Abstract

With advances in state-of-the-art technology, trendy diagnostic and prognostic molecular markers, and cutting-edge surgical techniques, the overall survival for patients with many types of cancers has improved. However, there is a disconnect between esophageal cancer and the acceleration in cancer care seen in other malignancies. Based on data reported by Surveillance, Epidemiology, and End Results Program (SEER), the 5-year survival rate for patients with esophageal cancer is only 19.9% [1]. Poor prognosis is likely due to an overwhelming number of patients with advanced disease during the time of diagnosis, and is also reflective of the unsatisfactory outcomes from current treatments.

In this article, we will review the epidemiology and the recently revised staging of esophageal and esophagogastric junction cancers. We will discuss the current roles of endoscopic resection, surgery, radiation therapy, and systemic therapy used individually, or as components of multimodality treatment. We will describe the changes in treatment landscape with targeted therapy and immunotherapy. The focus of clinical investigations continues to shift from the traditional empiric chemotherapy to more individualized treatments based on molecular oncology and use of immunotherapy. Further identification of prognostic values may help clarify the optimal approach to treatment and management for patients with esophageal cancer, and hopefully improve survival.

Introduction

Esophageal cancer poses a significant health risk as the 8th most common cancer worldwide, owning close to 456,000 new cases and 400,000 deaths each year [2]. The majority of esophageal cancers fall into two histologic subtypes, Esophageal Squamous Cell Carcinoma (ESCC) and Adenocarcinoma of the Esophagus (EAC). These are separated by well-recognized differences in global distribution, racial predilection, risk factors, molecular pathogenesis, and anatomic distribution [3]. Controversy exists, however, as to the variations in biological behavior, patterns of spread, response to therapy, and proper approach to treatment. Historically, the majority of cancers of esophageal origin were classified as ESCC. While still true, the epidemiology shifted dramatically between 1960 and 1990, favoring higher incidence rates of EAC and declining rates of ESCC in both previously ESCC-dominant countries and white male populations of higher income countries [4]. New reports suggest that by 2030, over 1 in 100 men in the UK will develop EAC before the age of 75. The exact etiology of this gradient in EAC towards high income countries is still unknown, but may be attributed to higher obesity rates and genetic predisposition, while the decreased incidence of ESCC may be reflective of the decline in smoking.

In an effort to improve the classification of esophageal cancer beyond histopathologic and epidemiologic characteristics, to better understand the demarcation between esophageal and gastric cancers, and to discover potential targets for therapy, The Cancer Genome Atlas Research Network (TCGA) performed a comprehensive molecular analysis of 559 esophageal and gastric cancer samples from patients around the world [5]. Frequent findings in ESCC included genomic amplifications of CCND1 and SOX2 and/or TP63. In contrast, tumors of adenocarcinoma histology consisted of amplifications in ERBB2, VEGFA, GATA4,
and GATA6. In addition, the EAC tumors strongly resembled chromosomally unstable variants of gastric adenocarcinoma. These findings supported the notion that cancers of the upper esophagus more closely resemble head and neck cancers, and cancers of the lower esophagus are almost indistinguishable from cancers of the stomach with chromosomal instability. The recently reported molecular signatures and antitotal discrepancies in response to therapy between ESCC and EAC validate the decision to separate these two disease entities when staging and determining overall prognosis, particularly in conducting clinical trials.

