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Current Therapy for Esophageal Adenocarcinoma

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1. Introduction

Esophageal adenocarcinoma (EAC) affects approximately 17,000 individuals per year in the United States, is increasing in incidence, and is associated with an exceptionally high mortality rate. [1, 2] Overall five-year survival despite aggressive treatment in large, multidisciplinary oncology centers ranges between 15 and 25%. Poor outcome in patients with EAC is reflective of both deficiencies in early detection - the disease is typically diagnosed at an advanced (unresectable) stage - and the inadequacy of available standard therapies across stages. Advanced/recurrent disease is incurable and carries a median survival of 9-12 months. Fully 50% of cases are metastatic at diagnosis, and cure rates with multimodality therapy for locally advanced disease do not exceed 40%--resulting in the majority of these patients eventually requiring palliative chemotherapy. Innumerable regimens have been studied. However, few are validated by phase III trials. Furthermore, trial eligibility ranges between histologies (Squamous cell carcinoma; SCC vs. Adenocarcinoma) as well as location in the upper gastrointestinal tract (distal esophagus, esophagogastric junction [EGJ], stomach). With these limitations in mind, there are a few guiding principles for treatment of advanced/metastatic disease. Chemotherapy is usually given in doublets and is chosen based on projected efficacy, patient performance status/medical co-morbidities, and side effect profile of the agents used. There is significant experience with combinations of cisplatin and 5-fluorouracil (5-FU), particularly with SCC, which are variously validated as better than best supportive care.[3] More recently, with the epidemiologic shift from SCC to EAC, newer regimens focus on GEJ/gastric cancer, use three drugs and sometimes incorporate biologic/targeted therapies.

2. Epidemiology and histology

SCC has become increasingly less common, accounting for fewer than 30% of all esophageal malignancies in North America and many Western European countries.[4] Although EAC is diagnosed predominantly in white men in whom the incidence has risen, EAC also is gradually increasing in men of all ethnic backgrounds and in women also.[5] Several risk

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factors for EAC have been established such as obesity and high body mass index (BMI).[6-8] Individuals in the highest quartile for BMI had a 7.6-fold increased risk of developing EAC compared with those in the lowest quartile, whereas SCC was not associated with BMI.[9, 10] Gastroesophageal reflux disease (GERD) and Barrett's esophagus are the other two major risk factors for EAC.[11-15] GERD is associated with high BMI and is also a risk factor for Barrett's esophagus. Barrett's esophagus is a condition in which the normal squamous epithelium of the esophagus that damaged by GERD is replaced by a metaplastic, columnar, or glandular epithelium of the esophagus that is predisposed to malignancy.[15] Patients with Barrett's esophagus have 30 to 60 times of greater risk of developing EAC than the general population.[13]

3. Staging

The American Joint Committee on Cancer (AJCC) staging classification has revised in 2010.[16] The tumor (T), node (N), and metastasis (M) classification developed by AJCC 2002 was based on pathologic review of the surgical specimen in patients who had surgery as primary therapy. The revised 2010 AJCC staging classification is based on the risk-adjusted random forest analysis of the data generated by the Worldwide Esophageal Cancer Collaboration (WECC) in 4627 patients who were treated with esophagectomy alone without induction or postoperative therapy. The revised version includes separate stage grouping for SCC and EAC (table 1.). The revised staging system is for the esophageal and EGJ cancers, including cancer within the first 5cm of the stomach that extends into the EGJ or distal thoracic esophagus. T4 disease is sub-classified into T4a (potentially resectable) and T4b (unresectable). Staging and evaluation for respectability requires endoscopic ultrasound (EUS) for T staging (focusing on the possibility of T4 disease), computed tomography (CT), and [18F]-2-deoxy-D-glucose positron emission tomography (FDG-PET), which is often integrated with CT (PET/CT).

3.1 Esophagogastric junction (EGJ)

In the revised AJCC staging system, tumors whose midpoint is in the lower thoracic esophagus, EGJ or within the proximal 5cm of the stomach that extends into the EGJ or esophagus, are classified as adenocarcinoma of the esophagus for the purposes of staging. All other cancers with a midpoint in the stomach lying more than 5cm distal to the EGJ, or those within 5cm of the EGJ but not extending into the EGJ or esophagus are staged using the gastric cancer staging system.

