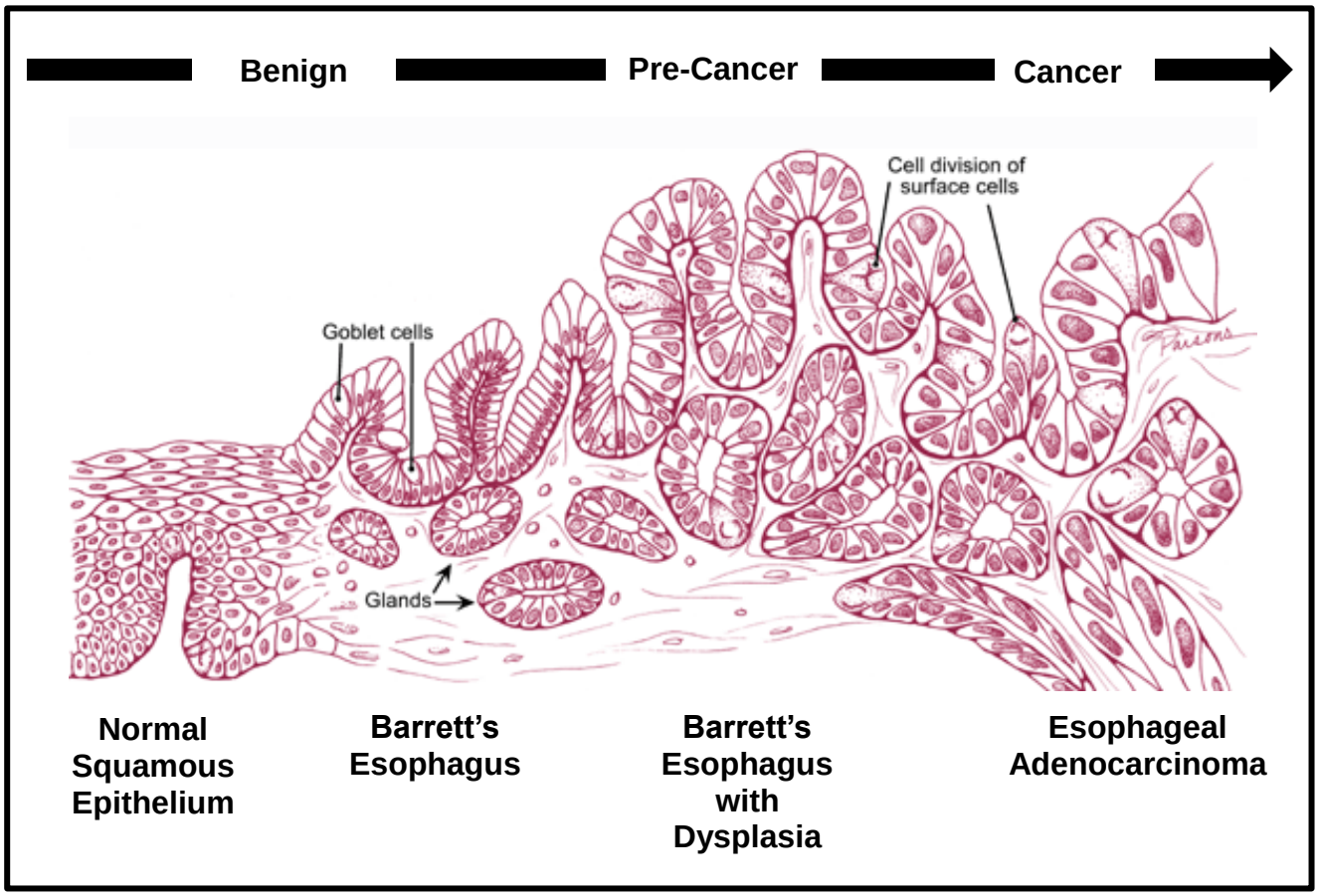
Esophageal Cancer Treatment: Potential Insight from the Development of Barrett's Esophagus—Can it BE?



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This is to acknowledge that David Wang, M.D., Ph.D., has disclosed that he does not have any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Wang will be discussing off-label uses in his presentation.

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Purpose and Overview: The purpose of this presentation is to review the current treatment of esophageal cancer, highlighting data from randomized clinical trials. In addition, the Barrett's metaplasia-dysplasia-cancer sequence will be presented along with recommendations for endoscopic surveillance and ablation in patients with Barrett's esophagus. Ongoing translational research that may impact future treatment of esophageal cancer will be discussed.

Objectives:

1) To review the multi-modality treatment of localized esophageal cancer.
2) To review the benefits of palliative chemotherapy in patients with metastatic esophageal cancer.
3) To review the management of patients with Barrett's esophagus.
4) To identify signaling pathways for development of molecularly targeted therapy for esophageal cancer.

