Current Oncology Reports (2022) 24:375–385
https://doi.org/10.1007/s11912-021-01153-4

GASTROINTESTINAL CANCERS (J MEYER, SECTION EDITOR)

Update on Management of Squamous Cell Esophageal Cancer

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Accepted: 12 October 2021 / Published online: 10 February 2022

Abstract

Purpose of the Review Esophageal cancer is the sixth most common cause of cancer death globally. Squamous cell carcinoma of the esophagus (ESCC) is the predominant histologic type in the world. Treatment strategies have evolved in the last decade and new paradigms are replacing traditional approaches at all stages of cancer. This review will summarize the epidemiology, diagnosis, staging, and treatment of esophageal squamous cell carcinoma.

Recent Findings Novel approaches to screening may be cost-effective in regions with a high incidence of ESCC. Multidisciplinary evaluation and treatment has become the standard of care. Endoscopic resection may be an option for early stage ESCC. Minimally invasive esophagectomy can be performed safely as a primary therapy or after-induction chemoradiation. Several recent studies have found a survival benefit to immunotherapy for patients with metastatic or persistent disease.

Summary Multi-disciplinary evaluation and multi-modal therapy including cytotoxic chemotherapy, radiation, surgery, and immunotherapy have improved survival compared to surgery alone.

Keywords Squamous cell carcinoma · Neoadjuvant therapy · Chemoradiation · Esophageal cancer · Checkpoint inhibitor · Esophageal cancer staging

Introduction

Esophageal cancer is the ninth most common malignancy and the seventh most common cause of cancer death [1]. In 2018, 572,034 people worldwide were diagnosed with esophageal cancer and 508,585 people died from this disease [1]. Proportionally, esophageal cancer is less common in the USA. In 2020, 18,440 Americans were diagnosed with esophageal cancer and 16,170 people died from the disease. In the USA, esophageal cancer represents the 11th most common cause of cancer death [2]. Accurate diagnosis and staging determines treatment. In the last decade, the treatment paradigm for esophageal cancer has changed markedly. Early stage cancers may be treated endoscopically, while locally advanced disease is routinely treated with neoadjuvant chemoradiotherapy (NCRT) followed by surgery; cervical cancers are typically treated with definitive chemoradiation. We seek to summarize the multidisciplinary approach to squamous cell carcinoma of the esophagus.

Epidemiology

There are several epidemiologic trends in esophageal cancer. Although the incidence of adenocarcinoma continues to rise, squamous cell carcinoma (ESCC) remains the most common histology worldwide with the highest incidence in Iran, Central Asia, and China [3•]. Esophageal cancer affects men more than women [4]. Disease prevalence is higher in patients with lower socioeconomic status [5, 6]. High endemic areas include the "Esophageal Cancer Belt," affecting countries such as Iran, Turkey, Iraq, southern former Soviet states (Kazakhstan, Turkmenistan, Uzbekistan, Tajikistan), Mongolia, and Northwestern China [7, 8]. Risk factors include smoking and alcohol consumption [9–13], gastroesophageal reflux disease [14], Barrett's esophagus [15–17], morbid obesity [18–21], betel-quid chewing [22–26] and consumption of hot, mate teas [27–29] and

This article is part of the Topical Collection on *Gastrointestinal Cancers*

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smoked meats [30, 31]. Predisposing genetic conditions include tylosis [32–34], Bloom Syndrome [35, 36], and Fanconi anemia [37], and ALDH2, ADH1B [38, 39] and missense PTPRJ, PTPN13 polymorphisms [40].

Diagnosis

As in most solid organ cancers, early diagnosis provides the best chance for cure. Esophageal cancer may represent the most extreme example of this principle. Lymphatics located in the lamina propria, superficial to the muscularis mucosa provide a conduit for malignant cells to disseminate. Upper endoscopy with biopsy remains the gold standard for diagnosis. Indications for endoscopy include dysphagia, long-standing, concerning or refractory reflux symptoms or as part of a screening program [41, 42]. Generalized population screening is not recommended in North America and Europe [43•]. In areas where ESCC is more prevalent such as China or in the esophageal cancer belt there is evidence to support endoscopic screening [44•]. Non-sedated transnasal endoscopy and non-endoscopic approaches may allow cost effective screening of high risk populations [43•, 44•].