Primary tumor (T)	
TX	primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High grade dysplasia
T1	Tumor invades lamina propria, mucularis mucosae, or submucosa

Primary tumor (T)	
T1a	Tumor invades lamina propria, mucularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Resectable tumor invading plura, pericardium, or diaphragm
T4b	Unresectable tumor invading other adjacent structures, such as aorta, vertebral body, trachea, etc
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1-2 regional lymph nodes
N2	Metastasis in 3-6 regional lymph nodes
N3	Metastasis in seven or more regional lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
Histologic grade (G)	
GX	Grade cannot be assessed - stage grouping as G1
G1	Well differenciated
G2	Moderately differenciated
G3	Poorly differentiated
G4	Undifferentiated - stage grouping as G3 squamous

Adenocarcinoma				
Stage	T	N	M	Grade
0	Tis (HGD)	N0	M0	1, X
IA	T1	N0	M0	1-2, X
IB	T1	N0	M0	3
	T2	N0	M0	1-2, X
IIA	T2	N0	M0	3
IIB	T3	N0	M0	Any
	T1-2	N1	M0	Any
IIIA	T1-2	N2	M0	Any
	T3	N1	M0	Any
	T4a	N0	M0	Any
IIIB	T3	N2	M0	Any
IIIC	T4a	N1-2	M0	Any
	T4b	Any	M0	Any
	Any	N3	M0	Any
IV	Any	Any	M1	Any

Table 1. AJCC 2010 TNM staging of esophagogastric junction (EGJ) adenocarcinoma.

4. Current therapy for resectable esophageal adenocarcinoma

EMR or ablation are good primary treatment options for patients with Tis and T1a tumors where as esophagectomy is still preferred treatment for T1a tumor. For patients with T1b, esophagectomy is the preferred treatment option for those with non-cervical cancer. Chemoradiation therapy is the preferred treatment for patients with cervical cancer.[17]

Primary treatment options for patients with locally advanced resectable esophageal cancer include preoperative chemoradiation therapy, definitive chemoradiation therapy, preoperative chemotherapy, or esphagectomy.

4.1 Chemoradiation therapy

Since the overall poor survival rates of patients who have been treated with resection alone, multiple modalities have been used for the treatment of esophageal cancer. Concomitant chemotherapy and radiation therapy has been studied in the preoperative setting and as definitive nonoperative treatment.

4.1.1 Preoperative concurrent chemoradiation therapy

Preoperative chemoradiation followed by surgery is the most common approach for patients with resectable esophageal cancer. Several trials have directly compared surgery with or without preoperative chemoradiation therapy for patients with potentially resectable esophageal cancer.[18-24] Of the five completed randomized trials compared preoperative concurrent chemoradiation therapy versus surgery alone, only two showed a statically significant survival benefit for chemoradiation therapy.[23, 24] Walsh et al.[23] randomized 113 patients with esophageal or EGJ adenocarcinoma to receive either surgery alone or preoperative chemoradiation therapy. The chemoradiation therapy consisted of two courses of cisplatin (75 mg/m^2 on day 7 of each cycle) and 5-fluorouracil (15mg/kg by bolus days 1 to 5), and radiation therapy was administered in 15 fractions over a three week period to a total of 40 Gy. Only one of the cycles of chemotherapy was actually given concurrently with the radiation. The combined-modality therapy provided a significant improvement in median survival (16 versus 11 months; p =0.01) and in three year survival (32% versus 6 %) compared with surgery alone. These results were criticized because of the lower than expected survival with surgery alone.