Introduction

Patients with an esophageal malignancy typically present with progressive dysphagia, sometimes with odynophagia, and weight loss. Less frequent presenting symptoms such as non-specific chest or abdominal pain, fatigue, upper gastrointestinal bleeding or unexplained anemia, hoarseness, recurrent pneumonia or persistent cough, hiccups, or dyspnea that are not attributable to other causes should prompt diagnostic evaluation for an esophageal cancer. This can be done initially with either a double-contrast barium esophagram or an endoscopy, though an endoscopy generally is preferred as it allows tissue sampling to establish a histological diagnosis [1,2].

Natural History of Esophageal Cancer

The two most frequent histological types of esophageal cancer are squamous cell carcinoma and adenocarcinoma. For most of the 20th century, squamous cell carcinoma was by far the most common type in the United States. Data from 62,563 patients with primary carcinoma of the esophagus or gastric cardia from the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) program between 1973 and 2007 demonstrate that adenocarcinoma recently has become the predominant histology in this country[3]. The percentage of esophageal cancers in the SEER database that are adenocarcinomas has increased from 35% in the 1970s to 61% in the 2000s[3]. This is despite the percentage of distal esophageal tumors remaining relatively stable around 40%[3]. Advances in esophageal cancer diagnosis and treatment are likely responsible for a meaningful improvement in median survival in patients with local or regional disease, but not in those with metastatic disease, over the last three decades. Patients with local or organ-confined esophageal cancers in the 2000s have a median survival of 35 months as compared to 11 months in the 1970s, while patients with regional disease (direct tumor extension into adjacent organs or lymph node involvement) have a median survival of 15 months in the 2000s compared to 10 months in the 1970s[3]. Median survival for patients with metastatic disease has increased marginally from 4 months in the 1970s to 6 months in the 2000s[3].

AJCC Staging System

In the seventh edition of the American Joint Committee on Cancer (AJCC)'s Staging Manual (**Table 1**)[4,5], updated in 2010, separate staging systems for esophageal squamous cell carcinoma and esophageal adenocarcinoma were established, and the category of grade (G, i.e. differentiation) was added to the tumor (T), node (N), metastasis (M) classification system. In addition, tumor location within the esophagus was incorporated into the staging system for squamous cell carcinoma. Though these changes might seem to complicate the staging process, they were added to align staging groups with all-cause, time-related mortality based on survival data from 4627 patients with resected esophageal or gastroesophageal junction (GEJ) cancer from 13 institutions in North America, Europe, and Asia[5]. Other changes included expanding the T1 classification to distinguish mucosal (T1a) and submucosal tumors (T1b), a crucial distinction for deciding if endoscopic eradication therapy is appropriate, and expanding the T4 classification to distinguish resectable tumors (T4a) from unresectable tumors (T4b); adjusting the N classification to quantify the number of involved paraesophageal lymph nodes; and removing cervical or celiac lymph node involvement from the M1 category. Since the survival data were generated from patients who underwent surgical resection, pathologic TNM staging could be accurately matched to patient outcome[3]. Overall, patients with resected early stage adenocarcinoma fared better than those with resected early stage squamous cell carcinoma[5].

TABLE 1: AJCC 7th Edition TNM Staging System for Esophageal Cancer

Adenocarcinoma/GEJ cancer

Stage	T	N	M	G
0	Tis	N0	M0	G1, X
IA	T1	N0	M0	G1-2, X
IB	T1	N0	M0	G3
	T2	N0	M0	G1-2, X
IIA	T2	N0	M0	G3
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

Esophageal squamous cell carcinoma

Stage	T	N	M	G	Tumor location
0	Tis	N0	M0	G1, X	Any
IA	T1	N0	M0	G1, X	Any
IB	T1	N0	M0	G2-3	Any
	T2-3	N0	M0	G1, X	Lower, X
IIA	T2-3	N0	M0	G1, X	Upper, Middle
	T2-3	N0	M0	G2-3	Lower, X
IIB	T2-3	N0	M0	G2-3	Upper, Middle
	T1-2	N1	M0	Any	Any
IIIA	T1-2	N2	M0	Any	Any
	T3	N1	M0	Any	Any
	T4a	N0	M0	Any	Any
IIIB	T3	N2	M0	Any	Any
IIIC	T4a	N1-2	M0	Any	Any
	T4b	Any	M0	Any	Any
	Any	N3	M0	Any	Any
IV	Any	Any	M1	Any	Any

T staging

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High grade dysplasia
T1	
T1a	Tumor invades lamina propria, muscularis mucosa
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Resectable (pleura, pericardium, diaphragm)
T4b	Unresectable (great vessels, trachea, vertebra)

N staging

NX	Regional nodes can't be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1-2 regional lymph nodes
N2	Metastasis in 3-4 regional lymph nodes
N3	Metastasis in 5-6 regional lymph nodes

M staging

M0	No metastases
M1	Distant metastases

G staging

GX	Grade can't be assessed-stage grouping as G1
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated-stage grouping as G3 squamous

Since GEJ tumors have a worse prognosis than more distal gastric cancers, GEJ tumors were included with esophageal adenocarcinoma for AJCC staging purposes[5]. Siewert defined GEJ tumors as those centered within five centimeters of the GEJ: Siewert type I tumors are distal esophageal tumors that cross the GEJ from above, type II tumors are centered at the GEJ, and type III tumors are proximal gastric tumors that cross the GEJ from below[6].

