Esophageal Cancer: New Insights into a Heterogenous Disease

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Keywords

Esophageal cancer · Multimodal treatment · Chemoradiation

Abstract

Background: Esophageal cancer represents a heterogeneous malignancy mostly diagnosed in advanced stages. Worldwide, squamous cell carcinomas (SCCs) continue to be the most prevalent subtype; however, in the Western countries, the incidence of adenocarcinomas is increasing and will exceed that of SCC in the near future. During the last decade, several landmark trials contributed to a better understanding of the disease and emphasized the importance of multimodal treatment protocols. **Summary:** With the introduction of perioperative or neoadjuvant approaches, the survival of both subtypes of esophageal cancer has significantly improved. Several trials confirmed a survival benefit for perioperative chemotherapy or neoadjuvant chemoradiation, respectively, for patients with resectable locally advanced adenocarcinomas. However, the question of whether perioperative chemotherapy or neoadjuvant chemoradiation is more effective for the long-term survival in this population has yet to be fully elucidated. In SCCs, neoadjuvant chemoradiation followed by surgery or definitive chemoradiation in case of functional inoperability represent the preferred treatment options. Compared to neoadjuvant protocols, adjuvant chemotherapy or chemoradiation have only minor effects and are associated with enhanced toxicities. Current preclinical and clinical trials investigate efficacy

and tolerability of novel drugs aiming to modulate immune check-points and dual inhibition of HER2. In this “to-the-point” article, we review the current standard and summarize the most recent and encouraging therapeutic advances in esophageal cancer. Multimodal treatment approaches for esophageal cancer should be discussed in a multidisciplinary team based on histology, tumor localization, and patient performance status. Neoadjuvant chemoradiation is beneficial for patients with locally advanced SCC and adenocarcinomas of the esophagus and the gastroesophageal junction (GEJ), with perioperative chemotherapy representing a valid alternative for GEJ adenocarcinomas. Combination therapies are indicated for metastatic adenocarcinomas, while the benefit of palliative chemotherapy in SCC remains controversial. Trastuzumab is indicated in HER2+ metastatic adenocarcinomas.

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Epidemiology of Esophageal Cancer

Based on the most recent cancer statistics, in 2016, approximately 17,000 patients are being diagnosed with esophageal cancer in the US [1], 80% of them being male patients. The German cancer registry reports a similar incidence with 7,200 estimated new cases in 2016 and overall 5-year survival rates of 23% [2]. Worldwide, half a million patients with esophageal cancer is diagnosed each year resulting in more than 400,000 deaths per year [3]. Although the incidence of esophageal cancer is relatively

low compared to other gastrointestinal malignancies such as colon cancer, the mortality rate of approximately 93% reflects the appalling prognosis that has only marginally improved during last decades [1].

Esophageal cancer primarily occurs in elderly patients (peak age 65–70 years). Lifestyle factors including smoking, alcohol, obesity, and diabetes are regarded as important risk factors [4, 5]. Esophageal cancer can be classified into 2 different subtypes, squamous cell carcinoma (SCC), and adenocarcinoma. Worldwide, the incidence of SCC continues to be the leading malignancy of the esophagus especially in South-Eastern Asia, Eastern Africa, and Latin America. However, esophageal adenocarcinoma is exponentially on the rise in the Western world already exceeding the SCC rates in, for example, the Netherlands or the UK [6, 7].

While SCCs are more frequently diagnosed in the proximal and middle esophagus, adenocarcinomas exclusively originate from Barrett's mucosa in the distal part of the esophagus and the gastroesophageal junction (GEJ).

Disease Biology of Esophageal Cancer

Only few data exist on the pathogenesis of SCC. As mentioned above, risk factors include tobacco use, alcohol consumption, low social status, poor oral hygiene, and nutritional status. Mutations in enzymes which metabolize alcohol might influence the effect of the metabolite aldehyde, known as carcinogen [8]. Very recently, a Chinese group characterized 67 somatic genomes in SCC via whole-genome and whole-exome sequencing [9], followed by functional analysis. In this study, somatic mutations in several genes were identified, among them VANG-like planar cell polarity protein 1 and other coding and non-coding genes, which might play a role in driving tumor development by regulating proliferation, invasion, and metastasis. Interestingly, some events might be therapeutically targetable.