In the phase III multicenter CROSS trial from the Netherlands[24], 364 patients with potentially resectable (T2-3, N0-1, M0) esophageal or EGJ cancer were randomized to surgery alone or weekly paclitaxel 50 mg/m2 plus carboplatin [AUC =2] on days 1, 8, 15, 22, and 29, administered with concurrent radiotherapy with 41.4 Gy in 23 fractions over five weeks. Surgery was conducted within 6 weeks of completing chemoradiation therapy. The median survival of patients who received preoperative chemoradiation therapy and surgery was 49 months, compared to 26 months for those who received surgery alone. When adjusted for baseline covariates, the hazard ratio was 0.66 (p = 0.008). After a median follow-up of 32 months, the 1-,2- and 3-year survival rates were 82 percent, 67 percent and 59 percent, respectively, for chemoradiation therapy plus surgery verses 70 percent, 52 percent, and 48 percent for surgery alone with 0.67 of hazard ratio (p = 0.011). In a preliminary report presented at the 2010 ASCO meeting, preoperative chemoradiation therapy was well tolerated, with the only grade 3 or higher toxicity being leucopenia (7%). The complete (R0) resection rate was higher with chemoradiation therapy (92 vs. 65%), and 33 % of those treated with chemoradiation therapy had a pCR.

In contrast, three other trials have not shown a significant survival advantage for this approach. In the trial from University of Michigan[19], 100 patients with locoregional esophageal or EGJ cancer were randomly assigned to surgery with or without preoperative chemoradiation therapy with cisplatin, 5-FU and vinblastine. A pCR was observed in 28 percent of patients after preoperative treatment. At a median follow-up of 8.2 years, the median survival was similar (16.9 vs. 17.6 months for multimodality therapy and surgery respectively). However, three-year survival was nearly twice higher in chemoradiation therapy (30% vs. 16%), although there was no statistically significant.

The CALGB 9781 trial[24] was a prospective randomized Intergroup trial comparing trimodality therapy with surgery alone in 500 patients with stage I through III esophageal or EGJ cancer. Patients were staged with upper endoscopy, barium esophagram, and CT. Staging EUS and thoracoscopy/laparoscopy were encouraged. Due to poor accrual, the study fell short prematurely with only 56 patients enrolled. Those patients were randomized to undergo either surgery alone or concurrent chemoradiation therapy with cisplatin and 5-fluorouracil. A pCR was achieved in 10 of 25 assessable patients in the trimodality therapy (40%), and neither perioperative morbidity nor mortality was increased compared to surgery alone. Patients receiving trimodality therapy also had a better 5-year survival rate (39% vs. 16%), although the difference was not statistically significant.

The benefit of preoperative chemoradiation therapy in smaller resectable tumors was addressed in the French FFCD 9901 trial[25], which randomly assigned 195 patients with stage I or II esophageal or EGJ cancer to preoperative chemoradiation therapy (cisplatin plus 5-FU and concurrent radiation therapy [45Gy]) versus surgery alone. In a preliminary report of an interim analysis, at a median follow-up of 69 months, preoperative chemoradiation therapy did not improve median overall survival (32 vs. 44 months with surgery alone), and it was associated with significantly more serious adverse events (65% vs. 35%) and a significantly higher rate of perioperative mortality (7.3% vs. 1.1%). Full publications of these data are awaited.

A meta-analysis of randomized trials comparing preoperative chemoradiation therapy versus surgery alone included 1116 patients enrolled on nine trials[26]. When compared to surgery alone, there was only a nonsignificant trend towards improved survival with chemoradiation therapy (odds ratio 0.79, 0.77, and 0.66 for one-, two- and three-year mortality, respectively). The improvement in three-year survival was statistically significant when the analysis was restricted to trials of concurrent chemoradiation therapy (odds ratio for mortality 0.45, 95% CI 0.26-0.79). A second meta-analysis of 10 randomized comparing preoperative chemoradiation therapy and surgery alone showed same conlusion[27]. Compared to surgery alone, preoperative chemoradiation therapy was associated with significantly better two-year all cause mortality (hazard ratio 0.81, 95% CI 0.70-0.93). This corresponded to a 13 percent absolute difference in survival at two years.

In brief summary, with several trials and at least two meta-analyses demonstrating better survival with preoperative concurrent chemoradiation, the majority of patient potentially resectable localized cancer of the thoracic esophagus and EGJ now undergo some form of combined modality therapy rather than local therapy alone.