**Staging**

The Tumor Node Metastasis (TNM) staging system of the American Joint Committee on Cancer (AJCC) is used universally and is critical for guiding treatment and determining prognosis. In the seventh edition of AJCC staging, prognostication for esophageal cancer is based on pathologic findings obtained after surgery alone. To determine the utility of the seventh edition, the Worldwide Esophageal Cancer Collaboration (WECC) analyzed a series of patient and cancer characteristics from 33 institutions in 6 continents [6,7]. The group generated the following conclusions: First, the seventh edition clinical staging system is unreliable and inaccurate, as it is primarily based on imaging without significant considerations of histologic and biomarker information. Second, the pathologic staging based on esophagectomy alone is relevant to early-stage disease, but not to advanced esophageal cancers. And lastly, taking into account for both the effects of neoadjuvant treatment and esophagectomy on tumor depth, nodal status, and metastasis, is better informative of prognosis than using factors based on esophagectomy alone. Based on these findings, the eighth edition of AJCC staging manual now includes major changes in staging epithelial cancers of the esophagus and Esophagogastric Junction (EGJ). Cancers of the esophagus and EGJ are now classified separately. ESCC and EAC have individual staging classifications as well. Tumors are now classified into clinical (cTNM), pathologic (pTNM), and postneoadjuvant pathologic (ypTNM) groups, which include non-anatomic categories, grade (G) for both histologic types and location (L) for squamous cell cancer. The definition of tumor location has also been changed for esophageal cancer from the position of the lower edge of the cancer to the epicenter, determined from the upper and lower border measurements. If the epicenter of a tumor is 2 cm or less from the gastric cardia, it is considered EAC. Those that are more than 2 cm into the gastric cardia are staged as gastric adenocarcinoma. This is a change from the seventh edition AJCC staging, in which tumors arising at the EGJ or at the gastric cardia within 5 cm of the EGJ are classified as esophageal cancer rather than gastric. The revisions contained in the eighth edition of the AJCC staging manual took effect on January 1, 2018.

**Approach to Treatment**

Surgery remains the cornerstone of treatment for localized disease in patients who are considered medically fit for surgery. Emerging data suggest patients with early esophageal cancer limited to the lamina propria or muscularis mucosa may be effectively treated with endoscopic resection. Multimodality treatment with neoadjuvant chemotherapy and Radiation Therapy (RT) followed by surgery is generally indicated for tumors invading the submucosa and beyond without invasion of adjacent structures, and/or those with lymph node involvement. For patients with locally advanced and metastatic disease, the goal of treatment is often palliative. Palliation may be achieved by systemic treatment (chemotherapy, targeted therapy, and immunotherapy) and local modalities such as RT and endoscopic interventions. Supportive measures include efforts to relieve esophageal obstruction, to establish adequate nutrition and pain control, and to manage blood loss. In addition to the approved treatment options, the National Comprehensive Cancer Network (NCCN) highly recommends participation in all phases of clinical trials.

**Endoscopy & Surgery**

Endoscopic Resection (ER) allows for precise assessment of tumor depth and complete eradication of early-stage disease (including Tis or high-grade dysplasia or carcinoma in situ, T1a and select superficial T1b tumors less than or equal to 2 cm without lymphovascular invasion). Since superficial tumors carry a low risk of lymph node involvement, local or distant recurrence, and death following endoscopic therapy, the less radical approach of ER is preferred in order to preserve the esophagus and spare patients from the morbidity of surgery [8]. Common endoscopic techniques include Endoscopic Mucosal Resection (EMR) or Endoscopic Submucosal Dissection (ESD) with or without ablative treatments including Radiofrequency Ablation (RFA), cryoablation, and Photodynamic Therapy (PDT). With close to 90% of all relapses occurring within the first two years after local therapy, the NCCN outlines guidelines by stage for careful surveillance with upper GI endoscopy (EGD) [9]. In tumors invading the submucosa, the risk of lymph node spread is as high as 20% [10]. Therefore, patients with such tumors should be evaluated for esophagectomy. Numerous studies have shown that risk of lymph node invasion may differ depending on the depth of pT1b tumors. Because of this, some experts favor pragmatically dividing the submucosa into equal thirds (sm1/2/3) in order to determine whether endoscopic therapy or esophagectomy is indicated [11]. Regardless of histology, esophagectomy can be performed in a number of ways depending on the location, disease extent, and preference and expertise of the surgeon.

Esophagectomy, either as initial therapy or after neoadjuvant therapy, can be performed with curative intent in early, resectable
Multimodality Therapy

Multimodality therapy combining the cytotoxicity of chemotherapy and sensitizing effects of RT with surgery is given with curative intent and is not given in the context of metastatic disease. In locally advanced disease, a number of studies have shown that treatment with trimodality therapy with concurrent chemotherapy and RT followed by surgery is superior to monotherapy with either surgery or RT. Treatment with surgery alone is associated with higher recurrence rates and poorer Overall Survival (OS) compared to multimodality therapy [25]. The 5-year survival rates associated with RT at conventional doses is only 0-10%. Thus, monotherapy with RT is not curative and is reserved for palliation or for those who are unable to tolerate chemotherapy [26-28]. Such poor long-term outcomes with monotherapy further strengthen the need for a multimodality approach.

