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Esophageal cancer: the latest on chemoprevention and state of the art therapies

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Abstract

Esophageal cancer is currently the 8th most common cancer worldwide and the 6th leading cause of cancer-related mortality. Despite remarkable advances, the mortality for those suffering from esophageal cancer remains high, with 5-year survival rates of less than 20%. In part, because most patients present with late-stage disease, long-term survival even after resection and therapy is disappointingly low. As we will discuss in this review, multiple characteristics specific to the disease stage and patient must be considered when choosing a treatment plan. This article will summarize current standard therapies, potential application of chemoprevention drugs and the promise and partial failure of personalized medicine, as well as novel treatments addressing this disease.

Introduction

Esophageal cancer is currently the 8th most common cancer worldwide and the 6th leading cause of cancer-related mortality (1–3). This year, an estimated 17,000 adults (13,500 men and 3,500 women) in the United States will be diagnosed with esophageal cancer. It is expected that almost 16,000 deaths from this disease will occur this year. In the period from 2005–2011 the 5-years survival was 17.9 % according to the SEER Cancer Statistics review.

As we will discuss in this review, multiple characteristics specific to the disease stage and patient are considered when choosing a treatment plan. With incidence rates rising and the 5-year survival being stagnant at below 20%, we must develop better diagnostics and therapies. In part, because most patients present with late-stage disease, long-term survival even after resection and therapy is disappointingly low. For advanced cancer, multimodal therapy such as chemoradiation or combination chemotherapy are the current standards. Yet,

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targeted therapies, e.g. against the programmed cell death protein 1 signaling pathway (PD1-PDL1), a so-called immune checkpoint, show promise.

Upon review of clinical presentation and diagnosis, we will focus on standard therapies and the promise of personalized medicine and novel treatments addressing this devastating disease.

Epidemiology

Two major histological subtypes arise: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). Overall, esophageal cancer incidence is three times higher in men than women and varies geographically by subtype (3).

ESCC

ESCC prevalence is highest in East Asia, Eastern and Southern Africa and some parts of Europe (4). ESCC incidence has decreased over the past three decades in developed countries, where annual incidence rates are generally less than 10 per 100,000 per year (5), on the other hand, ESCC incidence has remained high in less-developed countries with incidence rates exceeding 100 per 100,000 per year, particularly in high-risk areas of China (6), Iran (7,8) and South Africa (9). The use of tobacco products, including cigarettes, cigars, pipes, and chewing tobacco, is a major risk factor together with alcohol consumption for developing esophageal cancer (10, 11). ESCC is also a disease with health disparities affecting more black males in Western countries and the United States, especially in the context of high risk behavior (12).

EAC

With ESCC rates declining, EAC now constitutes half of the esophageal cancer cases in Western countries (13). The increased incidence rates are a reflection of life-style changes leading to high rates of obesity and acid reflux, major factors contributing to Barrett's esophagus, a premalignant lesion, which predisposes the patients for a higher risk of developing EAC (14). Overall, incidence rates rise steadily with advancing age (15). A meta-analysis of population-based studies showed a 5-fold increased risk for EAC for weekly acid reflux symptoms (16). Obesity, in particular a body mass index of >30 is associated with an approximate 2-fold increased risk for EAC (17). Strong epidemiologic risk factors include aging, male gender, obesity and smoking (18). The regional differences observed in the incidence of EAC indicate that race is a strong risk factor for EAC. In the United Kingdom, the incidence of EAC is much lower among people of Asian and African descent compared with Caucasians (19). In the United States, Asian and African Americans have a greatly decreased risk of EAC compared with non-Hispanic white people, with white Hispanics having an intermediate risk (20).

Clinical Diagnosis and Presentation

The clinical presentation of patients with esophageal cancer can be attributed to the direct effects of tumor growth on local and regional structures. Both, ESCC and EAC show similar manifestations, such as difficulties swallowing (dysphagia) being the most common

symptom. Dysphagia initially occurs upon ingestion of dense solid food, and progresses gradually to interference with the consumption of soft foods and ultimately even liquids. Pain is a common symptom even in the absence of dysphagia, so is weight loss, which correlates with the occurrence of tumor-related anorexia (21).