4.1.2 Preoperative sequential chemoradiation therapy

Several trials comparing sequentially administered chemotherapy and radiation therapy followed by surgery to surgery alone have failed to show any survival advantage to combined modality therapy.[18, 20, 21]

4.1.3 Definitive chemoradiation therapy

In randomized studies, the addition of cisplatin-based chemotherapy to radiation therapy significantly improves survival over radiation alone, however, the available data are almost

exclusively in SCC, and none of the trials have performed adequate pretreatment staging to reliably correlate outcome with locoregional tumor extent such as locally advanced unresectable versus potentially operable disease.[28-30]

In the RTOG 85-01 trial, patients with locoregional thoracic esophageal SCC or AC received 4 cycles of 5-FU and cisplatin. Radiation therapy (50Gy) was administered concurrently with day 1 of chemotherapy[28]. The control therapy arm was radiation therapy alone which was higher dose (64Gy) than I the combined modality therapy arm. Patients who were randomly assigned to receive combined modality therapy showed a significant improvement in both median survival (14 vs. 9 months) and 5-year overall survival (27% vs. 0%) with projected 8- and 10-year survival rates of 22% and 20%, respectively[29]. As a result of this trial, definitive chemoradiation therapy became the standard care for patients with inoperable disease even though 90 percent of patients had SCC.

The US Intergroup Study 0123 (INT 0123) was designed as the follow-up trial to RTOG 85-01[31]. The trial compared two different radiation doses (50.4 Gy or 64.8 Gy) used with the same chemotherapy regimen as RTOG 85-01 (cisplatin and 5-FU). 236 Patients with nonmetastatic SCC (85%) and AC (15%) of the thoracic esophagus were randomly assigned. No significant difference was observed in median survival (13.0 vs. 18.1 months), two-year survival (31% vs. 40%), and locoregional failure or locoregional persistence of cancer (56% vs. 52%) between the high-dose and standard-dose radiation therapy groups. High-dose radiation therapy was significantly more toxic.

After the results of these studies, definitive chemoradiation therapy with 5-FU and cisplatin using the radiation therapy dose of 50.4 Gy was established as the standard approach for patients with esophageal cancer.

4.1.4 Postoperative chemoradiation therapy

In a phase II nonrandomized trial evaluating postoperative concurrent chemoradiation with cisplatin and 5-FU in patients with poor prognosis esophageal and EGJ cancers, the projected rates of 4-year overall survival, freedom from recurrence, distant metastatic control, and locoregional control were 51%, 50%, 56%, and 86%, respectively[32]. However, the efficacy of postoperative chemoradiation therapy has not been compared with surgery alone in a randomized trial involving patients with esophageal cancer.

The Intergroup trial SWOG 9008/INT-0116 investigated the effect of surgery and postoperative chemoradiation therapy on the survival of patients with resectable adenocarcinoma of the stomach (80%) or EGJ (20%)[33]. 556 patients were randomly assigned to surgery plus postoperative chemoradiation therapy (leucovorin and 5-FU) or surgery alone. Median overall survival in the surgery alone was 27 months compared with 36 months in the postoperative chemoradiation group. The postoperative chemoradiation group had better 3-year survival rates (50% vs. 41%) and significantly improved overall survival for all patients. A major criticism of this study is that surgery was not part of this protocol. Moreover, 54% of patients had a D0 resection, 36% had a D1 resection, and only 10% had a D2 resection. However, the results of this study have established postoperative chemoradiation therapy as a reasonable option of patients with EGJ adenocarcinoma.

4.2 Chemotherapy

4.2.1 Preoperative chemotherapy

Several randomized trials have evaluated the benefit of preoperative chemotherapy in patients with esophageal cancer limited to the primary and regional nodes by clinical assessment[34-39].