In esophageal adenocarcinomas and Barrett's mucosa, a couple of genome-wide association studies verified commonly occurring mutations in key genes such as *TP53*, *CDKN2A*, *SMAD4*, *ARID1A*, and *PIK3CA*, but also identified yet unknown loci in potentially tumor-relevant genes such as *MSR1*, *CRTC1*, *BARX1*, and *FOXP1* [10–12]. The Oesophageal Cancer Clinical and Molecular Stratification Consortium recently published a landscape of mutational patterns in adenocarcinomas, thereby clustering these patterns into 3 dominant subtypes [13], the DNA-damage-response (DDR)-impaired, the C>A/T dominant, and the mutagenic subtype. This classification

indicates the molecular heterogeneity within one histological entity. The strength of this work is the potential translation into practical treatment approaches based on the 3 subtypes. Whereas the mutagenic class might be susceptible to immunotherapy, the DDR-impaired and C>A/T dominant clusters could be candidates for platinum-based chemotherapy and receptor-tyrosine kinase inhibitors, respectively. Therefore, the distinct molecular characteristics within one histological subtype of esophageal cancer reflect the large heterogeneity in the clinical course of patients. It rather keeps challenging to implement preclinical achievements in routine patient care.

Multimodal Treatment

The majority of patients newly diagnosed with an esophageal cancer present with locally advanced or metastatic disease. Locally advanced stages are defined as T3/T4 tumors or tumors with positive regional lymph nodes. Based on anatomical characteristics of the esophagus, the lymphatic drainage strongly varies depending on cervical, thoracic, or abdominal localization of the tumor. Importantly, the current version of the TNM classification regards tumor spread into celiac lymph nodes of any primary localization as regional disease, thus allowing a curative therapeutic approach in these patients [14]. In contrast, positive supraclavicular lymph nodes are still categorized as distant metastases resulting in palliative treatment [14].

During the last decade, the concept of a multimodal therapy consisting of radiotherapy, chemotherapy, and surgery significantly improved the outcome of patients with esophageal cancer. Particularly noteworthy is the introduction of neoadjuvant treatment schedules in locally advanced disease. Generally, treatment options for patients eligible for multimodal therapies should always be discussed in a multidisciplinary team.

Perioperative and Neoadjuvant Chemotherapy followed by Surgery

Several studies evaluated the combination of perioperative chemotherapy followed by surgery in esophageal and gastric cancer (Table 1). However, in many of these studies, cancer of esophageal origin represented only a minority of the included cases, limiting the transferability of the results to esophageal cancer.

In 2002, the Medical Research Council Oesophageal Cancer Working Party presented a multicenter European

Table 1. Completed clinical trials for multimodal treatment approaches in advanced esophageal cancer