Mucosal changes associated with early cancers may be subtle and missed by standard white light endoscopy [45]. Techniques exist to enhance the detection of early lesions include chromoendoscopy with Lugol's solution and narrow band imaging (NBI). Lugol's solution stains the glycogen in normal squamous epithelium brown, while glycogen depleted dysplastic cells do not stain [46]. NBI filters two specific wavelengths to enhance the vascular patterns of the mucosa. NBI may be preferred since it does not require the dye application which may cause chest pain and or be aspirated [45]. NBI is included in most endoscopy processors. Further increases in sensitivity can be achieved through magnified endoscopy combined with NBI [46]. Any mucosal changes should be biopsied.

Staging

Once the diagnosis is established, staging must be completed to guide treatment. Staging is performed using the TNM classification as described by the American Joint Committee Cancer [47]. Location of the tumor is not a determinant of staging but does have implications for treatment. Location descriptors include cervical, upper, middle and lower esophagus based on the tumor epicenter. Cervical cancers are located above the thoracic inlet, upper third tumors occur between the thoracic inlet and the azygos vein, middle esophageal tumors are between the azygos vein and the inferior pulmonary vein and lower esophageal carcinomas range from the inferior pulmonary vein to the stomach including the esophagogastric junction [48].

Clinical staging is based on endoscopic ultrasound (EUS) and radiologic findings and histologic grade [48]. Standard staging should include EUS, CT chest and abdomen and pelvis or neck and FDG-PET/CT. Each of these staging modalities is complementary and provides different information.

EUS has been shown to have an accuracy for T classification of 79% for ESCC [49]. Differentiation between T1a (invades lamina propria and muscularis mucosa) and T1b (invades submucosa) may not always be possible by EUS. Endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) may be necessary to provide definitive T classification and rule out invasion into the muscularis propria [48]. For nodular lesions ≤ 2 cm, endoscopic resection should be considered for accurate assessment of depth of invasion [50].

Clinical nodal classification (N) is determined by EUS with or without FNA and CT and FDG-PET scanning. The specificity of EUS can be as low as 20% without biopsy while diagnostic accuracy can range from 64 to 71% [49, 51]. EUS guided fine needle aspiration increases diagnostic accuracy and should be encouraged [48, 52].

Distant metastatic disease is typically detected by imaging. FDG-PET/CT increases the overall accuracy of compare to CT alone [48]. Confirmatory tissue biopsy should be considered prior to staging a patient as M1 [47].

Adjunctive staging procedures can be useful in specific circumstances. In patients with upper and middle third cancers, bronchoscopy with biopsy should be routinely performed to evaluate for tracheobronchial invasion which renders the patient T4b and unresectable. Endobronchial ultrasound (EBUS) and narrow band imaging may be useful in detecting occult invasion. Laparoscopy with careful inspection of the peritoneum and liver with biopsy and peritoneal cytology has efficacy in lower third cancers and is used routinely in many centers [53]. Repeat staging laparoscopy should be considered after induction therapy, either as a separate procedure or at the beginning of a planned resection [54].

Histopathology

Despite a rising incidence of esophageal adenocarcinoma in high-income countries [55–58], squamous cell carcinoma represents nearly ninety percent of all esophageal cancer cases [3•, 59, 60].

Over half of all case of squamous cell carcinoma occur in China (in particular in Henan, Hebei, and Jiangsu provinces) [61, 62]. This tumor type demonstrates a predominance of mid-esophageal invasion with a high propensity for local and lymphatic spread [57]. Squamous cell dysplasia is

believed to be associated with development of precancerous cellular clones with TP53, NFE2L2, CDKN2A, FBXW7, NOTCH1 mutations [63]. Molecular studies have suggested that genetic alterations affect various stages of the cell cycle, contributing to carcinogenesis [64•, 65, 66].

Therapy

Cervical Esophageal Cancer

Cervical esophageal cancer is defined as tumor within 5 cm of the cricopharyngeus muscle. This definition however has been extended in clinical trials to any esophageal tumor above the thoracic inlet/sternal notch [67]. Cervical esophageal cancer represents between 2 and 10% of esophageal cancer cases, with squamous cell carcinoma as the predominant histology [68].