In the US Intergroup trial 0113, 467 patients with potentially resectable esophageal or EGJ cancer were randomly assigned to surgery alone or preoperative chemotherapy with cisplatin and 5-FU followed by surgery[34]. The majority of patients had adenocarcinoma (55%) and outcomes were similar for both histologies. The preliminary results did not show any survival benefit between the groups. In a later update of long-term outcomes (median follow-up with 8.8 years), preoperative chemotherapy decreased the incidence of R1 resection (4% vs. 15% in the surgery alone group), however, no improvement was seen in overall survival between the groups.

In contrast to Intergroup 0113, a couple of trials suggest a survival benefit for preoperative chemotherapy compared to surgery alone. The Medical Research Council (MRC) OEO2 trial randomly assigned 802 patients with AC (69%) or SCC (31%) of the esophagus to surgery alone or preoperative chemotherapy with cisplatin and 5-FU[39]. At a median follow-up of 6 years, disease-free and overall survivals were significantly longer for the preoperative chemotherapy group. The 16 percent reduction in the risk of death favoring chemotherapy translated into a significant improvement in five year survival (23 vs. 17%).

The phase III study conducted by the French Study group (FNLCC ACCORD07-FFCD 9703) compared preoperative chemotherapy (5-FU and cisplatin) followed by surgery with surgery alone[40]. 224 patients with potentially resectable stage II or greater adenocarcinoma of EGJ (n=144), distal esophagus (n=25), or stomach (n=55) were randomly assigned.

At a median follow-up of 5.7 years, 3- and 5- year overall survival rates were 48% and 38%, respectively, for patients with preoperative chemotherapy compared with 35% and 21%, respectively, for those with surgery alone.

In a meta-analysis of eight randomized trials of surgery alone or preoperative chemotherapy followed by surgery for esophageal cancer (1724 patients, any histology, excluding cervical esophageal cancers) suggested a small survival benefit for preoperative chemotherapy group[27]. The hazard ratio for all cause survival at two years favored chemotherapy followed by surgery (hazard ratio for all-cause mortality 0.90, 95% CI 0.81-1.0), a difference which translated into a two-year absolute survival benefit of 7 percent. There was no significant benefit for chemotherapy for patients with SCC, however, with patients with EAC, there was a significant benefit, which was based on data from the United Kingdom MRC OEO2 trial.

4.2.2 Perioperative chemotherapy

Investigators with the MRC conducted a second study of preoperative chemotherapy[38]. In contrast to the previous MRC study (MRC OEO2 trial), they included patients with resectable gastric (74%), EGJ (15%), or distal esophageal adenocarcinoma (11%). This UK MAGIC trial evaluated the effect of perioperative chemotherapy with the ECF (epirubicin,

cisplatin, and 5-FU) regimen given before and after surgery in resectable gastroesophageal cancer. A total of 503 patients were randomly assigned to surgery with or without perioperative chemotherapy. Most of the patients had gastric cancer (74%), while small group of patients had adenocarcinoma of lower esophagus (14%) and EGJ (11%). At a median follow-up of four years, 5-year overall survival was significantly better in the perioperative chemotherapy group compared with surgery alone (36 vs. 23%).

5. Current therapy for unresectable and metastatic esophageal adenocarcinoma

The goals of therapy for patients with advanced unresectable and metastatic esophageal cancer are to palliate symptoms, including malignant dysphagia, and improve survival. Patients with advanced adenocarcinoma of esophagus and EGJ can be treated using the regimens included in the gastric cancer guide-lined for advanced gastric cancer. Since the mid 1970s, the incidence of SCC in the United States has been declining, while the incidence of adenocarcinoma in white males rose by 350 percent from 1970s to 1990s[41]. Adenocarcinoma became the dominant histology in the early 1990s. In addition, the incidence of distal gastric adenocarcinoma declined, while the incidence of adenocarcinoma of EGJ and proximal stomach has increased. The increasing incidence has paralleled the rise in incidence of EAC. These histories suggest that adenocarcinomas of the distal esophagus, EGJ and proximal stomach share a common pathogenesis.

5.1 Chemotherapy for advanced unresectable or metastatic esophageal adenocarcinoma

In randomized clinical trials, no consistent benefit was seen for any specific chemotherapy regimen, and chemotherapy showed no survival benefit compared with best supportive care for patients with advanced esophageal cancer[3]. However, palliative chemotherapy may improve quality of life in patients with unresectable or metastatic esophageal cancer.