Staging Studies

Once a patient has been diagnosed histopathologically with esophageal cancer and undergone a history and physical exam, staging studies should be performed to determine the appropriate treatment. In general, staging procedures should include endoscopic ultrasonography (EUS) and whole body ^{18}F-FDG positron emission tomography (PET) along with a dedicated chest and abdominal CT or with a combined PET/CT study. These tests are used to estimate the depth of tumor invasion, assess for tumor involvement of paraesophageal lymph nodes, and search for distant metastases[7-10]. Recent meta-analyses have documented the accuracy of EUS staging of esophageal cancer[11-13]. The pooled sensitivity and specificity of diagnosing T1 tumors by EUS were 82% and 99%, for T2 tumors sensitivity and specificity were 81% and 96%, for T3 tumors 91% and 94%, and for T4 tumors 92% and 97%[11]. Discrimination between T1a and T1b tumors by EUS is also possible with a pooled sensitivity of 85-86% and a pooled specificity of 86-87%[12]. Endoscopic mucosal resection (EMR) is recommended for areas of nodularity within lesions judged to be T1a by EUS, because EMR often reveals submucosal invasion (T1b) in these nodules.

Detection of regional lymph node involvement by EUS has a sensitivity of 80% and specificity of 70%[13]. With the addition of fine needle aspiration (FNA), EUS sensitivity for detecting regional lymph node involvement increases to 97%[11]. By comparison, the sensitivity and specificity of detecting involved regional lymph nodes by CT scan are 50% and 83%, while those of PET scan are 57% and 85%, respectively[13]. For identifying distant esophageal cancer metastases, PET is more accurate than combined use of CT and EUS, with a sensitivity of 74% and a specificity of 90% as compared to 47% and 78% for combined CT and EUS[8]. Sequencing a PET/CT study prior to EUS has two advantages: It allows foregoing EUS if distant metastases are found, and it may identify hypermetabolic paraesophageal lymph nodes to target for biopsy sampling by FNA[7].

If the esophageal tumor is located at the level of the tracheal bifurcation or higher then, in addition to EUS and PET/CT, bronchoscopy with biopsies and brush and washing cytologies should be performed to assess for airway invasion[14,15]. Invasion into the trachea renders the tumor unresectable[16]. Staging laparoscopy should be considered in distal esophageal and GEJ cancers as this procedure is more accurate than either EUS or CT in detecting peritoneal metastases, and has been shown to prevent unnecessary esophagectomies in patients with previously undetected stage IV disease in the abdomen[17]. Staging laparoscopy can be performed at the time of planned resection or during the initial staging workup. This can facilitate placement of a jejunostomy feeding tube for nutritional support during neoadjuvant chemoradiation.

Treatment Summary

All patients with esophageal cancer should be evaluated by a multidisciplinary team composed of gastroenterologists and surgical, radiation, and medical oncologists. Treatment of

esophageal cancer has evolved from the results of disparate clinical trials that often included patients with esophageal squamous cell carcinoma, esophageal adenocarcinoma, GEJ carcinoma, and gastric adenocarcinoma[16]. The patient population should be considered in interpreting individual trial results. In general, all patients with resectable disease (stage 0 to stage IIIC) should be considered for esophagectomy. Endoscopic eradication therapy is an option for patients with high-grade dysplasia (Tis) or T1a disease without lymph node involvement[16,18]. In patients with T1b disease, occult lymph node metastases have been found in over 10% of cases[19,20], and these patients generally are advised to undergo esophagectomy. The added benefit of neoadjuvant chemoradiation before esophagectomy is unclear in stage I patients[21]. For patients who are surgical candidates with T2 disease or higher or lymph node involvement, neoadjuvant chemoradiation followed by esophagectomy is preferred[16]. Perioperative chemotherapy and esophagectomy (in adenocarcinomas) or definitive chemoradiation (in squamous cell carcinomas or non-surgical candidates) are also acceptable alternatives[16]. In patients with stage IV disease or T4b tumors, a palliative approach should be taken. Guidelines support using gastric cancer chemotherapy regimens in the treatment of metastatic esophageal or GEJ adenocarcinomas[16].