Authors	Year	Number of patients	Study design	Schedule	Histology	mOS	Survival rates	Specifics
Walsh et al. [54]	1996	103	Surgery vs. surgery + RCTx	Cisplatin + 5-FU + 40 Gy	103 (100%) adenocarcinoma	11.0 vs. 16.0	3-year: 6 vs. 32%	25% CR in RCTx group
Allum et al. [55, 56]	2002 and 2009	802	Perioperative CTx + surgery vs. surgery alone	Cisplatin + 5-FU	533 (66%) adenocarcinoma 247 (31%) SCC	16.8 vs. 13.3	5-year: 23 vs. 17.1%	Better survival across both subtypes
Burmeister et al. [57]	2005	256	Surgery vs. surgery + RCTx	Cisplatin + 5-FU + 35 Gy	158 (62%) adenocarcinoma 95 (37%) SCC 3 (1%) others	19.3 vs. 22.2		TTP: 12.0 vs. 16.0 SCC: $p = 0.014$
Tepper et al. [58]	2008	56	Surgery vs. surgery + RCTx	Cisplatin + 5-FU + 50.4 Gy	14 (25%) SCC 42 (75%) adenocarcinoma	21.5 vs. 53.8	5-year: 16 vs. 39%	mPFS: 12 vs. 42 33.3% CR in RCTx group
Yang et al. [59]	2012	123	Surgery vs. surgery + RCTx	Vinorelbine + cisplatin + 40 Gy	123 (100%) SCC		2-year: 66 vs. 79%	30% CR in RCTx group R0 96%
Mariette et al. [60]	2014	195	Surgery vs. surgery + RCTx	Cisplatin + 5-FU + 45 Gy	137 (70%) SCC 57 (29%) adenocarcinoma 1 (0.5%) other	41.2 vs. 31.8	3-year: 53 vs. 47.5%	Mortality 11.1% in RCTx arm after surgery 33.3% CR in RCTx group
Shapiro et al. [61]	2015	366	Surgery vs. surgery + RCTx	Carboplatin + paclitaxel + 41.4 Gy	84 (23%) SCC 275 (75%) adenocarcinomas 7 (2%) others	24.0 vs. 48.6	5-year: 33 vs. 47%	mOS SCC: 81.6 mOS adeno: 43.2

study investigating the impact of perioperative chemotherapy (2 cycles of cisplatin 80 mg/m² d1 plus 5-FU 1,000 mg/m² daily as a continuous infusion over 96 h every 3 weeks) with surgery vs. surgery alone in 802 patients [15]. Among the study cohort, 10% of patients had cancer of the GEJ, 90% had esophageal cancer, two-thirds of which were adenocarcinomas. By adding chemotherapy, R0 resection rates (60 vs. 54%, $p < 0.0001$) and median overall survival (OS) were significantly improved (16.8 vs. 13.3 m, hazards ratio [HR] 0.79, $p = 0.004$). Subgroup analysis provided evidence that patients with adenocarcinomas had the greatest benefit from perioperative chemotherapy. This translated also into a long-term survival advantage with 5-year survival rates of 23.0% for neoadjuvant chemotherapy vs. 17.1% ($p = 0.03$) for surgery alone [17].

Another important study in this context was published by Cunningham et al. [18] (participants in the Medical

Research Council Adjuvant Gastric Infusional Chemotherapy/MAGIC) in 2006. Although in this trial the large majority of patients had GEJ and stomach cancer, some patients with adenocarcinomas of the esophagus were included. Esophageal and GEJ cases accounted for approximately 26% of the total study population. Although no subgroup analysis was performed, all patients benefited from perioperative treatment with the ECF regimen (epirubicin, cisplatin, 5-FU; 3 cycles – surgery – 3 cycles) compared to surgery alone. PFS and OS were significantly improved and 5-year survival rates showed a robust survival benefit after perioperative chemotherapy (23 vs. 36%). It has been speculated that the neoadjuvant part of the perioperative protocol was mainly responsible for the survival benefit, since only 42% of the patients completed the whole protocol and 34% of patients did not receive any adjuvant treatment at all. Based on these results, Pennathur

et al. [19] assessed the neoadjuvant efficacy of a different chemotherapy regimen (cisplatin + 5-FU + paclitaxel) in surgically resectable locally advanced esophageal carcinoma patients. Although this study was a phase II trial without control arm, the survival data of the entire cohort (70 patients, 4 SCC, 66 adenocarcinomas) showed comparable results with a median OS of 27.4 months. Of note, patients with a response to the preoperative chemotherapy showed the most pronounced survival benefit. This long-term survival benefit was also supported by a French multicenter phase III trial, which showed improved 5-year survival rates of 34% after perioperative chemotherapy (5-FU and cisplatin) followed by surgery vs. surgery alone (19%) in a patient population comprising mainly distal esophageal or GEJ adenocarcinomas [20].