<table>
<thead>
<tr>
<th>Transhiatal</th>
<th>Upper midline laparotomy and left neck incisions allow dissection of the middle and distal thirds of the esophagus. Thoracic esophagus is mobilized and blunt dissection through the diaphragmatic hiatus is performed. A gastric tube is created, and anastomosis is made with cervical esophagus. Some studies have shown that transhiatal esophagectomy is associated with a lower 30-day morbidity and mortality compared to the transthoracic approach; however, some studies report better oncologic outcomes with en bloc transthoracic esophagectomy [20-23].</th>
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<tr>
<td>Ivor-Lewis Transthoracic</td>
<td>This technique involves right thoracotomy and abdominal laparotomy. Esophagus is divided at or above the level of the azygous vein. Gastric tube, like the one employed in transhiatal esophagectomy, is created and anastomosed at this location.</td>
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<tr>
<td>Tri-incisional (McKeown)</td>
<td>Three incisions are made, combining thoracotomy, laparotomy, and neck incision. Thoracotomy allows en bloc resection including esophagus and mediastinal and upper abdominal lymph nodes. Laparotomy is utilized for abdominal exploration and stomach mobilization for gastric conduit. Lastly, neck incision allows exposure to create an esophagogastric anastomosis.</td>
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<tr>
<td>Minimally invasive</td>
<td>A minimally invasive technique, as compared to the aforementioned open esophagectomy approaches, provides smaller incisions, less blood loss, decreased postoperative pain, faster return to bowel function, decreased ICU and hospital stay, and improved cosmetic appearance compared to the conventional open procedures [24]. With this technique, surgeons are able to perform with or without thoracoscopic dissection of intrathoracic esophagus.</td>
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Table 1: Esophagectomy Techniques.
Preoperative Chemoradiation Therapy

Preoperative or neoadjuvant therapy is treatment given prior to surgery with the potential to downsize tumors, to minimize micrometastatic disease, and to decrease risk of subsequent distant metastasis. Neoadjuvant therapy commonly consists of combined modality treatment with chemotherapy and RT. It is the most commonly used treatment approach in resectable disease, with curative intent. At least two randomized trials and many meta-analysis studies have demonstrated that trimodality therapy with neoadjuvant CRT is associated with superior outcomes compared to surgery alone in resectable disease [29,30].

The phase III CROSS trial consisted of 368 patients (75% adenocarcinoma, 23% ESCC) with potentially resectable esophageal or EGC tumors. Patients were randomly assigned to either surgery upfront or preoperative CRT with weekly paclitaxel and carboplatin concurrently given with 41.4 Gy of RT [25]. The preoperative CRT arm was associated with acceptable toxicity, higher complete (R0) resection rates (92% vs. 65%), and longer median survival (49 vs. 24 months). At a median follow-up of 24 months, those in the preoperative CRT arm had a more significant reduction in overall rate of recurrence (35% vs. 58%) compared to the arm with surgery alone. Preoperative CRT also showed reduced locoregional recurrence from 34% to 14% (P < 0.001) and peritoneal carcinomatosis from 14% to 4% (P < 0.001) [31]. Based on these findings, preoperative CRT followed by surgery was established as one of the standard treatments for potentially curable esophageal and EGC cancer.

The CALGB 9781 was a smaller randomized trial comparing trimodality therapy with RT and combination fluorouracil and cisplatin versus surgery alone in patients with stage I-III esophageal and EGC cancer [32]. The study was prematurely closed due to poor accrual with only 42 and 14 patients with EAC and ESCC, respectively. Of the 25 accessible patients receiving trimodality therapy, 10 achieved pathologic complete response (pCR) (40%). Though not statistically significant, those in the trimodality arm also had longer 5-year survival rates than the arm with surgery alone (39% vs. 16%). Results showed no significant difference in perioperative morbidity or mortality.