Esophagectomy

Since esophagectomy is often required for cure, an understanding of the various surgical techniques is helpful. Open approaches include transhiatal esophagectomy (THE), transthoracic esophagectomy (TTE) such as the Ivor-Lewis procedure, and esophagectomy with three field lymph node dissection[22,23]. THE consists of a laparotomy and a left-sided cervical incision with a cervical anastomosis, while TTE consists of a laparotomy and a right-sided thoracotomy with an intrathoracic anastomosis[23]. THE and TTE are performed on mid-esophageal, distal esophageal, and GEJ cancers. A three field lymph node dissection is usually performed for esophageal cancers at the level of the carina or higher and consists of thoracotomy, laparotomy, and cervical anastomosis (McKeown procedure). Advantages of a THE include lower surgical morbidity, a statistically similar survival rate to TTE despite higher recurrence rates, and less catastrophic anastomotic leaks[22,24]. Disadvantages of THE include a higher frequency of anastomotic leaks and recurrent laryngeal nerve injury. Advantages of TTE include improved access to the tumor, more thorough mediastinal lymph node dissection, and fewer anastomotic leaks, although such leaks that occur within the chest are often fatal[22,25]. Disadvantages of TTE include higher surgical morbidity and longer recovery. The median hospital stay for THE is 15 days and for TTE is 19 days.

Multiple studies have demonstrated that institutional esophagectomy volume is inversely related to mortality rate, though the definitions of “high volume” centers vary[26,27]. It is recommended that patients undergo esophagectomy at a center with experience in surgical treatment of esophageal cancer, preferably performing at least 10-12 cases per year.

Minimally invasive esophagectomy (MIE) has been gaining increased interest and is performed in specialized centers. The MIE surgical flow is similar to a TTE but consists of laparoscopy and thoracoscopy[23]. A series from the University of Pittsburgh of 222 patients who underwent a MIE reported a median ICU stay of one day and median hospitalization of seven days with a 30 day all-cause mortality rate of 1.4%[28]. ECOG 2202, a prospective phase II trial evaluating mortality following MIE in 16 institutions, had a 30 day mortality rate of 2%, confirming the benefit of MIE[29].

Radiation Therapy

Radiation can be delivered to the esophagus using external beam radiation therapy (EBRT) or brachytherapy (BT), while metastases may sometimes be treated with stereotactic body radiation therapy (SBRT). Definitive EBRT, which has fallen out of favor, is usually delivered to a dose between 60 and 66 Gy using divided 1.8-2.0 Gy fractions to minimize toxicity[30,31]. EBRT given concurrently with chemotherapy ranges from a total dose of 41.4 Gy to 50.4 Gy[32]. Palliative EBRT is usually delivered as 30-40 Gy with fractions of 2.5-3 Gy. BT can be used as an alternative to stenting for dysphagia or tumor bleeding[31]. A catheter is placed into the esophagus and then a radioactive source is placed within the catheter to treat the luminal component of the tumor. Doses of 16-18 Gy in two or three divided fractions are used[31].

Treatment of Stage IA Cancer

Stage IA cancers generally are treated with endoscopic eradication therapy. A single-institution prospective study of German patients with Barrett's associated adenocarcinoma describes the safety and efficacy of endoscopic eradication therapy using radiofrequency ablation or photodynamic therapy in 349 patients with high grade intra-epithelial neoplasia or mucosal adenocarcinoma[18]. Three hundred thirty-seven patients who achieved a complete response were enrolled in an intensive surveillance program with endoscopies at 1, 2, 3, 6, 9, 12 months and then every 6 months thereafter up to 5 years followed by annual exams after 5 years. Overall survival, at a median follow-up of 63 months, of patients who underwent endoscopic eradiation therapy was found to be similar to the general population that was age and gender-matched[18].

Esophagectomy is preferred for patients with stage IA cancers in long-segment Barrett's esophagus containing multiple foci of dysplasia or intramucosal carcinoma, which can be difficult to eradicate endoscopically. Esophagectomy also is used when endoscopic eradication therapy fails to eradicate the neoplasia, or when submucosal invasion or lymph node metastases occur despite endoscopic eradication. Another important factor to consider when choosing between endoscopic therapy and esophagectomy for stage IA cancer is the patient's willingness and reliability to adhere to a rigorous follow-up process. Endoscopic therapy usually requires multiple treatment sessions to achieve complete eradication, and frequent, regular surveillance for recurrences. Patients unwilling or unable to comply with the frequent follow-up required for successful endoscopic eradication might be better advised to have surgery.

Surgical Candidates with Stage IB-Stage IIIC Cancer

Multiple studies have demonstrated the added survival benefit of adding chemotherapy or chemoradiation to surgical resection in patients with esophageal cancer. The following discussion reviews the clinical trials that support definitive chemoradiation, neoadjuvant chemotherapy and chemoradiation, perioperative chemotherapy, and adjuvant chemotherapy and chemoradiation. The current, preferred multimodality therapy for resectable esophageal cancer is either neoadjuvant chemoradiation, based on the RTOG 8501[30] and CROSS trials[33], or perioperative chemotherapy, based on the MAGIC trial[34]. Induction chemotherapy and the use of imaging studies to assess response during treatment are also reviewed below.