Based on these data, the positive effect of perioperative/neoadjuvant chemotherapy is undisputed in patients with esophageal or GEJ adenocarcinomas [21, 22]. However, in patients with SCC of the esophagus (SCC) a consistent benefit of chemotherapy alone without the addition of radiotherapy is controversial and currently does not represent the standard of care [23].

Adjuvant Treatment

If adjuvant treatment is considered in patients with esophageal cancer, 2 major issues must be taken into account: First, the complete resection of the tumors is prerequisite which is, however, only reached in 50–75% [24]. Second, due to significant postoperative morbidity, only patients with adequate performance status are candidates for adjuvant therapy. Based on the currently available data, for patients with SCC, no positive recommendation is given for adjuvant chemotherapy, radiotherapy, or chemoradiation [25]. The situation in patients with adenocarcinomas of the esophagus is more complicated. The GASTRIC group published a meta-analysis favoring adjuvant chemotherapy with a significant OS benefit (HR 0.82), but the absolute risk reduction for death after 5 years was only 5% (49.6 vs. 55.3%) [26]. Based on the robust survival data obtained by the neoadjuvant/perioperative approaches and the better tolerability of systemic therapy when given preoperatively, neoadjuvant approaches should be given priority. However, in patients with risk factors such as positive lymph nodes after resection, who did not receive preoperative treatment and have an adequate postoperative performance status, adjuvant therapy (chemotherapy or chemoradiation) can be considered and should be discussed on an individual basis in a multidisciplinary team.

Neoadjuvant or Definitive Chemoradiation

Several trials assessed the role of neoadjuvant chemoradiation followed by surgery vs. surgical resection only (Table 1). Older studies showed ambiguous results based on different chemotherapy backbones and variable radiation modalities. A meta-analysis published in 2007 revealed a better prognosis for patients with esophageal cancer treated with chemoradiation before surgery in both SCC and adenocarcinomas [27]. Recently, a new meta-analysis by Kumagai et al. [28] confirmed these results. Chemoradiation can lead to preoperative complete response rates in up to 30% of the patients, which is a strong surrogate parameter of OS. Additionally, chemoradiation facilitates R0 resections and reduces the risk for locoregional recurrence. A milestone trial in this context was published by the CROSS group in 2012 and updated in 2015 including long-term results [24, 29]. In this study, only patients with resectable, locally advanced esophageal, or GEJ cancer were included. Both patients with SCC and adenocarcinoma had significant benefits from neoadjuvant chemoradiation followed by surgery compared to surgery alone with median survival rates of 81.6 and 43.2 months, respectively (compared to 21.1 and 27.7 months, respectively). Based on these data, the study group proposed to use neoadjuvant chemoradiation as the standard of care in all patients who had locoregionally advanced esophageal cancers.

Recently, a multicenter trial compared chemoradiation vs. chemotherapy as a neoadjuvant approach [30]. Although the primary study end point with histological complete responses was reached in favor of chemoradiation, no difference in OS could be shown. The addition of radiation did not influence the surgical outcome. However, more severe complications occurred in the group with radiation plus chemotherapy.

Based on these data, neoadjuvant chemoradiation represents the standard therapy for advanced SCC. To date, it remains to be clarified if neoadjuvant chemoradiation is also indicated for esophageal or GEJ adenocarcinomas. Head-to-head comparisons with newer chemotherapy combinations and state-of-the-art radiation techniques are still pending. In this context, Stahl et al. [31] evaluated patients specifically with GEJ adenocarcinomas using a protocol that started with a lead-in phase of 2 cycles of cisplatin and 5-FU/leucovorin (PLF) followed by either another cycle of PLF and surgery or the combination of chemoradiation (cisplatin and etoposide) and subsequent surgery. Unfortunately, the study was closed early due to poor accrual. However, there was a trend favoring

Fig. 1. Therapeutic algorithm in patients with resectable esophageal cancers. * Applies for squamous cell carcinomas (SCCs); 1: perioperative chemotherapy for adenocarcinoma of the esophagus; 2: neoadjuvant radiochemotherapy for adenocarcinomas or SCCs; 3: for SCCs, especially of proximal location.

upfront chemoradiation resulting in improved 3-year survival rates of 47.4 vs. 27.7%. Further studies are urgently needed to definitely address the role of neoadjuvant chemoradiation vs. chemotherapy in esophageal or GEJ adenocarcinomas.