The phase III randomized trial Federation Francophone de Cancerologie Digestive (FFCD 9901) investigated the use of preoperative CRT using cisplatin and continuous infusion fluorouracil with 45 Gy of RT versus surgery alone in resectable stage I and II thoracic ESCC or EAC [33]. The trial was terminated after enrolling 195 patients due to an interim analysis showing low probability of demonstrating superiority of either arms. Compared to surgery alone, preoperative CRT did not improve R0 resection rates or 3-year survival rates, but rather showed higher postoperative mortality. Preoperative CRT with FOLFOX (fluorouracil, oxaliplatin, folinic acid) in locally advanced esophageal and EGC cancers of both squamous cell carcinoma and adenocarcinoma are ongoing [34].

Postoperative Chemoradiation Therapy

Postoperative CRT is one of the standards of care for patients with completely resected gastric or EGC adenocarcinoma who have not previously received preoperative therapy. The Intergroup 0116 (SWOG 9008/INT-0116) randomized phase III trial evaluated the benefit of surgery followed by CRT in patients with >T3 and/or node-positive gastric cancers [35]. Patients were assigned to either surgery alone or surgery followed by CRT consisting of bolus fluorouracil and leucovorin. After a median follow-up of over 10 years, OS and Relapse-Free Survival (RFS) showed continued benefit from postoperative CRT.

Definitive Chemoradiation Therapy

For patients who are medically unfit for surgery or have inoperative disease, definitive CRT is an appropriate choice. The RTOG 85-01 study compared the use of definitive CRT versus RT alone in patients with ESCC or EAC who were medically unfit for surgery. Patients who received the combined CRT therapy had a significantly better median survival (12.5 vs. 8.9 months), 5-year survival (26% vs. 0%), and lower incidence of local (P < 0.02) and distant recurrences (P < 0.01) compared to those randomized to the RT alone arm [36,37]. Based on these results, definitive CRT is one of the treatment options for unresectable locally advanced esophageal cancer. A follow up trial, INT-0123 showed that higher doses of RT (64.8 Gy) were not associated with improved local-regional control or survival compared to the standard RT dose (50.4 Gy) [38].

The FFCD 9102 study was a randomized trial that compared CRT alone with CRT followed by surgery in patients who were considered responders to CRT with locally advanced ESCC [39]. Patients with operable T3N0-1M0 thoracic esophageal cancer received fluorouracil and cisplatin and either conventional or split course concomitant RT. Patients were randomized to either surgery or continuation of CRT. The results suggested that patients responding to CRT have no additional benefit from surgery. The median survival was 17.7 months for those who had surgery compared to 19.3 months in the no surgery arm. The 3-month mortality rate was 9.3% for the surgery arm compared to 0.8% in the no surgery arm. Analysis of the Cochrane database also supported these findings showing that addition of esophagectomy in patients with localized ESCC with good responses to CRT provides little to no difference in OS and may be associated with higher treatment mortality [40].

The NCCN guidelines recommend paclitaxel and carboplatin, fluorouracil and oxaliplatin, fluorouracil and cisplatin (with capecitabine as a suitable replacement for fluorouracil) as preferred regimens for definitive CRT. Some studies also support
the use of docetaxel and cisplatin, carboplatin and paclitaxel, and FOLFOX [41-43].

Preoperative Chemotherapy

The role of preoperative chemotherapy in patients with locally advanced esophageal cancer was investigated in a number of randomized clinical trials. In the Intergroup trial, 467 patients with potentially resectable ESCC or EAC were randomized to receive preoperative chemotherapy with cisplatin and fluorouracil followed by surgery or surgery alone [44]. At a median follow-up of 8.8 months, preoperative chemotherapy decreased the incidence of microscopic residual cancer (R1) resection (4% vs. 15%); However, there was no difference in OS between the groups.