Definitive Chemoradiation

RTOG 8501[30] was a phase III trial that enrolled 121 patients with resectable esophageal cancer that did not undergo surgery. Any gastric involvement was an exclusion criterion; 88%

of patients had squamous cell carcinoma and 12% had adenocarcinoma. Patients were randomized to either radiation alone (64 Gy), or to chemoradiation with a total radiation dose of 50 Gy. The chemotherapy consisted of 5FU administered via continuous infusion over 96 hours and cisplatin given on day 1. This was repeated every four weeks for four total cycles, with the first two cycles given concurrently with radiation therapy. Median overall survival of 12.5 months in the chemoradiation arm was statistically significantly different from 8.9 months in the radiation therapy arm. Long-term follow-up demonstrated that five-year overall survival was 26% for patients who received chemoradiation and 0% for patients who received radiation alone[35]. The INT 0123 clinical trial[36] confirmed 50.4 Gy as the appropropriate radiation dose to be given with chemotherapy as there was no survival benefit for treating patients with chemotherapy and higher doses of concurrent radiation. The proportion of patients with squamous cell and adenocarcinoma was 86% and 14%, respectively, similar to the RTOG 8501 trial. FFCD 9102 was a randomized controlled trial of 444 patients with T1-3, N0-1 resectable esophageal cancer[37]. All patients were treated with chemoradiation. Those who demonstrated a treatment response were then randomized to esophagectomy or continued chemoradiation. Median overall survival was 17.7 months in the surgical arm versus 19.3 months in the chemoradiation arm, demonstrating equivalence. Since 88% of randomized patients had squamous cell carcinoma and 11% had adenocarcinoma, chemoradiation as an acceptable alternative to esophagectomy, especially in poor surgical candidates, is more accepted in patients with squamous cell carcinoma.

Several conclusions can be drawn from these clinical trials. First, definitive chemoradiation is superior to definitive radiation therapy alone. Second, the optimal radiation dose is no higher than 50.4 Gy. Third, definitive chemoradiation appears to be equivalent to surgical resection in patients with esophageal squamous cell carcinoma. In patients with esophageal adenocarcinoma, surgical resection is still preferred[4], but definitive chemoradiation based on RTOG 8501 can be considered in non-surgical candidates. In such patients, all 4 cycles of chemotherapy should be given.

Neoadjuvant Radiation Therapy

Five prospective randomized trials have examined the effects of neoadjuvant radiation therapy followed by surgery versus surgery alone in esophageal cancer, and all but one limited enrollment to patients with squamous cell carcinoma[38]. A meta-analysis of a total of 1147 patients demonstrated a 3% survival diffference at 5 years, which was not statistically significant[38]. The authors of this meta-analysis concluded that neoadjuvant radiation should not be considered outside of a clinical trial. There was no significant difference in morbidity between the radiation then surgery or surgery alone treatment arms.

Neoadjuvant Chemotherapy

The next question was whether neoadjuvant chemotherapy could improve on surgical resection alone. The INT 0113 was a multi-institutional randomized controlled trial that enrolled 440 patients in the United States with stage I-III esophageal cancer[39]. Histology was divided as 46% squamous cell carcinoma, and 54% adenocarcinoma of the distal esophagus or GEJ. Patients were randomized to receive either surgery alone or 3 cycles of chemotherapy administered every four weeks followed by surgery. Chemotherapy was given as continuous infusion 5FU over five days and cisplatin on day 1. At the time of resection, a determination of treatment response was made in patients who received neoadjuvant chemotherapy. For those patients who had a treatment response and were able to tolerate it, two additional cycles of chemotherapy were given post-operatively using similar doses of 5FU and cisplatin. Median

overall survival was 14.9 months in the chemotherapy and surgery arm and 16.1 months in the surgery only arm, which was not statistically different.

A trial in the United Kingdom also investigated the potential benefit of adding neoadjuvant chemotherapy to surgery in esophageal cancer. The OEO-2 trial[40] was a randomized controlled trial that enrolled 802 patients, 31% with squamous cell carcinoma, 63% with esophageal adenocarcinoma, and 10% with GEJ adenocarcinoma. Patients were randomized to immediate surgery or to two cycles of 5FU/cisplatin chemotherapy followed by surgery. OEO-2 demonstrated a significant survival benefit with a median overall survival of 16.8 months in the chemotherapy and surgery arm as compared to 13.3 months in the surgery only arm. More importantly, five-year overall survival between the two arms was significantly different with 17.1% of the patients in the chemotherapy and surgery arm alive compared to 5.1% in the surgery only arm.

Several reasons for the negative result seen in INT 0113 and the positive effect to neoadjuvant chemotherapy seen in OEO-2 have been considered[40]. First, OEO-2 had almost twice as many patients, which may have enabled detection of a small, but significant, survival difference. Second, a higher proportion of patients had adenocarcinomas in OEO-2 than in INT 0113 (73% versus 54%). Third, the time to surgery was longer in INT 113 compared to OEO-2, because of the chemotherapy regimen, possibly allowing more time for micrometastases to develop. The ongoing OEO-5 trial is designed to improve on these results by intensifying the chemotherapy by adding epirubicin, and by increasing the number of cycles to four.