5.1.1 Single agent

Cisplatin is one of the most active agents, with a single-response rate consistently in the range of 20% or greater[42]. Newer agents such as irinotecan[43-45], docetaxel[46, 47], paclitaxel[48-50], and etoposide[51] have also shown activity as single agents in advanced esophageal cancer.

5.1.2 Combination chemotherapy

The combination of cisplatin and fluorouracil has been one of the most commonly used regimens in both metastatic and localized esophageal cancer due to its activity and well-established toxicity profile. Cisplatin also has been combined with taxanes[50, 52-54], irinotecan[55], mitomycin[56], and gemcitabine[57, 58].

Capecitabine is designed oral fluoropyrimidine that is converted to 5-FU in three-step enzymatic process[59]. In the REAL-2 trial[60], multicenter phase III study assessed by a randomized 2x2 design, 1002 patients with histologically confirmed EAC, SCC, or undifferentiated cancer of esophagus, EGJ, or stomach randomly assigned to receive one of four epirubicin-based regimens ([ECF]; epirubicin, cisplatin, 5-FU, [EOF]; epirubicin,

oxaliplatin, 5-FU, [ECX]; epirubicin, cisplatin, capecitabine, [EOX]; epirubicin, oxaliplatin, capecitabine). The primary outcome in this study was non-inferiority in overall survival. The primary endpoint was reached and there was a trend toward better overall survival for the capecitabine and oxaliplatin groups.

Regimens containing irinotecan have been studied. Irinotecan has been combined with cisplatin[61], docetaxel[62], and fluoropyrimidines[63]. Irinotecan plus cisplatin is active and well tolerated in several studies. Combinations of irinotecan and docetaxel with or without cisplatin are active but toxic. Combinations of irinotecan and oxaliplatin are highly efficacious and tolerated[63]. There are no phase III trials comparing an irinotecan-based combination with a cisplatin-based regimen.

Tables show brief regimens listed in the guidelines for metastatic or locally advanced esophageal or EGJ cancers (Table 2 and 3).

First-line therapy
DCF or its modifications (category 1 for docetaxel, cisplatin, and fluorouracil; category 2B for docetaxel, carboplatin, and fluorouracil; category 2A for all other combinations
ECF or its modifications (category 1)
Fluoropyrimidine- or taxane-based regimens, single agent or combination therapy, (category 1 for combination of fluoropyrimidine and cisplatin; category 2A for all other regimens)
Trastuzumab with chemotherapy (category 1 for combination with cisplatin and fluoropyrimidine; category 2B for combination with other chemotherapy agents) for patients who are HER2-neu positive, as determined by a standardized method.

Table 2. First-line therapy for Recurrent and Metastatic Esophageal Cancer.

Second-line therapy
Trastuzumab with chemotherapy (category 1 for combination with cisplatin and fluoropyrimidine; category 2B for combination with other chemotherapy agents) for patients who are HER2-neu-positive, if not used as first-line therapy
Docetaxel or paclitaxel (category 2B)
Irinotecan-based single-agent or combination therapy (category 2B)

Table 3. Second-line therapy for Recurrent and Metastatic Esophageal Cancer.

6. Biological/Targeted therapy

With the recent development of small molecules and antibodies designed form biologic first principles, biologic/targeted therapies are now incorporating with chemotherapy. The most commonly used agents include angiogenesis inhibitors (bevacizumab) and epidermal growth

factor receptor inhibitors (panitumumab, cetuximab, erlotinib). Shah et al. carried out a phase II trial of 47 patients to study the addition of the anti-vascular endothelial growth factor monoclonal antibody, bevacizumab, to weekly cisplatin and irinotecan in patients with advanced gastroesphageal cancer.[64] The median survival was 12.3 months (95% CI, 11.3 to 17.2 months), and there was no increase in chemotherapy related toxicity. The ongoing REAL-3 trial is testing epirubicin, oxaliplatin and capecitabine (EOX) with or without panitumumab in previously untreated advanced esophagogastric cancer. Pittsburgh group is carrying a phase II study of irinotecan plus panitumumab as second line treatment for advanced EAC. In the setting of locally advanced disease, ECOG 2205 investigated the addition of cetuximab to chemoradiation therapy for resectable EAC, and ACOSOG Z4051 is enrolling patients with adenocarcinoma to chemoradiation therapy plus panitumumab.