Historic treatments of cervical esophageal cancer included radiation and surgery. Several studies however have demonstrated equivalent outcomes between chemoradiation and surgery, which has altered the treatment paradigm [69–71]. Additional concerns with surgical therapy in the neck revolve around cervical tumor extension into nearby structures, which necessitates pharyngolaryngectomy. Currently, surgery is considered as a salvage therapy following chemoradiation failures, but results have been mixed [72, 73].

Optimal chemoradiation regimens for cervical esophageal tumors are unclear. The best results seem to come from single or double platinum-based regimens with concomitant radiation [74–76]. Drug regimens include cisplatin (60 mg/m2) plus 5-FU (300 mg/m2/24 h) [75]; cisplatin (80 mg/m2) plus docetaxel (60 mg/m2) [75]; cisplatin (70 mg/m2) plus 5-FU (700 mg/m2/24 h) [77]; docetaxel (60 mg/m2) plus nedaplatin (70 mg/m2) [76]; 5-FU plus mitomycin C plus cisplatin [67]; high dose cisplatin alone (100 mg/m2) [67]. Chemotherapy has been provided with induction, consolidation, or adjuvant intent at various timing intervals and for variable durations.

Radiation has historically been provided with 2D and 3D conformational techniques. Clinical target volumes include the primary tumor and 0–3 cm craniocaudal-transverse margins [76]; primary tumor with 1–2 cm craniocaudal and 0.5–1 cm circumferential extension [77]; primary tumor with 0–3 cm extension [67]. Intensity modulated radiation therapy (IMRT) has recently been proposed as a more modern treatment option help preserve normal tissue around cervical tumors [67]. Extrapolation from the head and neck literature has suggested that radiation doses as high as 60–70 Gy can be used [78]. Higher doses of radiation however have not shown improved survival [78].

Overall 3-year survival ranges for patients suffering from cervical esophageal cancer range between 50 and 65%. Progression free survival approximates 40–50%. Chemoradiation toxicity must be carefully balanced against local disease control as there is a not insignificant incidence of grade 3 mucositis, GI toxicity, hematologic abnormalities and fistula formation with current regimens [75, 77].

There currently are no prospective immunotherapy clinical trials dedicated to cervical esophageal cancer. KeyNote 181 is ongoing for study of patients with metastatic, unresectable esophageal cancer where pembrolizumab (anti-PD-1 antibody) is provided as second line therapy; preliminary results are promising [79•].

Squamous Cell Carcinoma of the Thoracic Esophagus and EG Junction

The therapy for non-cervical ESCC is determined by stage, patient fitness and available expertise. A multi-disciplinary team with experience in treating esophageal cancer should evaluate all patients.

For early stage cancers, including carcinoma in situ (Tis) and T1a tumors, endoscopic resection by EMR or ESD should be considered for all patients provided there is no evidence of lymph node involvement. ESD is a more technically demanding but allows en bloc resection of larger lesions. ESD appears to be associated with higher R0 resection rates and excellent long-term survivial [43•]. All patients should be considered for surgery because of the possibility of occult nodal disease in patients with high risk histologic features or deeper levels of invasion [46, 50]. Additional therapies such as adjuvant radiation or chemoradiation should be considered in patients with poor prognostic factors such as poorly differentiated tumors, positive margins or deep submucosal invasion [80]. Tumors that invade the deep muscularis mucosa (M3 lesions) have an approximately 10% risk of nodal metastasis [81]. Patients who have found to have T1b disease after ESD should be referred for additional therapy such as esophagectomy or chemoradiation. Esophagectomy appears to be associated with better outcomes [82]. Endoscopic ablation of residual or multifocal dysplasia should be considered. All patients who undergo endoscopic therapy should be enrolled in a surveillance program including endoscopy every 3 months for the first year, then every 4–6 months for the next year and then annually [50]. Patients with multifocal disease, those who refuse endoscopic therapy or when endoscopic expertise is not available should be considered for esophagectomy.

cT1b and low risk cT2N0 lesions can be considered for esophagectomy [50]. Squamous carcinomas that invade beyond the upper third of the submucosa (200 µm) have a rate of lymph node metastasis between 36 and 55% [81]. cT1b patients who are deemed medically unfit for surgery

should be considered for endoscopic therapy with surveillance or definitive chemoradiation particularly if the margin is positive, there is lymphovascular invasion, tumors larger than 2 cm or is poorly differentiated [50, 81].