The Medical Research Council Oesophageal Cancer Working Group (MRC-OE02) was a much larger randomized trial that favored a different conclusion [45]. The trial included 802 patients with potentially resectable esophageal cancer of any histology. Patients were randomly assigned to preoperative cisplatin and fluorouracil followed by surgery or surgery alone. The decision to give patients preoperative RT was based on the clinicians’ choosing. At a median follow-up of 6 years, those who received preoperative chemotherapy had superior disease-free survival and OS than those who underwent surgery alone. Postoperative complications were reported in 41% of patients in the preoperative chemotherapy arm and 42% in surgery alone arm. The authors concluded that preoperative cisplatin and fluorouracil improved survival without additional serious adverse events in the treatment of patients with resectable esophageal cancer. The French study, FNCLCC ACCORD07-FFCD 9703, also compared preoperative cisplatin and fluorouracil followed by surgery with surgery alone. Preoperative cisplatin and fluorouracil was found to improve disease-free survival and OS in patients with resectable adenocarcinoma of the stomach and lower esophagus [46]. The Medical Research Council OE05 trial compared neoadjuvant ECX (epirubicin, oxaliplatin, capecitabine) with cisplatin and fluorouracil in patients with adenocarcinoma of the thoracic esophagus and EGJ [47]. ECX did not improve OS and was associated with higher toxicity. For this reason, preoperative chemotherapy with fluorouracil and cisplatin is recommended for adenocarcinoma of the thoracic esophagus and EGJ.

Two meta-analysis studies also showed survival benefit with use of preoperative chemotherapy in patients with resectable esophageal cancer compared to surgery alone. Sjoquist, et al. updated a previous meta-analysis with originally seventeen studies and an additional seven comparing neoadjuvant CRT or chemotherapy to surgery alone. They determined that neoadjuvant CRT or chemotherapy provided survival benefit compared to surgery alone in patients with resectable disease. However, it is not clear whether there is an advantage of neoadjuvant CRT over preoperative chemotherapy [29]. A second report by Kidane, et al. analyzed a total of 13 randomized trials and found that preoperative chemotherapy plus surgery was associated with superior survival advantage compared to surgery alone in patients with resectable thoracic esophageal cancer, with added toxicity from chemotherapy ranging from 11-90% [48].

Perioperative Chemotherapy

The MAGIC trial was a phase III randomized study performed by the British Medical Research Council [49]. The results of this trial established the role of perioperative chemotherapy with ECF (epirubicin, cisplatin, and fluorouracil) as a standard treatment for resectable gastric and EGI adenocarcinoma. Over 500 patients were randomly assigned to perioperative ECF and surgery or surgery alone. ECF resulted in decreased tumor size and stage. With a median follow up of 4 years, the perioperative-chemistry group had higher likelihood of OS (Hazard Ratio [HR] for death, 0.75; 95% Confidence Interval [CI], 0.60-0.93; P = 0.009; 5-year survival rate, 36% vs. 23%) and Progression-Free Survival (PFS) (HR for progression, 0.66; 95% CI, 0.53-0.81; P < 0.001). Perioperative fluorouracil and cisplatin is another viable treatment option for those with locally advanced resectable gastroesophageal cancers. In the FNCLCC and FFCD multicenter phase III trial, Ychou, et al. reported that treatment with perioperative fluorouracil and cisplatin for resectable adenocarcinoma of the lower esophagus, EGJ, and stomach was associated increased curative resection rate, disease-free survival, and OS compared to surgery alone [50].

With previously reported efficacy in docetaxel, researchers at the Institute of Clinical Oncology Research in Germany conducted the FLOT4 phase III clinical trial which compared perioperative chemotherapy with docetaxel, oxaliplatin, fluorouracil, and leucovorin (FLOT) to epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX) in the treatment of locally advanced, resectable gastric or EGI adenocarcinoma [51,52]. Compared to ECF/ECX, FLOT was associated with longer PFS (30 months vs. 18 months, HR 0.75, P = 0.004), more R0 resection rates (84% vs. 77%, P = 0.011), higher number of pT0 and pT1 tumors (25% vs. 15%, P = 0.001), as well as longer OS (50 months vs. 35 months, HR 0.77, CI, 0.63-0.94, P = 0.012). FLOT results in a 10% increase in pCR, even in patients with advanced age, small tumors, negative nodal status, or signet cell components - factors that were once considered reasons to avoid perioperative therapy. In addition, FLOT administration is more convenient and consists of a single 24-hour infusion every 2 weeks instead of the continuous infusion used with ECF. With no significant differences in perioperative complications between the groups, results suggest perioperative FLOT is a superior regimen.