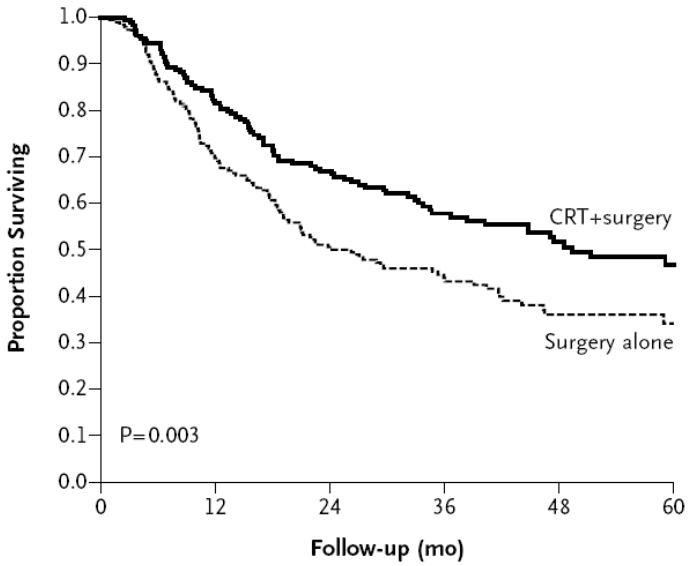

Figure 1: CROSS trial[33]. Kaplan-Meier curve demonstrating overall survival in patients treated with pre-operative chemoradiation (CRT) and surgery compared to surgery alone.

Neoadjuvant Chemoradiation

A recent meta-analysis found that neoadjuvant chemotherapy improves survival compared to surgery alone, but that neoadjuvant chemoradiation is even better[41]. While four previous trials[42-45] gave conflicting results, possibly due to methodologic problems, the recently completed CROSS trial[33] clearly demonstrates the benefit of neoadjuvant chemoradiation.

The CROSS trial[33] (**Figure 1**) enrolled 368 patients (366 available in the final analysis) with esophageal cancer or GEJ cancer that were considered resectable, T2-3 and N0-1. Patients were randomized to neoadjuvant chemoradiation followed by surgery or surgery alone. Chemotherapy was administered weekly for 5 weeks using paclitaxel 50 mg/m2 and carboplatin dosed to achieve an area under the curve of 2 mg/ml/min. This regimen has the advantage of being given peripherally without use of an infusion pump. The total radiation dose was 41.4 Gy given in 23 divided fractions. Of the patients enrolled, 75% had esophageal or GEJ adenocarcinoma and 23% had squamous cell carcinoma. Median survival was significantly improved in the chemotherapy and surgery arm (49.4 months) as compared to the surgery alone arm (24 months). Importantly, the rate of resecting all visible tumor (R0 resection) improved significantly from 69% in the surgery alone arm to 92% in the chemoradiation and surgery arm. A pathologic complete response was found in 29% of patients who received neoadjuvant therapy. The chemotherapy regimen in this trial was well-tolerated with a single grade 4 toxicity of leukopenia. This study provided data that a lower dose of radiation could be used and that a well-tolerated carboplatin and paclitaxel regimen is an acceptable alternative to cisplatin and infusional 5FU. A recent update demonstrated that neoadjuvant chemoradiation significantly increased disease free survival and significantly decreased the rates of locoregional recurrence and of developing peritoneal carcinomatosis as compared to surgery alone[46].

Perioperative Chemotherapy

The Medical Research Council of the United Kingdom undertook the MAGIC trial[34] to investigate the role of perioperative chemotherapy in gastroesophageal cancer. 503 patients with stage II or higher resectable adenocarcinoma (15% with lower esophageal, 12% with GEJ, and 74% with gastric), were randomized to surgery alone or to 3 cycles of epirubicin, cisplatin, 5FU (ECF) followed by surgery, followed by another 3 cycles of ECF. ECF consisted of epirubicin and cisplatin given on day 1 and continuous infusion of 5FU over days 1-21. This three-drug chemotherapy regimen was repeated every three weeks. There was a statistically significant five-year overall survival difference: 36% in the chemotherapy plus surgery arm compared to 23% in the surgery alone arm. Only 42% of the patients randomized to chemotherapy and surgery were able to complete all 6 cycles of chemotherapy due to toxicity. Given the inclusion of lower esophageal and GEJ adenocarcinoma patients in the MAGIC trial, these results are used to treat esophageal adenocarcinoma patients where radiation therapy is unavailable or where addition of radiation therapy could lead to treatment delay.