The morbidity of esophagectomy remains substantial and the patient's physiologic fitness for resection should be determined by an experienced esophageal surgeon. Common parameters include ECOG status, frailty, pulmonary function testing and cardiac risk stratification. Abstinence from tobacco and nicotine is crucial to minimize anastomotic and pulmonary complications. Common comorbidities including diabetes, chronic obstructive pulmonary disease and congestive heart failure should be optimized prior to considering esophagectomy [83]. Prehabilitation prior to surgery may reduce perioperative morbidity.

Esophagectomy can be performed using various techniques. The most common strategies include transhiatal, three field (Mckeown or modified McKweon) and two field (Ivor Lewis) esophagectomy. Transhiatal esophagectomy includes an abdominal approach and a cervical incision with a cervical esophagogastrostomy. Mckeown esophagectomy includes a right thoracic approach followed by an abdominal and left neck incisions with a cervical esophagogastrostomy. Ivor Lewis esophagectomy begins with an abdominal approach followed by a right chest approach with an intrathoracic esophagastrostomy. Adequate resection should include an abdominal and thoracic lymph node dissection. The addition of a cervical lymphadenectomy remains controversial. Each of these operative strategies can be conducted via an open (laparotomy and thoracotomy) technique or minimally invasive techniques. Minimally invasive esophagectomy (MIE) includes laparoscopy, thoracoscopy with or without robotic assistance. Minimally invasive approaches appear to have equivalent oncologic outcomes to open resection. MIE has been associated with lower rates of perioperative pneumonia [84]. The choice of resection should be predicated primarily on the location of the tumor. Distal esophageal tumors can be adequately resected via Mckeown or Ivor Lewis esophagectomies. Siewart III tumors that involve the gastric cardia typically require an Ivor Lewis approach or total gastrectomy. Tumors at or above the carina should treated with a three field approach to obtain an adequate proximal margin [85]. Extensive tumors that involve a both the stomach and esophagus can be treated with total esophagogastrectomy with colon interposition or jejunal interposition augmented by microvascular anastomosis [86].

Multi-modality Therapy

Cancers that are clinically more locally advanced—including high-risk T2N0 lesions and any N + tumors or cT3 or cT4a Nx tumors should undergo multi-modal therapy. The publication of the CROSS trial (Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study), in 2012, made neoadjuvant chemoradiation and surgery the standard treatment strategy for locally advanced esophageal carcinoma [87••]. However, 75% of patients in the CROSS trial had adenocarcinoma [87••]. Stahl et al. presented the results of 172 patients with locally advanced squamous cell cancer who were randomized to 40 Gy of chemoradiation followed by surgery or additional chemoradiation to 65 Gy. There was equivalent overall survival between the two treatment arms, with superior local progression in the surgical arm [88•, 89•]. FFCD 9102, a French study of 259 locally advanced thoracic esophageal carcinomas treated with induction chemoradiation and surgery or induction therapy followed by additional chemoradiation after randomization, revealed no significant difference in overall survival. This study consisted of 88.8% squamous cell carcinomas [90]. A Cochrane metaanalysis of these two studies concluded that esophagectomy after induction chemoradiation probably improved the rate of locoregional recurrence [90]. FFCD9102 has been criticized for failure to include EUS in all patients and some patients had a split course of radiation therapy in one of its treatment arms which has been shown to be inferior [91]. The total dose in that treatment arm was 30 Gy which is less than typical induction or definitive dosing. Also noteworthy was the exclusion of non-responding patients.. The surgical mortality reported by Stahl et al. was 11.3% which is higher than other more contemporary series, while FFCD 9102 reported a 9% (12/129) 3 month mortality (6 surgical complications, 3 disease progression and 3 other) which is concordant with current reports [92••, 93]. Other studies have confirmed the superiority of neoadjuvant chemoradiation to surgery alone for squamous cell carcinoma [94••, 95•]. The lack of modern randomized trials comparing definitive chemoradiation versus induction chemoradiation followed by surgery creates a therapeutic dilemma in medically fit patients. A network meta-analysis concluded that neoadjuvant chemoradation optimized the benefit of a multimodality strategy especially if low perioperative mortality can be achieved [96]. In a retrospective matched series from Memorial Sloan Kettering, Barbetta et al. demonstrated improved overall survival in patients who underwent chemoradiation followed by surgery compared to definitive chemoradiation [92••]. Recommendations differ between the National Comprehensive Cancer Network (NCCN) and European Society of Medical Oncology [50, 97]. NCCN recommends preoperative chemoradiation for non-cervical locoregional disease followed by surgery [50]. ESMO guidelines, which were last updated in 2016, state that neoadjuvant chemoradiation followed by resection is equivalent to definitive chemoradiation. The guidelines caution that esophagectomy should only be performed in high volume centers [97]. The Japan Esophageal Society guidelines recommend induction