Imaging modalities such as endoscopy, endoscopic ultrasonography, narrow band imaging or computed tomography and others are used in the diagnosis and staging of ESCC. Endoscopic screening as well as brush cytologic testing has been performed in China for patients with mild, moderate and severe dysplasia who have an increased risk of developing squamous cell carcinoma (22). Screenings can prevent progression to more aggressive tumor growth and thereby aid the reduction of mortality (23).

As Barrett's esophagus is considered a risk factor for esophageal adenocarcinoma, patients with gastroesophageal reflux diseases (GERD), who are at risk for high grade dysplasia of Barrett's esophagus, undergo endoscopy for screening (24). Barrett's esophagus patients undergo surveillance endoscopy yet less than 15% of EAC are detected and most Barrett's patients will never progress to develop esophageal adenocarcinoma (25). Subjecting biopsy material to next-generation sequencing has been shown to identify patients with Barrett's esophagus who might have an increased risk for EAC, based on common mutations for example in tumor suppressors such as TP53, as well as APC and CDKN2A (26). So far, screening, counseling on lifestyle changes and preventative treatments are recommended (27, 28).

Prevention

Acid reflux is a risk factor for Barrett's esophagus and for the progression to esophageal cancer. Therefore, the use of proton pump inhibitors is recommended for the reduction of gastric acid production. Yet, recent studies also found a reduction in cancer risk in people with Barrett's esophagus who take aspirin or similar. Some studies identified statins, which are commonly used to treat high cholesterol, to be effective in lowering cancer risk but are not prescribed as a preventative as they have serious side effects.

Proton Pump Inhibitors (PPI)

Proton pump inhibitors reduce stomach acid secretion through inhibition of the H⁺/K⁺-ATPase in the stomach. This treatment targets patients with GERD as a risk factor for Barrett's esophagus and esophageal adenocarcinoma. A significant association of PPI treatment with a decreased risk of high-grade dysplasia and adenocarcinoma has been shown in clinic-based cohort studies for patients with Barrett's esophagus (29–31). The indirect evidence supporting PPIs as a cancer-preventative promises a cost-effective treatment for all patients with Barrett's esophagus after they have been informed of the potential risks of long-term PPI therapy (32). There is some controversy as prolonged PPI use possibly promotes progression to EAC through increased gastric pH associated with bile salt toxicity (33).

Aspirin and NSAIDs

Results from observational studies demonstrated a protective association between aspirin or non-steroidal anti-inflammatory drugs (NSAID) and esophageal cancer (34), which prompted a large ongoing randomized, phase III study of aspirin and esomeprazole, a PPI, in the prevention of esophageal cancer in patients with Barrett's esophagus. Long-term data are needed on the use of aspirin in Barrett esophagus patients. The ongoing AspECT trial will be completed in 2017 and will give more information on clinical outcomes. Aspirin has been proven effective as an analgesic and anti-inflammatory agent. Inflammation is frequently associated with tumorigenesis, and inflammatory cells are often seen in Barrett's esophagus as a result of COX-2 upregulation. Furthermore, inflammatory signaling through IL-6 and IL-1 β can be induced in response to acid reflux (35). However, aspirin is a key antiplatelet drug in the pharmacological prevention of cardiovascular diseases at low doses, with the caveat that it could put patients at risk for gastrointestinal bleeding due to damage of the mucosa (36). Recently, a study using an acute animal model of reflux esophagitis, which mimicks the esophageal injury of acid reflux, has shown that nitric oxide derivatives of aspirin exerted protective effects against reflux disease, while conventional NSAIDs like aspirin augmented esophagitis (37).

Statins

Considerable research has focused on the potential anti-cancer effects of statins (3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase inhibitors) (38). Commonly prescribed for the primary and secondary prevention of cardiovascular disease (39), recent research studies have demonstrated that statins promote apoptosis and limit proliferation in EAC and ESCC cell lines (40–43). In Denmark, a population-based cohort showed that statin use prior to diagnosis of esophageal cancer was associated with a 19% decrease in cancer-specific mortality (44).