Systemic Therapy

As discussed in the previous sections, a number of chemotherapy regimens given concurrently with RT are used as...
part of multimodality therapy for localized and locally advanced disease. For patients with locally advanced unresectable and metastatic disease who desire systemic therapy and have adequate performance status, combination chemotherapy is the best approach, since it may better limit disease and provide symptomatic relief from dysphagia, nausea, obstruction, perforation, bleeding, and pain. Treatment is guided by the histological subtype of esophageal cancer and HER2 tumor status.

Chemotherapy for Locally Advanced Unresectable and Metastatic Disease

First-line therapy for metastatic disease is a two-drug chemotherapy regimen. A third chemotherapy drug can be given to patients who are able to tolerate the toxicities of added therapy. Though the optimal regimen is not clear, cisplatin-based therapies are thought to be superior to non-cisplatin-containing regimens [53]. Tumor assessment for HER2 expression, PD-L1 overexpression, and dMMR are important for guiding therapy. Factors to consider include patient performance status, comorbidity, quality of life, patient preference, histologic type, and availability of clinical trials.

Targeted Therapy

Human Epidermal Growth Factor Receptor 2 (HER2), involved in cell proliferation and differentiation, is overexpressed in 15-30% of EAC and 5-13% in ESCC [54-57]. HER2 overexpression can be targeted by trastuzumab, a monoclonal antibody against HER2. In the Trastuzumab for Gastric or Gastro-oesophageal Junction center (ToGA) open-label international phase III trial, 594 patients with HER2-positive, locally advanced, recurrent, or metastatic gastric or EGJ adenocarcinoma were randomized to receive trastuzumab plus chemotherapy (cisplatin plus fluorouracil or capcitabine) or chemotherapy alone [58]. Those receiving trastuzumab plus chemotherapy demonstrated a higher median OS of 13.8 months compared to 11.1 months in those only treated with chemotherapy. The prognostic use of HER2 expression in esophageal adenocarcinoma remains unclear. Regardless, trastuzumab is recommended as first-line chemotherapy in combination with fluoropyrimidine and cisplatin for patients with HER2 overexpression in metastatic adenocarcinoma. In a small retrospective study, trastuzumab in combination with a modified FOLFOX regimen showed an acceptable safety profile for patients with HER2-positive gastroesophageal cancers; however, further investigation with prospective studies are needed [59].

Elevated levels of Vascular Endothelial Growth Factor (VEGF), a key contributor in tumor angiogenesis and hematogenous spread, are associated with a poor prognosis in gastric and EGJ adenocarcinomas [60]. Ramucirumab, a VEGFR-2 antagonist monoclonal antibody, has shown therapeutic value in two trials leading to its approval in previously treated gastric and EGJ adenocarcinoma. In the REGARD trial, patients with progression after first-line platinum-containing or fluoropyrimidine-containing chemotherapy were randomly assigned to receive best supportive care plus either ramucirumab or placebo [61]. The arm receiving ramucirumab had superior median PFS (2.1 vs. 1.3 months) and OS (5.2 vs. 3.8 months) compared to those who received placebo. Similarly, in the RAINBOW trial, the efficacy of paclitaxel plus ramucirumab versus paclitaxel plus placebo was assessed in patients with metastatic gastric or EGJ adenocarcinoma who experienced disease progression after the first-line chemotherapy [62]. The median OS (9.6 vs. 7.4 months) and PFS (4.4 vs. 2.9 months) were significantly better in the ramucirumab arm compared to the placebo arm. Other VEGF-blocking agents such as bevacizumab and apatinib, tyrosine kinase inhibitors like sunitinib and sorafenib, and mTOR inhibitors are being investigated, but have not yet been approved by the FDA.