chemotherapy followed by resection in medically fit patients; while stating that definitive chemoradiotherapy is also a potentially curative treatment strategy [98]. Treatment decisions should be made in the context of patient preference and available expertise.

Response to induction or definitive therapy can be difficult to accurately assess [99]. Many patients and physicians question the need for esophagectomy in patients with a complete clinical response. Piessen et al. recommended esophagectomy in patients with complete clinical response in a matched trial of predominantly squamous carcinomas citing better overall survival [99]. Conversely, in a group of 77 consecutive patients with squamous cell cancer who had a complete clinical response approximately half of the patients refused surgery or were unfit for surgery, no significant 5-year survival difference was identified. Ten patients in the observation group went on to have surgery later with eight of ten undergoing R0 resection with acceptable morbidity [100] The pathologic complete response rate was 64.4% and 69.2% in these two studies highlighting the inadequacies of restaging [99, 100]. In the CROSS patient cohort, the pathologic complete response rate after induction therapy was 23% for adenocarcinoma and 49% for squamous cell carcinoma [87••]. Comparatively fewer patients with locally advanced squamous cell carcinoma undergo induction chemoradiation and surgery compared to patients with adenocarcinoma of the esophagus. This may reflect therapeutic nihilism, the perceived morbidity of esophagectomy or improved response to chemoradiation seen in squamous carcinomas [92••, 93]. There is no consensus regarding the necessity of esophagectomy for squamous cell carcinoma. As surgical morbidity and mortality continues to improve, surgery may become more palatable. For patients who are at high surgical risk or refuse surgery, definitive non-operative therapy remains an excellent option. Early or late salvage procedures can be performed with acceptable results in patients with persistent or locally recurrent disease (see section on salvage esophagectomy below).

At the time of diagnosis, many patients may have a poor performance status secondary to malnutrition. In patients with significant dysphagia and weight loss, enteral feeding access may allow patients to tolerate induction or definitive therapy while maintaining their weight. Most surgeons recommend a feeding jejunostomy in surgical candidates in order to preserve the stomach for a gastric conduit; however, a feeding gastrostomy is not a contraindication to esophagectomy. Pull-through percutaneous endoscopic gastrostomy (PEG) should be avoided because of the high risk of tumor seeding of the gastrostomy site, which can approach 10% [101]. Patients with greater than 10% unintentional weight loss have decreased overall survival after esophagectomy but no difference in perioperative outcomes [102]. A multidisciplinary approach to treatment planning should occur at the time diagnosis with evaluation by all treating specialists including medical and radiation oncologists and surgeons. It is preferable to estimate suitability for resection prior to the initiation of therapy in order avoid a patient being deemed unfit for resection after receiving induction therapy instead of definitive therapy and therefore be undertreated. Induction chemoradiation dosing without surgery is associated with inferior rates of control [50]. Patients with marginal performance status should be re-evaluated after a short interval of nutritional therapy prior to initiation of therapy.

Treatment Regimens

Current NCRT protocols include: carboplatin 2 mg/ml/min area under the curve and paclitaxel 50 mg/m^2 and 41.4 Gy of concurrent radiation in 23 fractions over five weeks (CROSS) [87••]. NEOCRTEC5010 included vinorelbine 25 mg/m^2 and cisplatin75 mg/ m^2 with 40.0 Gy of concurrent radiation [94••]. The choice of chemotherapy agents continues to evolve is currently the subject of several clinical trials [103, 104]. Other regimens include fluorouracil and oxaliplatin [50]. ESCC patients are more likely to have complete pathologic response to neoadjuvant chemoradiation [105].

