with chemotherapy, without requiring radiotherapy, in more than half of patients [85]. Palliation of dysphagia can also be achieved with endoscopic methods, including covered metal stent placement, endoscopic delivery of radiotherapy, and external beam radiotherapy with or without concurrent chemotherapy.

Adding immune checkpoint inhibitors to first-line chemotherapy in metastatic esophageal and GEJ EAC and ESC has become the new standard of care. Nivolumab added to first line FOLFOX improved response, progression-free, and overall survival over chemotherapy alone in esophageal and GEJ EAC [86]. Pembrolizumab added to first-line 5-FU/cisplatin-based chemotherapy in esophageal and GEJ EAC and ESC also improved all treatment outcomes [87]. Benefits of adding immune checkpoint inhibitors, however, appear to be limited to patients with overexpression of programmed death receptor ligand-1 (PDL-1). Survival benefits are limited for nivolumab to patients with PDL-1 expression $\geq 5\%$, and for pembrolizumab to patients with expression $\geq 10\%$, as measured by an immunohistochemistry score assessing PDL-1 expression in the tumor, macrophages, and lymphocytes. For ESC, adding nivolumab to fluorinated

pyrimidine/platinum chemotherapy improved response tumors testing ≥1% PDL-1 (TPS) [88]. The non-chemotherapy regimen of nivolumab combined with the anti-CTLA4 antibody ipilimumab was also superior to chemotherapy in these patients.

For esophageal EAC having mutations in DNA mismatch repair proteins can lead to microsatellite instability as tested by genomic profiling, or to loss of expression of DNA mismatch repair proteins as assessed by immunohistochemistry. Immune checkpoint inhibitors have dramatically increased anti-tumor activity administered with or without chemotherapy in MSI high or DNA mismatch repair protein-deficient cancers [89]. This biomarker is rarely found in EAC, but its presence indicates preferential use of immune checkpoint inhibitors early on in therapy. Trials evaluating immune checkpoint inhibitors alone as presurgical treatment in MSI high, or DNA mismatch repair protein-deficient EAC, have achieved high rates of pathologic complete response [90]. Further study of these agents in the locally advanced disease setting continues.

In patients with EAC with overexpression of HER2 at high levels by immunohistochemistry, adding trastuzumab to first-line chemotherapy improved response, progression-free, and overall survival [91]. Adding the immune checkpoint inhibitor pembrolizumab to first-line trastuzumab-based chemotherapy resulted in a substantial increase in response rate over chemotherapy alone. Pembrolizumab is now conditionally approved to combine with trastuzumab and chemotherapy in first-line treatment [92]. Recently, in second-line therapy after disease progression on trastuzumab based treatment, the antibody drug conjugate trastuzumab deruxtecan was approved given high rates of response, progression-free, and overall survival, with demonstrable superiority over conventional second-line chemotherapy [93].

For patients progressing on first-line chemotherapy, adding ramucirumab, which blocks ligand binding to the vascular endothelial growth factor receptor, to second-line chemotherapy with paclitaxel improved response, progression-free, and overall survival [94]. Paclitaxel plus ramucirumab is the standard second-line treatment in EAC. In third- or later-line treatment in EAC, the fluorinated pyrimidine trifluridine/tipiracil improved progression-free survival and overall survival compared to supportive care alone and represents another later line therapy option [95].

12 | Emerging Therapy

Novel targets for new drugs are emerging in esophageal cancer beyond immunotherapy agents. Testing for overexpression by immunohistochemistry of target proteins, or next-generation sequencing of the cancer genome by tissue or blood-based testing, is identifying new treatment pathways tailored to the tumor profile. Recently, zolbetuximab, a monoclonal antibody targeting the gap junction protein Claudin 18.2, improved progression-free and overall survival when combined with first-line FOLFOX or capecitabine/oxaliplatin in adenocarcinoma of the GEJ and stomach testing positive for overexpression of Claudin 18.2 [96].

TABLE 2 | Comparison of squamous carcinoma and adenocarcinoma of esophagus.

	Squamous cell carcinoma (ESC)	Adenocarcinoma (EAC)
Prevalent region	Asia	Europe and North America
Male to female ratio	2.5:1	6.5:1
Location of tumor	Mid or lower esophagus	Lower esophagus
Risk factors	Smoking Alcohol Hot beverages	BE Obesity
Mutations	*TP53*, *PIK3CA*, *ARID1A*, and *CDKN2A*	*TP53*, *PIK3CA*, *ARID1A*, and *CDKN2A*
Chromosomal gain or loss	Gain in chromosomes 3q, 8q, and 11q Loss in chromosomes 4 and 9	Loss of chromosomes 9 and 17
Therapy		
• Pre-op therapy	FLOT 5-FU + carboplatin/paclitaxel radiotherapy	FLOT 5-FU + carboplatin/paclitaxel radiotherapy
• Surgery	Esophagectomy or Observe if CR with chemo	Esophagectomy
• Palliative endoscopy	Stenting	Stenting
	Dilation	Dilation
	Ablative therapy	Ablative therapy
• Palliative chemotherapy	FOLFOX	FOLFOX
	Immunotherapy	Immunotherapy

Other promising emerging targets include the fibroblast growth factor receptor. Next-generation sequencing of cancers may also identify rare but targetable genomic abnormalities, including NTRK gene fusion, BRAF V600E mutation, and RET gene fusion. New classes of agents continue to emerge, including novel antibody drug conjugations and bispecific antibodies that simultaneously target a cellular protein and lead to local immune cell recruitment. The emerging technology of cellular therapies, using engineered T cells to target tumor antigens and stimulate a local immune response, is also under active research investigation.

13 | Conclusion

Carcinoma of the esophagus is a common malignant disease with changing epidemiology. ESC and EAC represent two distinct conditions with differences in location of tumor, pathogenesis, genetic, and environmental risk factors, and yet the presentations and therapeutics options overlap (Table 2). In the past decade, major advances have been made in the screening (endoscopy and noninvasive methods), endoscopic therapy (EMR and ESD), chemotherapy, immunotherapy, and surgical treatment. Early detection with effective endoscopic and nonsurgical therapy will significantly change the clinical outcome of carcinoma of esophagus in future.

Conflicts of Interest

D.I. reports consultancy for AMGEN, Bayer, Lilly, Roche, AstraZeneca, Bristol Myers Squibb, Astellas, Merck, Daiichi Sankyo, and Taiho as well as research funding from Taiho, Astellas; is supported by Memorial Sloan Kettering Cancer Center Support Grant (Core Grant P30 CA008748). P.S. reports consultancy for Olympus Corporation, Boston Scientific, Salix Pharmaceuticals, Cipla, Medtronic, Takeda, Samsung Bioepis, and CDx as well as research funding from ERBE and Fujifilm. R.F. receives research fundings from Roche, Medtronic and Astra Zeneca; has filed a patent of The Cytosponge technology (device and associated assays) and licensed by the Medical Research Council to Covidien (now Medtronic); is supported by the Medical Research Council (MR/W014122/1, G111260) and the Cancer Research UK–funded Experimental Cancer Medicine Center; is co-founder and shareholder in Cyted Ltd < 3% with no paid role and board role in the company. J.S. was the former editor-in-chief of JGH and a co-author of this article. To minimize bias, he was excluded from all editorial decision-making related to the acceptance of this article for publication. The other authors declare no conflicts of interest.

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