Observational studies have demonstrated that statin use in Barrett's patients is associated with a lower incidence in EAC (45, 46). Multivariable-adjusted hazard ratios were 0.85 for death unrelated to cancer (95% confidence interval [CI], 0.83 to 0.87) and 0.85 for cancer-related death (95% CI, 0.82 to 0.87) for statin users, when compared with patients who had never used statins (44). A cohort study conducted in the UK reported an increased median survival of 14.9 month in subjects treated with statins after diagnosis compared to 8.1 month in non-users. However, while patients with esophageal adenocarcinoma had a reduced risk of esophageal cancer-specific mortality (HR, 0.61; 95% CI 0.38–0.96) and all-cause mortality (HR, 0.63; 95% 0.43–0.92) upon statin use after diagnosis, no such effect was observed for ESCC (47).

Antibacterial drugs

The normal esophageal microbiome is composed of six major phyla (Firmicutes, Bacteroides, Actinobacteria, Proteobacteria, Fusobacteria, and TM7) and is dominated by the genus *Streptococcus* (48). The microbiome of the distal esophagus can be classified into two groups, type I and type II (49).

The type I microbiome is composed primarily of Gram-positive bacteria and is more closely associated with a normal esophagus whereas the type II microbiome is enriched with Gram-negative bacteria and is generally associated with an abnormal esophagus. *Streptococcus* is the most dominant genus in the esophageal microbiome and its relative abundance is significantly higher in the type I microbiome than in the type II microbiome. GERD plays a role in the change of the esophageal microbiome as acidic gastric juice can convert the type I microbiome into the abnormal type II microbiome by killing acid-sensitive bacteria in the esophagus. The use of proton pump inhibitors therefore acts on several levels of chemoprevention: inhibiting acid-related injury, and preventing changes in the microbiome (50, 51). The changes in the microbiome hint at a potential use of antibiotics in the chemoprevention of esophageal adenocarcinoma. However, conversion of the altered “back to a normal” microbiota has not been tested yet. Invasion of pathogens is met with the innate immune response upon sensing of a variety of microbial components through Toll-like receptor (TLR) signaling. Due to the evidence for activation of the TLR-NF- κ B pathway, which is responsible for the host immune and inflammatory response to bacterial stimuli, it is plausible to utilize anti-inflammatory strategies in chemoprevention of esophageal adenocarcinoma, even in the context of microbial immune modulation. However, as little is known about the mechanisms of controlling the microbiome, more research in this area is warranted.

Tumor Staging

The stage of esophageal cancer is determined by the depth of infiltration of the tumor into the esophageal wall (T stage), by the presence of tumor cells in regional lymph nodes (N stage) and by distant metastases (M stage) (52). Imaging techniques such as endoscopic ultrasonography and ^{18}F -fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) have helped improve staging and detect the status of tumor and lymph-nodes infiltration with a relatively good accuracy (53, 54). In addition, the combination of computed tomography (CT) and FDG-PET can guide surgical decision making (55, 56). Current standard therapy for Stage I esophageal cancer, in which the tumor is localized to the esophagus is chemoradiation followed by surgery or surgery alone, while patients with advanced tumors (Stage IV), where the cancer has spread, will additionally undergo post-operative radiation therapy.

Esophageal squamous cell carcinoma and esophageal adenocarcinoma are now considered separately. EAC staging is based on its anatomical specificities as it is now included in a subset of tumors originating in close proximity to the gastro-esophageal junction (57, 58), Figure 1. Ultimately, the staging will determine the choice treatment.

Treatment

Much effort has been dedicated to improving treatment of patients suffering from ESCC and EAC. Treatment of esophageal tumors has traditionally involved surgery and esophagectomy, which is associated with a high risk of morbidity in elderly patients and patients suffering from concomitant diseases. Improvement in staging and in the evaluation of a patient's fitness for resection have reduced the perioperative risks, while the experience

of physicians and high volume center are strongly associated with better surgery outcome (59).

Ablation therapies such as radiofrequency ablation and photodynamic therapy are the new standard to treat patients with Barrett's esophagus or esophageal dysplasia. Endoscopic mucosal resection and submucosal dissection have been shown as effective and safe new methods to remove small and superficial lesions (60).

Aside from surgical resection the treatment options for advanced stage cancer have been limited to chemoradiotherapy as an alternative for patients unable to receive surgery. Combination of radiation and chemotherapy may be associated with improved survival if used in early stages of esophageal cancer (52, 61). The benefit of neoadjuvant chemoradiation at later stage remains unclear (62). To improve survival outcomes adjuvant or neo-adjuvant therapies are used in association with surgery. Chemotherapy is more often used in Europe and Asia, while chemoradiation is preferred in the United States. Combination treatments are standard therapy now as intensifying conventional chemotherapy drugs or increasing radiation dose have not been successful.