The results of the MAGIC trial were strengthened by the results of FFCD 9703[47]. In this phase III trial, 204 patients with resectable adenocarcinoma of the lower esophagus (11%), GEJ (64%), and stomach (25%) were randomized to surgery alone or to 6 cycles of peri-operative chemotherapy with surgery. The chemotherapy used was 5FU given on days 1-5 and cisplatin given on day 1. This was repeated every 4 weeks. The trial mandated a minimum of two cycles or a maximum of three cycles of chemotherapy be given preoperatively, with the remainder given postoperatively. Five-year overall survival was significantly in favor of chemotherapy added to surgery, with 38% of patients alive as compared to 24% of patients in the surgery alone group. Chemotherapy also improved the R0 resection rate. Importantly, the majority of patients in this trial had esophageal or GEJ cancer.

Adjuvant Therapy

Presently, the majority of patients with esophageal cancer who present to a multi-disciplinary esophageal cancer center prior to surgical resection are treated with neoadjuvant chemoradiation or peri-operative chemotherapy. In these patients there is no proven role for

adjuvant therapy. For those patients with distal esophageal or GEJ adenocarcinoma who undergo surgical resection before evaluation for neoadjuvant or perioperative therapy, adjuvant chemoradiation or chemotherapy still should be considered. Chemoradiation for these patients is based on findings from the INT 0116 trial[48], which randomized 556 patients with resected GEJ (20%) and gastric (80%) adenocarcinoma, non-metastatic stage IB-IV, to either observation or adjuvant chemoradiation. Adjuvant therapy was given as a single four week cycle of daily 5FU and leucovorin both given on days 1-5, followed by radiation to a total dose of 45 Gy in divided fractions over 5 weeks concurrently with 5FU and leucovorin given on the first four days and the last three days of radiation therapy, followed by two additional four week cycles of 5FU and leucovorin given in the same fashion as the first cycle. Median overall survival was significantly improved in the adjuvant chemoradiation arm (36 months) compared to patients who were observed without chemoradiation (27 months).

Interim results from the CALGB 80101 clinical trial[49] suggest that intensifying chemotherapy by using ECF before and after 5FU/cisplatin based chemoradiation in resected GEJ or gastric cancers is not superior to the INT 0116 regimen.

Assessing Response to Treatment

As discussed above, PET scans are effective in detecting metastatic disease[8]. There has also been interest in using PET scans to define treatment response and to select additional therapy. In a prospective trial of 65 patients with T3NX distal esophageal or GEJ (Siewert type I or II) adenocarcinoma treated with neoadjuvant chemotherapy, PET findings were able to predict overall survival[50]. Metabolic responders, defined as a decrease of FDG uptake greater than 35% on a day 14 scan compared to one done prior to treatment, had a 3 year overall survival rate of 70% compared to 35% in non-responders. In the MUNICON clinical trial[51], PET was used to select further therapy for 119 patients with GEJ adenocarcinomas treated with 5FU and cisplatin. After two weeks of chemotherapy, a repeat PET was performed and, if patients had a decrease in FDG avidity, they continued with additional chemotherapy. If not, they went on to immediate surgical resection. Two thirds of the patients (68%) had type I distal esophageal tumors. In a median follow-up of 2.3 years, non-responders had a median overall survival of 25.8 months, while median overall survival was not yet reached in responders. Progression-free survival was 29.7 months in metabolic responders and 14.1 months in non-responders. The ongoing CALGB 80803 trial is utilizing PET/CT to determine treatment response to two separate induction chemotherapy regimens prior to chemoradiation. Patients who do not achieve a metabolic response (defined as a decrease of 35% in FDG uptake) will be switched to an alternative induction chemotherapy regimen prior to chemoradiation.

Metastatic Disease

The goal of treatment for patients with metastatic disease is palliation, treating symptoms and prolonging survival while optimizing quality of life. Palliative radiation therapy can be used to control GI bleeding or improve dysphagia. Covered stents can be placed endoscopically in the airway and esophagus to treat tracheo- or broncho-esophageal fistulae. Palliative chemotherapy can extend survival and improve quality of life. A meta-analysis of chemotherapy in metastatic gastric cancer demonstrates that overall survival is improved with chemotherapy, and that response rates increase with more than one chemotherapeutic agent[52]. Typically, two or three agent regimens are used and individualized based on the patient's performance status, preferences, and medication side effect profile[53,54]. Patients with metastatic esophageal adenocarcinoma should have their tumor tested for expression of HER2/Neu due to

the results of the ToGA trial, which explored the use of Trastuzumab, a monoclonal antibody that interferes with the HER2/neu receptor [55].