Epidermal Growth Factor Receptor (EGFR) may also play a role within the tumor microenvironment of esophageal cancer. Overexpression of EGFR results in dysregulated cell proliferation and apoptosis. In colorectal cancer, elevated levels of EGFR are associated with tumor growth, metastasis, and resistance to chemotherapy [63]. In the treatment of colorectal cancer, absence of an activating KRAS mutation is highly predictive of response to anti-EGFR therapy [64]. Anti-EGFR therapies have been studied in patients with gastric or EGJ adenocarcinoma, but trials with cetuximab and panitumumab have not shown benefit compared to standard first-line therapies. The utility of KRAS as a biomarker for response to anti-EGFR therapy for esophageal cancer is not known [65-67].

Immunotherapy

Cancer immunotherapy revolves around the relationship between the tumor microenvironment and the ability of the immune system to prevent and eliminate cancer cells. Tumors escape immune surveillance through upregulation of programmed cell death ligand 1 (PD-L1, also called B7-H1 or CD274), interfering with T-cell activation and antitumor responses. PD-L1 is overexpressed in 40% of esophageal cancers and is associated with cancer progression and poor postoperative prognosis [68,69]. Pembrolizumab and nivolumab are monoclonal antibodies that inhibit PD-1 pathways and promote antitumor responses in esophageal cancer and other noncolorectal gastrointestinal cancers, demonstrated by the KEYNOTE and CheckMate-032 trials. Unfortunately, the antitumor activity of these drugs seems less in esophageal cancer compared to that in melanoma and lung cancers.

The phase Ib KEYNOTE-012 trial was the first trial showing that use of pembrolizumab in patients with recurrent or metastatic PD-L1 positive EGJ or gastric adenocarcinoma...
with two or more prior therapies was associated with antitumor activity and manageable toxicity [70]. In the phase II cohort 1 of the KEYNOTE-059 trial, the role of pembrolizumab monotherapy was evaluated in 259 patients with EGJ or gastric adenocarcinoma who progressed on two or more therapies [71]. In patients with PD-L1 positive tumors (n=143, 57.1%), the objective response rate (ORR) was 15.5%, with 2% of patients achieving complete response (CR). The median duration of response was 16.3 months. Cohorts 2 and 3 of KEYNOTE-059 are ongoing and will evaluate efficacy of first line monotherapy pembrolizumab or in combination with chemotherapy. The phase Ib KEYNOTE-028 trial extended participation to patients with either EAC or ESCC previously treated with two or more therapies [72]. Together, ESCC and EAC had an ORR of 30% and a median duration of response of 15 months. Separated by histologic subtype, patients with EAC were found to have superior ORR to ESCC (40% vs. 28%).

Disagreement exists as to the optimal timing for a trial of pembrolizumab. In the U.S., pembrolizumab is approved as third-line therapy in patients with PD-L1-expressing tumors (Combined positive score [CPS] 1 or higher) after failure of two separate chemotherapy regimens. However, evidence from two phase III trials support pembrolizumab as an appropriate second-line therapy. The KEYNOTE-181 trial showed superiority of pembrolizumab over chemotherapy for second-line treatment in patients with ESCC and adenocarcinoma of the esophagus or EGJ, Siewert type I, with a higher level of PD-L1 expression (CPS 10 or higher) [73]. In a preliminary report presented at the 2019 ASCO Gastrointestinal Cancers Symposium, of the 222 patients with PD-L1 positive tumors (CPS 10 or higher), the group treated with pembrolizumab had superior median OS, twice as many individuals alive, and fewer grade 3 to 5 drug-related adverse events compared to the chemotherapy group. In the KEYNOTE-061 trial, 592 patients with advanced gastric or EGJ cancer that had progressed on combination chemotherapy with platinum and fluoropyrimidine were assigned to receive either pembrolizumab or paclitaxel monotherapy. While pembrolizumab did not significantly prolong OS and only achieved similar ORR to the paclitaxel group, pembrolizumab was associated with a better adverse event profile. In post hoc analysis, the treatment effect of pembrolizumab was greatest in patients with PD-L1 CPS of 10 or greater and for those whose tumors were MSI-H, regardless of CPS status [74].