The revolution in biological/targeted therapies offers hope for improvement in survival for patients with advanced EAC. However, historically, the empiric addition of targeted agents such as cetuximab and bevacizumab to cytotoxic chemotherapy has yielded a modest improvement in survival for patients with solid tumors.[65-67] This relative failure of the current approach has led to great interest in either selecting patients for therapies or selecting therapies for patients, usually by tumor profiling and selective preclinical models.[68, 69] This project aims to test a novel direct translational model of target selection and inhibition with the goal of furthering the rational selection of targeted therapies for patients with advanced EAC.

6.1 Trastuzumab

HER2 is another member of the EGFR family that is associated with cell proliferation, migration, and differentiation. HER2 over-expression and/or amplification have been reported in EAC, along with some evidence supporting a prognostic utility. Various phase I and II trial have reported a possible benefit for HER2 blockage[70, 71]. Data from these trials served as the basis for a recent prospective phase III trial (ToGA)[72] that evaluated the therapeutic benefit of blocking this target in a randomized fashion.

In the ToGA trial, more than 594 patients with HER2-positive gastric and gastroesophageal cancer were treated with standard chemotherapy (infusional 5-FU or capecitabine plus cisplatin), either with or without trastuzumab. The tumors of the enrolled patients were either fluorescence in situ hybridization (FISH)-positive or positive for HER2 expression by immunohistochemistry (IHC). At a median follow-up of 17.1 to 18.6 months, median overall survival (the primary endpoint) was significantly improved with the addition of trastuzumab (13.8 vs. 11.1 months). Safety profiles were comparable, with no unexpected adverse events in the trastuzumab group and no difference was seen in symptomatic congestive heart failure between the arms. This establishes trastuzumab plus chemotherapy as a new standard of care for the treatment of patients with HER2-expressing advanced gastric and EGJ adenocarcinoma.

6.2 Cetuximab

As monotherapy, cetuximab, a monoclonal antibody targeting the EGFR, has limited activity as second-line therapy[73]. The safety and efficacy adding cetuximab to first-line

chemotherapy has been tested in several studies of advanced esophagogastric cancer[74, 75]. All suggest that this approach is safe and in some cases, objective response rates are over 50 percent and median survival is less than 10 months. Conclusions regarding the clinical utility of cetuximab in patients with advanced esophagogastric cancer need data from randomized phase III trial.

6.3 Gefitinib and erlotinib (small molecule tyrosine kinase inhibitors)

Another means of interfering with EGFR signaling is through the use of orally active tyrosine kinase inhibitors (TKIs), small molecules that block the binding site of the EGFR tyrosine kinase. Small molecule TKIs such as Gefitinib and Erlotinib have been tested as single agents in phase II trials in esophagogastric cancer.

In a phase II study of gefitinib in 36 patients who had failed one prior therapy for advanced esophageal cancer, there was only one partial response, but 10 patients had stable disease for at least eight weeks. Treatment was reasonably well tolerated[76].

In another trial, gefitinib was administered to 27 patients with advanced unresectable EAC. There were three partial responses, and seven had stable disease[77].

In SWOG trial, 70 patients with unresectable or metastatic adenocarcinoma originating in the EGJ or stomach received first line treatment with erlotinib[78]. Six patients had an objective response rate (9 percent, one complete), all of them were EGJ tumors. There was no molecular parameter of EGFR expression or mutations were predictive of clinical outcome. The reason for the apparent differential sensitivity of EGJ and gastric cancer s to EGFR blockade using erlotinib is unclear.