Multimodal treatment for ESCC

Data on neoadjuvant radiotherapy are controversial as compared to surgery alone a meta-analysis of the literature reported only a limited effect (63), while neoadjuvant radiotherapy before esophagectomy has been associated with increased overall survival (64).

The aim of chemotherapy is to reduce tumor size prior to surgery and target micrometastasis to avoid tumor spread. Chemotherapy, however, is associated with toxicity and the risk of selecting drug-resistant clones and delaying surgical treatment. Prior to surgery, chemotherapy has been shown to provide an overall and disease-free survival benefit over surgery alone as reported in a meta-analysis based on 12 randomized trials (65). E.g., preoperative chemotherapy using two cycles of cisplatin and fluorouracil improved survival for patients with resectable esophageal cancer (66), yet the overall benefit of neoadjuvant or adjuvant treatments over surgery is still unclear in the case of resectable ESCC (67). While few studies have shown a small benefits of the adjuvant treatment, but the effect on 5-year overall survival has not been consistently demonstrated (67–71). Similarly, overall survival after neoadjuvant chemotherapy versus upfront surgery for patients with late stage ESCC has not been demonstrated (72). Interestingly, immediate surgery might hold better outcome over neoadjuvant chemotherapy or definitive chemoradiotherapy for patients with stage III disease (73).

Multi-modal treatments for EAC and tumors of the gastro-esophageal junction (GEJ)

Due to the difficulty of conducting large scale studies, the benefit of neoadjuvant chemoradiotherapy or chemotherapy over surgery alone has remained controversial in esophageal adenocarcinoma for a long time (74). Recently, however, several studies have shown a consistent benefit of combining multimodal treatments, notably in the MAGIC trial, which was conducted using established guidelines for the administration of perioperative chemotherapy (cisplatin, 5-fluorouracil (5-FU), and epirubicin) in the surgical management of lower esophageal cancer; as well as in the "Chemoradiotherapy for Oesophageal Cancer

Followed by Surgery Study” (CROSS) (75–78). Similar effects were earlier demonstrated by Tepper et al., although the number of patients enrolled was low (79).

In a follow up to the CROSS study, Oppedijk et al. reported that patients who received chemoradiation therapy had reduced locoregional recurrence (80). This has been confirmed in a recent article by Thoen et al. showing low recurrence when neoadjuvant chemoradiotherapy was followed by surgery (81).

Positron emission tomography (PET): A role in evaluating prognosis

Positron emission tomography (PET) is considered as a method to evaluate the response to chemotherapy in ESCC. The maximum standard uptake value (SUV_{max}) together with the tumor/normal esophageal ratio could be used to evaluate the effect of neoadjuvant chemotherapy (82). Additionally, [(18)F] fluorodeoxyglucose (FDG)-PET positive lymph node analysis can be used to predict survival of patients who underwent neoadjuvant chemotherapy (83). Additional factors predicting outcome of neoadjuvant therapy can be found in a recent review by Tao et al. (84).

Chemotherapy advances: Improvements of the classics

Management of esophageal cancer has evolved to include new chemotherapy regimen, multi-model treatments and promising new approaches such as immunotherapy. However, most of the current protocols are based on novel combinations of standard chemotherapy drugs such as cisplatin and 5-Fluorouracil.

Cisplatin (Platinol), *SP-4-2*)-diamminedichloroplatinum(II), was the first member of a class of platinum-containing anti-cancer drugs, which now also includes carboplatin and oxaliplatin (Eloxatin). It is also called the “penicillin of cancer” because of its wide-spread use. Cisplatin interferes with DNA replication and kills the proliferating cells, representing in theory the bulk of the tumor cells. Following administration, one of the two chloride ligands is slowly displaced by water during aquation, *cis*-[PtCl(NH₃)₂(H₂O)]⁺. Dissociation of the chloride ligand is favored due to gradients between the intra- and extracellular chloride concentration (85).