Predictive factors for therapeutic response to PD-1 blockade include PD-L1 overexpression, microsatellite instability, and high tumor antigen load. Microsatellite instability (MSI, microsatellite instability-high or MSI-H) is a condition of hyper-mutability stemming from mismatch repair-deficient tumors (dMMR). These tumors make up to fifteen percent of colorectal cancers and have 10-100 times more somatic mutations in repair genes compared to mismatch repair-proficient tumors (pMMR), or tumors without defects in mismatch repair [75-77]. Roughly 3% are associated with Lynch syndrome (mutations in MSH2, MLH1, MSH6, and PMS2) and the remaining 12% are products of sporadic mutations with hypermethylation of the MLH1 gene promoter [78,79]. Tumors with MSI are thought to be more responsive to checkpoint inhibitors due to generation of neoantigens which may be recognized as “non-self” immunogenic antigens. The MK-3475 phase II study evaluated the therapeutic response of pembrolizumab in patients with progressive metastatic carcinoma with and without MSI. They found that dMMR tumors were more easily recognized by the immune system and were more susceptible to pembrolizumab. Compared to pMMR tumors, dMMR tumors had higher numbers of somatic mutations that correlated with prolonged PFS. Based on this trial, clinicians are better equipped in predicting response to pembrolizumab with MSI status in not only colorectal cancer, but also for unresectable or metastatic solid tumors of any origin [80].

In May 2017, the FDA approved pembrolizumab for the treatment of unresectable of metastatic MSI-H or dMMR solid tumors that have progressed with prior treatment and have no satisfactory alternative therapy options. Shortly after, in September 2017, FDA approval was extended to patients with PD-L1-overexpressing gastric and EGJ adenocarcinomas previously treated with two or more prior therapies with or without HER-2neu targeted therapy [81].

The safety and efficacy of nivolumab has also been demonstrated in patients with advanced, treatment refractory gastroesophageal adenocarcinoma and squamous cell carcinoma. The phase 3 ONO-4538 ATTRACTION 2 trial was the first immunotherapy trial to show improved survival benefit for patients with heavily pretreated gastric or gastroesophageal cancer [82]. The phase I/II, open-label CheckMate-032 study included 160 patients with advanced or metastatic esophageal, gastric, or EGJ cancer who progressed on one or more chemotherapy regimens. Patients were randomly assigned to nivolumab alone or a combination of ipilimumab, an anti CTLA-4 monoclonal antibody, and nivolumab [83]. Nivolumab with or without ipilimumab led to durable responses and long-term OS, regardless of PD-L1 status. Like the KEYNOTE-059 trial, it was also noted that PD-L1 positive patients had superior response rates (27%) compared to PD-L1 negative patients (12%). Only 17% of patients experienced grade 3 or 4 adverse effects, similar to studies done in other tumor types. Together, the CheckMate-032 and KEYNOTE trials suggest PD-1 blockade as a safe and effective treatment in both ESCC and EAC in pretreated patients.

Avelumab, another monoclonal antibody against PD-L1, has not been shown to improve OS or PFS in patients with esophageogastric cancer [84]. Likewise, ipilimumab has not been proven to lengthen immune-related progression-free survival and has a median survival comparative to best supportive care [85].
Studies investigating other immunotherapies for esophagogastric cancers are underway.

Summary

Major leaps have been made in advancing the science of treating esophageal cancer. Diagnostic and therapeutic endoscopy is essential in the management from early disease to palliation of advanced disease. Innovative techniques enable radiation oncologists to deliver more precise RT with improved efficacy and less toxicity. Improvements in surgical approach have reduced treatment morbidity and mortality. The application of the knowledge learned from molecular profiling in esophageal cancer has led to clinical investigations of novel agents targeting those changes. We are now living in the era of individualized medicine to identify the patients who will benefit the most, and have the least toxicity, from specific therapies. Following the breast cancer lead, HER2/neu is a clear target in the treatment of esophageal cancer. Patients with MSI-positive tumors represent individuals predicted to have favorable responses to checkpoint inhibition. Immunotherapy is generally less toxic and is associated with more durable responses in molecularly selected upper GI cancers. Trials looking at predictors of response are underway. The overall outcome from this disease, however, remains far from satisfactory. Clinical trials investigating strategies in prevention, early diagnosis, and treatment of early and advanced disease are guided by lessons learned in epidemiology, molecular genetics, pharmacogenomics, and precision medicine.

References