6.4 Bevacizumab

Elevated serum and tumor levels of vascular endothelial growth factor (VEGF) are associated with a poor prognosis in patients with resectable gastric cancer[79, 80]. Adding the anti-VEGF monoclonal antibody bevacizumab to chemotherapy in advanced upper GI cancer has been studied.

In the phase III AVAGAST trial, in which 774 patients with previously untreated locally advanced unresectable or metastatic gastric or EGJ cancer were randomly assigned to capecitabine plus cicplatin with either bevacizumab or placebo[81]. In a preliminary report, there was no significant benefit from bevacizumab in median overall survival (the primary endpoint, 12.1 vs. 10.1 months, hazard ratio 0.87, 95% CI 0.73-1.03) although the use of bevacizumab significantly improved both objective response rate and median progression-free survival.

7. Conclusion

The treatment of esophageal and EGJ cancer has undergone a major evolution over the past decades. However, the optimal therapy for these patients is still controversial. Although several advances have made in staging procedures and therapeutic approaches, esophageal cancer is often diagnosed late. Some forms of multimodal management are essential for treating patients with esophageal cancer. Most of the clinical studies have not differentiated

between SCC and adenocarcinoma so that most of approaches are similar for both histologies. However, there are an increasing amount of evidence supports the view that they differ in terms of their epidemiology, biology, and prognosis, etc. In recognition of these differences, the AJCC 2010 TNM staging criteria provides separate stage groupings for SCC and adenocarcinomas of the esophagus and EGJ. For patients with locally advanced resectable adenocarcinoma of esophagus and EGJ (T1b or higher, any N), primary treatment options include preoperative chemoradiation therapy, definitive chemoratiation, preoperative chemotherapy, or esophagectomy. Postoperative treatment is based on their staging. Fluoropyrimidine-based chemoradiation therapy is recommended for patients with node-positive adenocarcinoma of esophagus and EGJ. Perioperative chemotherapy is recommended for patients with completely resected adenocarcinoma of EGJ (MAGIC trial). All patients with residual disease at surgical margins may be treated with fluoropyrimidine-based chemoradiation. For patients with unresectable disease or those with resectable disease who choose not to undergo surgery, fluoropyrimidine- or taxane-based concurrent chemoradiation therapy is recommended. For patients with recurrent and metastatic disease, the goals of chemotherapy are to palliate symptoms and improve survival. Biologic/Targeted therapies have produced encouraging results in the treatment of patients with advanced adenocarcinoma of esophagus and EGJ. The efficacy of these new therapies in combination with chemotherapy still need results from randomized phase III trials.

Considerable advanced have been made in the treatment of adenocarcinoma of esophagus and EGJ. Novel therapeutic modalities, such as targeted therapies, antiangiogenic agents, gene therapy, and etc are being studied in clinical trials. More tailor-made treatment for patients with esophageal cancer may be needed and well-designed clinical trials are awaited to enable further advances.

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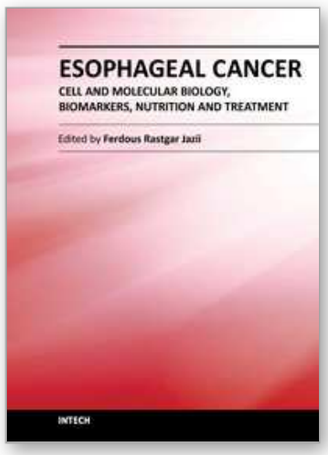

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Esophageal Cancer illustrates recent achievements and investigations in the esophageal tumorigenesis from different perspectives. Readers find mechanisms involved in esophageal tumorigenesis, cellular, molecular, genetic, epigenetics, and proteomics, their relevance as the novel biomarkers and application in esophageal cancer diagnosis and therapy. The book covers detailed effect of nutritional factors in addition to ethanol metabolic pathway in the inhibition of retinoic acid metabolism and supply. Diagnosis, classification, and treatment of esophageal cancer, application of both surgical and non surgical methods as well as follow up of the disease are described in detail. Moreover readers are endowed with especial features of esophageal cancer such as multiple early stage malignant melanoma and pulmonary edema induced by esophagectomy, the two features that received less attention elsewhere in literature.

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