Newer platinum-based drugs were introduced in the 1980s and show fewer side effects, such as nephrotoxicity, ototoxicity, nausea and vomiting. Oxaliplatin (Eloxatin), [(1*R*,2*R*)-cyclohexane-1,2-diamine](ethanedioato-*O*,*O'*)platinum(II), a new platinum-based drug, is frequently used in combination with other drug to achieve synergistic effects. Together with folinic acid (Leucovorin) and 5'FU, oxaliplatin is known as FOLXFOX, a combination chemotherapy regimen used as first line treatment in advanced and metastatic esophageal cancer. Positive outcomes of oxaliplatin/fluoropyrimidine-based combinations have spurred further testing of these regimens.

5-Fluorouracil, (5-FU or Adrucil), 5-Fluoro-1*H*,3*H*-pyrimidine-2,4-dione, is a pyrimidine analog, member of the anti-metabolite class of drugs, which irreversibly inhibits thymidylate synthase. By blocking thymidylate synthase, which is required for methylation of deoxyuridine monophosphate (dUMP) to form thymidine monophosphate (dTMP), it prevents synthesis of the pyrimidine thymidine needed for DNA replication. Administration

of 5-FU reduces dTMP, thereby inducing cell death (86). Biomedical modifications and pharmacomodulation resulted in increased therapeutic efficacy over a drug that has been reported first in 1957 as a new class of tumor inhibitors. Other pyrimidine antagonist are Foxuridine, Cytarabine, Capecitabine, and Gemcitabine. Combination of 5-FU with folinic acid (leucovorin) has been shown to have synergistic effects as adjuvant chemotherapy. Folinic acid is a folate, which constitutes a group of vitamins. It enhance the binding of 5-FU to thymidylate synthase increasing its action in the cell (87). A variant of 5-FU is capecitabine (Xeloda), entyl [1-(3,4-dihydroxy-5-methyltetrahydrofuran-2-yl)-5-fluoro-2-oxo-1H-pyrimidin-4-yl]carbamate. It is approved to treat advanced breast cancer and colorectal cancer and used off-label for esophageal and gastric cancer. It is a pro-drug, which is enzymatically converted into 5-FU, and classified as an anti-metabolite drug. Xeloda has been described as an oral chemotherapy drug, which could replace the use of cisplatin and 5-FU.

Paclitaxel (Taxol) is one of several drugs targeting the cytoskeleton, more specifically tubulin. Paclitaxel-treated cells have mitotic spindle assembly and cell division defects, as paclitaxel stabilizes the microtubules and prevent them from disassembly. This leads to disruption of mitosis and the cells undergo apoptosis (88). Another anti-mitotic chemotherapeutic is docetaxel (Taxotere). Taxol is one of the most successful and bestselling drugs since its FDA approval in 1984 for use in a number of cancer such as breast, lung and ovarian as reported by the NCI and is used in esophageal combination therapy to improve patient outcome.

Irinotecan (Camptosar), is a topoisomerase I inhibitor, a semisynthetic analogue of the natural alkaloid acamptothecin (89). This is a more novel drug and, while it has a modified toxicity profile when combined with radiation, its prognostic effectiveness has not yet been demonstrated. For colon cancer a combination regiment called FLFIRI, is used which consists of 5-FU, leucovorin and irinotecan and could potential benefit esophageal cancer patients as well.

A Phase I/II trial measuring the effectiveness of S-1, a novel oral fluoropyrimidine derivative that consists of tegafur, gimeracil and potassium oxonate, with cisplatin (JCOG 0604) showed favorable 3-year survival but did not meet its primary endpoint due to low patient enrollment numbers (90). A review by Tai et al. (91) describes how ongoing studies, ZTOG1201 and QUINTETT, exploring neoadjuvant vs. adjuvant treatments in detail.

The aim of new combination chemotherapies is to account for tumor cell heterogeneity and the role it plays for drug resistance. Ample clinical precedent for using multiple agents has been presented in the past demonstrating evidence for synergy or an additive effect between established chemotherapeutic agents and agents representing other classes. The overall supportive care has allowed patients to tolerate the toxicity better and retain a higher quality of life during treatment. Yet, given that every tumor is unique, we should aim to personalize treatments and reduce toxicity by targeting therapy. The discovery of new drugs as well as identification of targeted therapies that are more effective for esophageal cancer is ongoing.