Long-term survival data for definitive chemoradiation indicate 5-year survival rates up to 35% [32, 33]. For SCC, definitive chemoradiation is not inferior compared to chemoradiation followed by surgery [34]. Although locoregional control was improved after chemoradiation followed by surgery vs. chemoradiation alone, the 10-year survival rates were not significantly different (19 vs. 12%) [35]. Definitive chemoradiation without subsequent surgery might also be a choice in patients with cervical location of the disease in order to avoid laryngectomy for reasons of quality of life in patients with non-resectable tumors or in non-operable patients.

The current treatment algorithms for resectable esophageal cancer are depicted in Figure 1 in accordance with the recently published European guidelines [36].

Palliative Treatment in Metastatic and Recurrent Disease

The majority of patients with esophageal cancer suffers from metastatic disease at time of diagnosis or will experience disease recurrence after surgery or definitive chemoradiation. In this setting, extension of life time is as equally important as maintaining a satisfactory quality of life. Thus, palliative therapy also includes a comprehensive pain and nutrition management as well as a psycho-oncological service.

For SCC, palliative chemotherapy remains controversial. Currently, no significant benefit in OS has been demonstrated with palliative chemotherapy regimens [37]. However, palliative radiotherapy in combination with chemosensitizing chemotherapy or local radiotherapy applied as brachytherapy might be indicated to alleviate dysphagia, pain, or bleeding complications. Moreover, obstructive symptoms can be palliated by endoscopic placement of self-expanding metal stents. The indication for all treatment approaches is based on the severity of local complaints.

More positive data exist for the palliative treatment of patients with esophageal adenocarcinoma and GEJ. As demonstrated in previous studies with gastric and GEJ adenocarcinomas, the HER2 status allows an individualized therapy in patients with metastatic disease. HER2 positive tumors (IHC score 2 or 3 or FISH positive) better responded to a chemotherapy doublet in combination with trastuzumab compared to chemotherapy alone [38]. Interestingly, the HER2 positivity is higher in patients with GEJ tumors compared to gastric cancer (32.2 vs. 21.4%) [39]. The backbone of chemotherapy typically includes a combination of a platin- (cisplatin/oxaliplatin) and fluoropyrimidine-derivates (5-FU/capecitabine). If patients are not suitable for the targeted therapy with trastuzumab, a chemotherapy combination consisting of 2 or 3 active substances is feasible. Beside established platinum/5-FU combinations regimens including PLF, FLO, XP, and FOLFOX, triplets including epirubicin (ECF, EOF, ECX, EOX) or docetaxel (DCF, FLOT) or doublets including irinotecan (FOLFIRI) have been evaluated in the first-line setting [40–46]. The choice of therapy mainly depends on clinical parameters, particularly age, performance status, and remission pressure. After

Fig. 2. Therapeutic algorithm for first- and second-line treatment in advanced, meta-static, or recurrent disease.

Table 2. Ongoing phase III trials in esophageal cancer

Identifier	Estimated enrollment	Histology	Stage	Study design	Sequence	Target
NCT02611700	504	SCC	Metastatic	Paclitaxel + cisplatin vs. paclitaxel + cisplatin + nimotuzumab	First-line	EGFR
NCT02677597	268	SCC	Metastatic	Cisplatin + S1 vs. cisplatin + paclitaxel	First-line	
NCT02564263	600	SCC and adenocarcinoma	Advanced/metastatic	Pembrolizumab vs. docetaxel/paclitaxel/irinotecan	Second-line	PD-1
NCT01726452	366	Distal esophageal adenocarcinoma, AEGI	cT2-3, N+, M0	MAGIC vs. CROSS	Multimodal neoadjuvant perioperative	
NCT02625623	330	AEGI, gastric cancer, adenocarcinoma	Unresectable, recurrent, metastatic	Avelumab vs. BSC/paclitaxel/irinotecan	Third-line	PD-L1
NCT02314117	616	AEGI, gastric cancer, adenocarcinoma	Metastatic	Capecitabine + cisplatin vs. capecitabine + cisplatin + ramucirumab	First-line	VEGFR
NCT02509286	438	Esophageal + AEGI	cT1, N+, M0 cT2-4a, N0/+, M0	FLOT vs. CROSS	Perioperative neoadjuvant	