Definitive chemoradiation is recommended for patients who are not fit for or decline surgery but are candidates for curative treatment. Recommended radiation dose for the thoracic esophagus is 50–50.4 Gy given 1.8–2.0 Gy/day. The planned treatment field should include 3–4 cm proximally and distally, a 1 cm radially and 0.5–1.5 cm expansion around involved nodes. Nodal basins should be treated based on the location of the primary tumor [50]. Higher doses of radiation ranging from 50.4 to 64.8 Gy have been studied but data supporting a survival benefit are currently lacking [50, 106]. Preferred chemotherapy regimens include paclitaxel with carboplatin, fluorouracil with oxaliplatin or cisplatin [50]. Cervical and proximal tumors may be treated with higher doses of radiation when surgery is not planned. Patients with significant dysphagia undergoing definitive chemoradiation may benefit from enteral feeding access. Feeding gastrostomy is better tolerated than feeding jejunostomy. Pull-through percutaneous endoscopic gastrostomy (PEG) should be avoided because of the risk of tumor seeding of the gastrostomy site. Direct access gastrostomy or laparoscopic assisted gastrostomy should be performed [101]. Patients with persistent local disease after definitive chemoradiation may be reconsidered for salvage esophagectomy [107, 108].

Trimodality therapy was associated with a median overall survival of 49.4 months in CROSS trial and a greater than 50% 5-year survival for patients with squamous cell carcinoma receiving chemoradiation and

surgery [87••]. In a matched cohort of 112 patients with SCC, median overall survival was 2.3 years in the definitive CRT group and 3.1 years for trimodality therapy. 5-year overall survival was 29% for the definitive CRT patients and 45% for trimodality patients [92••]. In the NEOCRTEC5010 trial, patients receiving CRT followed by surgery had a median overall survival of 100.1 months and the 5-year overall survival exceeded 60% [94••].

Esophagectomy after Definitive Chemoradiation (Salvage Esophagectomy)

Current data support either neoadjuvant therapy followed by surgery or definitive chemoradiation for patients with locally advanced squamous cell carcinomas. Locally persistent or recurrence remains disease remains a frequent occurrence with frequencies as 60% [107]. A third treatment option is definitive chemoradiation and if there is persistent disease, consider esophagectomy if the patient is fit for surgery either within 6–12 weeks or after rehabilitation.

This is often termed salvage esophagectomy. Surgeons have traditionally been reluctant to offer salvage esophagectomy because of increased morbidity and mortality. A multi-center retrospective study in France compared salvage esophagectomy to post-induction chemoradiation patients, and found similar perioperative mortality but increased an anastomotic leak rate and surgical site infection with similar overall survival at 3 years. Patients with persistent disease had better survival than those with recurrent disease [108]. Meta-analysis of four studies with 219 patients revealed a survival benefit of salvage esophagectomy compared with second-line chemoradiation. Surgical mortality across these series ranged from 0 to 10% suggesting improvements in surgical and perioperative care [107]. In a recently published retrospective comparison of planned minimally invasive esophagectomy after induction therapy with salvage MIE, Broderick et al. reported no difference in perioperative outcomes including major complications, anastomotic leak and length of stay [109]. In the FFCD 9102 trial, 191 of 451 patients who did not respond to induction therapy were not randomized. Some of those non-responding patients were offered surgery based on investigator preference. The patients who underwent resection had superior survival compared to those patients who did not undergo resection and had equivalent survival to those patients were randomized in the original study (treatment responders) [110]. The data seem to support salvage esophagectomy in medically fit patients who had an incomplete response to chemoradiation.