Targeted therapies: Challenges

Several types of targeted therapies are currently being studied for esophageal cancer. The most well-known targeted approach to esophageal cancer has been the inhibition of epidermal growth factor receptor (EGFR). EGFR is a member of the ErbB family of receptor and consists of four closely related receptor tyrosine kinases (EGFR and Her2 through Her4). Cetuximab, a monoclonal immunoglobulin against EGFR, is effective against head and neck squamous cell carcinoma in combination with radiotherapy (92). However, addition of cetuximab to chemoradiation therapy showed no significant survival benefit for esophageal cancer, including ESCC, in a phase III study (93). Similarly, a phase III study of gefitinib (Iressa), a tyrosine kinase EGFR inhibitor, did not show an increase in overall survival in patients with ESCC (94). While more successful in small cell lung cancer and head-and neck cancer, the majority of patients does not respond to EGFR inhibitors. Resistance due to the accumulation of mutations in EGFR or pathway targets as well as overexpression of signaling targets. EGFR inhibitors and the mechanisms of resistance appear to be diverse between and within cancer tissue types and have failed to give hope to esophageal cancer patients.

Her2-receptor targeting has been mainly used for breast cancer, but has recently been applied to treat EAC and adenocarcinoma at the GEJ. Trastuzumab, sold under the brandname Herceptin among others is a monoclonal antibody that interferes mainly with the HER2/neu receptor (95). Additionally, researchers are investigating novel HER2 target drugs for use in patients with advanced esophageal adenocarcinomas, including combinations of trastuzumab and radiation therapy.

At the same time, researchers and clinicians are looking into drugs that block vascular endothelial growth factor (VEGF) signaling to inhibit neoangiogenesis. Particularly the use of the anti-VEGFR2 antibody ramucirumab combined with chemotherapy as the first treatment has become a novel option. In 2014, the FDA approved ramucirumab, as a single agent or in combination with paclitaxel for the treatment of advanced gastric or gastro-esophageal junction adenocarcinoma. Especially, for cases in which the disease has progressed despite fluoropyrimidine- or platinum-based therapy (96).

Precision medicine based on genomic data could lead to new methods for prevention, diagnosis, and treatment of esophageal cancer. Currently, the promise of personalized medicine has failed to give hope to improve the dire patient situation.

Immunotherapy: Failed hope and uncertainties

While monoclonal antibodies used as drugs against specific target in the bodies can be considered immunotherapy as they cause an immune response to the cancer cell, there are other types of immunotherapy. Immunotherapy, also referred to as biological therapy, is designed to improve, target, or restore the patient immune function to target cancer cells. Adoptive cell transfer is one of them, in which T cells from a patient's tumor are isolated and the most tumor-reactive ones applied to destroy the tumor cells. Another approach is to use cytokines such as interferons and interleukins to regulate immune responses. Interferon-

alpha treatment in melanoma was a recent hot topic due to price of the treatment and the marginal improvement in overall survival.

A current highlight are the use of immune checkpoint blockades, which have provided new therapeutic avenues in melanoma. Ongoing investigations will hopefully allow treatment of other tumor types including gastrointestinal malignancies. So far, esophageal and gastric cancers have represented a minority in early phase immune checkpoint inhibitor trials. Major advances have come from inhibitory antibody development, which can modulate immune checkpoints. Three checkpoint inhibitors, pembrolizumab, nivolumab, and ipilimumab, are now approved by the FDA. Ipilimumab is a human monoclonal antibody that binds cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed death ligand 1 (PD-L1). The outlook for their use in gastrointestinal cancer is uncertain as numbers in the multicenter phase I trial (e.g. for anti-PD-L1 mAb BMS-936559) are small with only 7 gastric cancer patients of 207 enrolled patients overall. A second line gastroesophageal-specific phase II trial (n=18) showed even discouraging results as the observed response rate to tremelimumab (anti-CTLA4 mAb) was only 5%, well below the response rate for cytotoxic chemotherapy (97).

Very few reports describe vaccine-based or adoptive cell transfer immunotherapy for esophageal carcinoma. A phase I trial was conducted with a peptide vaccine administered to 10 patients with stage III or IV ESCC whose disease had progressed on conventional treatment, with 1 complete response and stable disease in 3 patients (98).