failure of first-line therapy, several treatment options are available in clinical practice. Monotherapies with taxanes (docetaxel, paclitaxel) and irinotecan [47–50] can be applied. Recently, the anti-angiogenic monoclonal antibody, ramucirumab, directed against the VEGF receptor-2, showed consistent improvements in survival as single agent (REGARD trial) and in combination with paclitaxel (RAINBOW trial) in patients with GEJ and stomach cancer [51, 52]. Both trials introduced ramucirumab as a new targeted therapy, which is not restricted to the HER2 status and therefore ubiquitously applicable.

Ramucirumab monotherapy was well tolerated as an infusion treatment every 2 weeks with a median OS of 5.2 months. The addition of paclitaxel increased the survival to 9.6 months but was associated with more side effects. However, very recently, the multicenter US study by Yoon et al. [53] elucidated mFOLFOX6 with ramucirumab in a phase II trial. Half of the patients had advanced esophageal adenocarcinomas (48%); however, the primary end point to increase PFS was not met. Thus, the role of ramucirumab is not fully understood in esophageal adenocarcinomas and may depend on the chemotherapy

backbone. The current treatment algorithms or advanced esophageal cancer are summarized in Figure 2 in accordance with the current ESMO guidelines [36].

Perspectives

The therapy of esophageal cancer is increasingly complex involving multimodal therapy algorithms requiring close interactions within a multidisciplinary team including surgeons, radiotherapists, gastroenterologists, and oncologists. During the next decades, the incidence of adenocarcinomas of the GEJ will significantly increase, posing a great challenge for prevention, early detection, and optimal multimodal therapy.

One important issue which remains to be elucidated in esophageal adenocarcinoma is the questions of whether neoadjuvant chemoradiation is superior or not compared to chemotherapy alone (Table 2). In this context, 2 ongoing studies are of great interest, which evaluate the CROSS chemoradiation protocol vs. the MAGIC and the FLOT chemotherapy protocols (NCT01726452; NCT02509286). Furthermore, the increasing molecular understanding and new diagnostic tools will help to guide patients for specific, individualized therapies. Future studies in metastatic disease focus on further targeted therapies including pertuzumab, an inhibitor of HER2 dimerization, which might act synergistically with trastuzumab

(NCT01774786). Finally, immunotherapeutic approaches are entering the stage and will most likely expand the armamentarium for patients with gastric and GEJ cancer. Currently, checkpoint inhibitors such as pembrolizumab, avelumab, and nivolumab are being tested in different palliative treatment lines (+/- chemotherapy) and in the adjuvant setting. First results are eagerly awaited to further potentially improve the spectrum of effective treatments and to improve the still appalling prognosis of advanced esophageal cancer.

Key Points

1. Multimodal treatment approaches should be discussed in a multidisciplinary team based on histology, tumor localization, and patient performance status.
2. Neoadjuvant chemoradiation is beneficial for patients with locally advanced SCC and adenocarcinomas of the esophagus and GEJ with perioperative chemotherapy representing a valid alternative for GEJ adenocarcinomas.
3. Combination therapies are indicated for metastatic adenocarcinomas while the benefit of palliative chemotherapy in SCC remains controversial. Trastuzumab is indicated in HER2+ metastatic adenocarcinomas.
4. VEGFR2-blockade with ramucirumab represents a novel second-line option in metastatic adenocarcinomas.

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