Adjuvant Therapy

Although neoadjuvant chemoradiation is associated with improved survival compared to surgery alone, most patients do not have a complete pathologic response. Persistent disease especially in the lymph nodes is associated with decreased survival [111••]. Persistent nodal disease after induction chemoradiation and esophagectomy can be associated with a threefold risk of recurrence [112]. The efficacy of postoperative therapy for patients with residual disease has been the subject of debate with many retrospective series and large database studies showing benefit to adjuvant therapy [113, 114]. Many of these series have a predominance of adenocarcinoma. In a propensity matched study of 118 patients with squamous cell carcinoma who received neoadjuvant chemotherapy and resection, Yan et al. found no difference in disease-free survival or overall survival in the cohort that received adjuvant chemotherapy [115]. Conversely, other studies have found a benefit to adjuvant chemotherapy after induction chemotherapy [112]. A randomized controlled trial of 346 patients with squamous cell carcinoma evaluated the efficacy of preoperative versus perioperative chemotherapy. All patients received two cycles of paclitaxel, cisplatin and 5-fluorouracil prior to surgery and half of patients were randomized to receive two cycles after surgery. The group receiving adjuvant chemotherapy had an estimated improvement of 16% in 5 year survival [116].

Treatment strategies between the western countries and Asian countries differ regarding the use of induction chemotherapy alone versus chemoradiation. Definitive data has been lacking showing efficacy for post-operative adjuvant therapy. Kato et al. reported a survival benefit in patients previously treated patients with recurrent or advanced esophageal cancer who received the checkpoint inhibitor, nivolumab [117]. Checkmate 577 was randomized double-blind, placebo controlled trial of adjuvant nivolumab in patients with at least ypT1 or ypN1 disease after induction chemoradiation and R0 resection. Patients received either nivolumab or placebo for up to 1 year. There was an overall survival benefit to nivolumab for all patients. Squamous cell patients appeared to have a greater survival benefit compared to those with adenocarcinoma. The group of squamous carcinoma patients had a longer disease free interval in patients receiving nivolumab (29.7 months versus 11.0 months) [111••, 118]. Interestingly, nivolumab appeared to effective independent of tumor-cell PD-L1 expression [111••]. This study prompted the NCCN to recommend adjuvant nivolumab for all patients with residual disease after induction therapy and esophagectomy [50].

Advanced/Metastatic Disease and Palliative Therapy

Patients with locally advanced, metastatic disease or are not candidates for curative therapy should be considered for palliative therapy. This may include over 50% of patients diagnosed with esophageal cancer [119]. Therapy should be based on symptoms, patient preference and performance status. Guidance has been sparce regarding the optimal strategy and practice patterns vary [81]. Metastatic patients may be candidates for immunotherapy with or without cytotoxic chemotherapy and should be tested for PDL-1 overexpression [50, 120, 121]. The KEYNOTE-590 trial revealed that ESCC patients treated with pembrolizumab with high PD-L1 expression had the greatest survival benefit [121, 122].

Palliative external beam radiation can be beneficial for osseus metastases or severe dysphagia. Multi-disciplinary management of nutrition and pain should be considered for all patients. Dysphagia may be treated with self-expanding stents, external beam radiation, brachytherapy or endoscopic debulking. Tracheoesophageal fistula can be a devastating complication and is associated with poor survival. Distal feeding access should be considered.

Partially or fully covered stents may be the optimal therapy [119]. If an esophageal stent cannot be placed; a tracheal or bronchial stent may be an option. However, simultaneous tracheal and esophageal stents should be avoided, the radial force from both stents "kissing" can cause pressure necrosis and exacerbate the fistula.

Highly selected patients with oligometastatic disease may benefit from systemic therapy combined with local therapy to the metastases. Local therapy of the primary tumor including palliative resection or radiation has been associated with improved survival in appropriate patients [123].

Conclusions

Squamous cell carcinoma remains the most common type of esophageal cancer worldwide. Multi-disciplinary care should be utilized at all stages. Advances in diagnostic techniques and endoscopic therapy have revolutionized the treatment of early stage cancer. Multi-modal therapy with chemoradiation or neoadjuvant chemoradiation and surgery have become the treatment standards for locally advanced disease. Immunotherapy with PD-1 blocking antibodies are now indicated for metastatic and persistent disease and have been shown to be especially effective in high PD expressing tumors.

Declarations

Conflict of Interest John K. Waters declares that he has no conflict of interest. Scott I. Reznik is an investor/stockholder for OncoNano Medicine.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the authors.

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•• Of major importance

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