One phase I/II trial has been conducted for esophageal SCC with adoptive cell therapy (99). Additional trials are required to determine the efficacy of vaccine and T-cell-based therapies for esophageal carcinoma.

Today, researchers and clinicians are conducting a diverse range of studies aimed at developing the next generation therapies, including targeted and immune-based treatments.

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Figure 1.

Esophageal cancer risks and etiology. A. Alcohol and smoking are risk factors mainly for squamous cell carcinoma of the upper esophagus, yet also play a role in esophageal adenocarcinoma, which is confined to the lower esophagus or the gastro-esophageal junction. Gastroesophageal acid reflux disease induces injury in the lower esophagus resulting in metaplasia of the normal squamous epithelium. B. Morphology of the normal squamous epithelium compared to a well-differentiated esophageal squamous cancer and the glandular morphology of the esophageal adenocarcinoma. Immunohistochemistry staining using antibody against E-cadherin, a cell adhesion molecule, marking the epithelial and differentiated tumor tissue.

Table 1

Summary of recent publications of importance in the field of esophageal cancer treatments and their advances. Publication title and authors are listed.

Table 1: Recent publications of importance in the field of esophageal cancer treatments	
Title	Ref.
Neoadjuvant Chemotherapy with Divided-dose Docetaxel, Cisplatin and Fluorouracil for Patients with Squamous Cell Carcinoma of the Esophagus	Ojima T et al., Anticancer Res 2016, 36:829-34.
Nimotuzumab Plus Paclitaxel and Cisplatin as the 1st Line Treatment for Advanced Esophageal Squamous Cell Cancer(ESCC): a Single Centre Prospective Phase II Trial	Lu M et al., Cancer Sci 2016, 107:486-90.
A randomized clinical trial of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the oesophagus or gastro-oesophageal junction.	Klevebro F et al, Ann Oncol 2016, 27:660-7.
Association Between Statin Use After Diagnosis of Esophageal Cancer and Survival: a Population-based Cohort Study.	Alexandre L et al., Gastroenterology 2016, 150:854-865.
High-dose nimotuzumab improves the survival rate of esophageal cancer patients who underwent radiotherapy.	Wang C et al., Onco Targets Ther 2015, 9:117-22.
Phase I/II study of divided-dose docetaxel, cisplatin and fluorouracil for patients with recurrent or metastatic squamous cell carcinoma of the esophagus.	Ojima T et al., Dis Esophagus, 2016 Jan 3. doi: 10.111.
Preoperative low-dose weekly cisplatin and continuous infusion fluorouracil plus hyperfractionated radiotherapy in stage II-III esophageal carcinoma.	Caro M et al., Clin Transl Oncol 2016 Feb 8. doi:10.1007
Combination of cetuximab with radio-chemotherapy in patients with esophageal cancer: less is more!	Hofheinz RD et al., J Thorac Dis. 2015, 7:e629-32.
Possible prediction of the response of esophageal squamous cell carcinoma to neoadjuvant chemotherapy based on gene expression profiling.	Shen LY et al., Oncotarget 2016, 7:4531-41.
Adjuvant sunitinib following chemoradiotherapy and surgery for locally advanced esophageal cancer: a phase II trial.	Horgan AM et al., Dis Esophagus 2015 Dec 10, doi:10.1111.
Changes in tumour expression of programmed death-ligand 1 after neoadjuvant concurrent chemoradiotherapy in patients with squamous oesophageal cancer.	Lim SH et al., Eur J Cancer 2016, 52:1-9.
A randomized Phase II trial of systemic chemotherapy with and without trastuzumab followed by surgery in HER2-positive advanced gastric or esophagogastric junction adenocarcinoma with extensive lymph node metastasis: Japan Clinical Oncology Group study JCOG1301 (Trigger Study)	Kataoka K, Jpn J Clin Oncol 2015, 45:1082-6.
Metformin Use During Treatment of Potentially Curable Esophageal Cancer Patients is not Associated with Better Outcomes.	Spierings LE, Ann Surg Oncol 2015, suppl 3:766-71.
Neoadjuvant chemoradiotherapy with cisplatin plus vinorelbine versus cisplatin plus fluorouracil for esophageal squamous cell carcinoma: A matched case-control study.	Liu SL, Radiother Oncol 2015, 116:262-8.
Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial.	Shapiro J et al., Lancet Oncol 2015, 16:1090-8.
Association Between Clinically Staged Node-Negative Esophageal Adenocarcinoma and Overall Survival Benefit From Neoadjuvant Chemoradiation.	Gabriel E, JAMA Surg 2016, 151:234-45.
Cachexia in patients with oesophageal cancer	Anandavadevelan P and Lagergren P. Nat Rev Clin Oncol 2016, 13:185-98.

Table 1: Recent publications of importance in the field of esophageal cancer treatments	
Title	Ref.
Current concepts and future potential in neoadjuvant chemotherapy for esophageal cancer.	Blum Murphy MA et al., Expert Rev Gastroenterol Hepatol 2016, 10:383-92.
Current and Emerging Systemic Therapy in Gastro-Esophageal Cancer “The Old and New Therapy for Metastatic Disease, The Role of Adjuvant and Neoadjuvant Therapy for Localized Disease”	Lim B, Curr Clin Pharmacol 2015, 10: 267-78.
A germline predictive signature of response to platinum chemotherapy in esophageal cancer	Rumiato E, Transl Res 2015, S1931-5244 (15)00453-3.
Predictive Value of Ercc1 and Xpd Polymorphisms for Clinical Outcomes of Patients Receiving Neoadjuvant Therapy: A Prisma-Compliant Meta-Analysis.	Qixing M et al., Medicine 2015, 94:e1593.
Molecular Marker Expression Is Highly Heterogeneous in Esophageal Adenocarcinoma and Does Not Predict a Response to Neoadjuvant Therapy.	Bronson NW, J Gastrointest Surg 2015, 19:2105-10.
CD44, SHH and SOX2 as novel biomarkers in esophageal cancer patients treated with neoadjuvant chemoradiotherapy.	Honing J et al., Radiother Oncol 2015, 117:152-8.
IGFBP2 modulates the chemoresistant phenotype in esophageal adenocarcinoma.	Myers AL et al., Oncotarget 2015, 6:25897-916.
MiRNA Expression Analysis of Pretreatment Biopsies Predicts the Pathological Response of Esophageal Squamous Cell Carcinomas to Neoadjuvant Chemoradiotherapy.	Wen J et al., Ann Surg 2016, 263:942-8.
Reevaluation of Neoadjuvant Chemotherapy for Esophageal Squamous Cell Carcinoma: A Meta-Analysis of Randomized Controlled Trials Over the Past 20 Years	Zhen Y, eMedicine 2015, 94:e1102.

Table 2

A short list of currently ongoing trials reflecting some of the recent combination and novel targeted therapies.

Table 2 : Current Clinical Trials
Memorial Sloan Kettering Cancer Center, New York:
A Phase I Study of ADI-PEG 20 plus FOLFOX in Patients with Advanced Digestive Cancers
A Phase II Study of Afatinib (BIBW 2992) in Patients with Advanced HER2-Positive Esophagogastric Cancer Refractory to Trastuzumab
A Phase II Study of Neratinib in Patients with Solid Tumors Containing Mutated HER2
A Phase II Study of Nintedanib in Patients with Advanced Esophagogastric Cancer
A Phase II Study of Regorafenib versus Placebo in Patients with Node-Positive Esophageal Cancer Who Completed Chemotherapy, Radiation Therapy, and Surgery
A Phase III Study of Chemotherapy with or without Ramucirumab as Initial Treatment for Cancer of the Stomach or Gastroesophageal Junction
A Pilot Trial of PET Imaging with (89)Zr-DFO-Trastuzumab in Esophagogastric Cancer
A Prospective Clinical Trial to Evaluate Mesothelin as a Biomarker for the Clinical Management of Esophageal Cancer
M.D. Anderson, Texas:
A Phase I Study of LDE225 in Combination With Everolimus in Patients With Advanced Gastroesophageal Adenocarcinoma
Emory, Georgia; and Vanderbilt University, Tennessee:
A Phase I/II Study of Induction Chemotherapy with XELOX, Followed by Radiation Therapy and Dose Escalation of RAD001 in Patients With Esophageal Cancer
Multiple locations:
A Phase I/II Study of IMMU-132 (hRS7-SN38 Antibody Drug Conjugate) in Patients with Epithelial Cancers