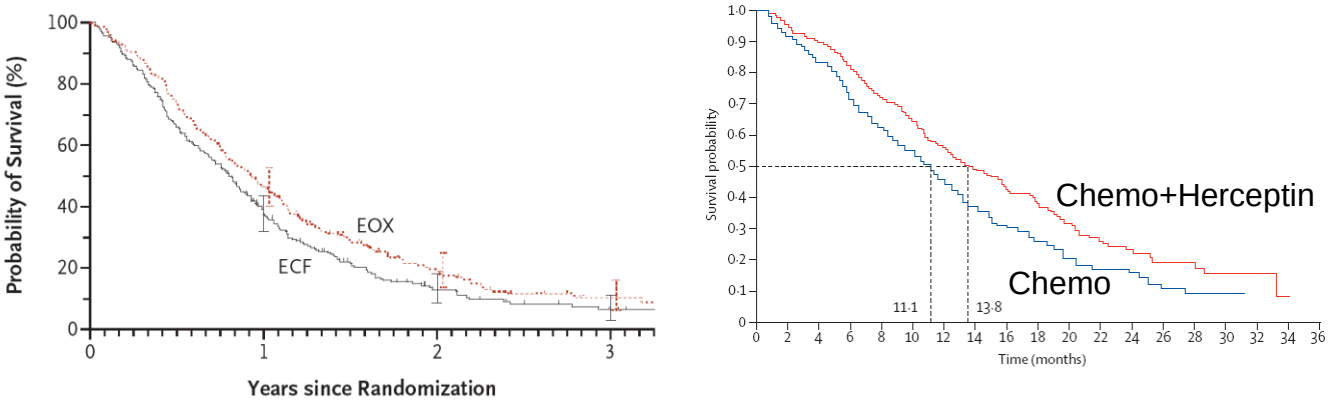

Figure 2: Phase III trials in metastatic disease. The REAL-2 trial[56] (left) demonstrated the equivalence of four common chemotherapeutic regimens used in treating patients with metastatic disease. EOX improved median survival compared to the previous standard ECF. The ToGA trial[55] (right) demonstrated the benefit of adding Herceptin to chemotherapy in patients with adenocarcinomas that overexpress HER2/neu. (Kaplan-Meier analysis).

Phase III Trials That Inform Current Treatment of Metastatic Disease

A common multi-drug chemotherapy regimen to treat metastatic esophageal cancer is ECF[16,57]. Given the development of newer platinum agents and capecitabine, an orally bio-available fluoropyrimidine pro-drug, the Medical Research Council of the United Kingdom conducted the REAL-2 trial (**Figure 2**)[56]. This was a non-inferiority study designed to demonstrate the equivalence of infusional 5FU to capecitabine and cisplatin to oxaliplatin. 1002 patients were randomized in a 2 x 2 format to epirubicin and cisplatin day 1, 5FU continuous infusion days 1-21 (ECF); epirubicin and oxaliplatin day 1, 5FU continuous infusion days 1-21 (EOF); epirubicin and cisplatin day 1, capecitabine orally twice daily days 1-21 (ECX); or epirubicin and oxaliplatin day1, capecitabine orally twice daily days 1-21 (EOX). All regimens were repeated every three weeks. Patients were previously untreated and were required to have inoperable or metastatic esophageal, GEJ, or gastric cancer; 90% of patients had adenocarcinoma and the number of patients was evenly divided among esophageal, GEJ, and gastric cancers. Median overall survival was 9.9 months for ECF, 9.9 months for ECX, 9.3 months for EOF, and 11.2 months for EOX. This has led to capecitabine-containing regimens being commonly used in metastatic esophageal cancer. Quality of life measures were not significantly different between the treatment groups.

Given the frequent overexpression of EGFR and other HER family members in esophagogastric cancers, the phase III ToGA trial (**Figure 2**)[55] randomized 594 patients with inoperable or metastatic GEJ (20%) or gastric (80%) adenocarcinoma that overexpressed HER2/Neu to receive a fluoropyrimidine with cisplatin, with or without Trastuzumab (Herceptin). Patients could have recurrent disease, but they could not have received prior treatment for metastatic disease. Chemotherapy consisted of 5FU given days 1-5 or capecitabine given orally twice daily for 14 days given along with cisplatin on day 1, repeated every three weeks. Patients randomized to receive Trastuzumab were given a loading dose on day 1, which was then followed by another dose every 3 weeks indefinitely until progression or unacceptable toxicity. Median overall survival was significantly improved in patients who received Trastuzumab (13.8 months) compared to those who did not (11.1 months). Trastuzumab

increased diarrhea, nausea, and neutropenia associated with the prescribed chemotherapy. The trial established criteria for determining HER2/Neu expression positivity in esophagogastric tumors, which differed from those used in breast cancer. Though not FDA-approved as second-line therapy, the ToGA regimen with Trastuzumab is commonly given to patients who progress on a conventional multi-agent chemotherapy regimen.

Refractory Disease

Recent data show that second-line chemotherapy is superior to best supportive care in patients with metastatic esophageal cancer, though multiple prediction factors have been proposed using clinical factors to identify patients who would benefit from chemotherapy[58]. In the randomized phase III trial COUGAR-02[59], docetaxel given every 3 weeks significantly improved overall survival versus active symptom control in patients with locally advanced or metatastatic gastroesophageal cancer who had progressed within 6 months of initial chemotherapy. Median overall survival was 5.2 months with docetaxel as compared to 3.6 months with active symptom control alone.

Molecularly-Targeted Therapy

Given the success of Trastuzumab, there has been great interest in targeting HER2 in other settings or with other agents. For example, RTOG 1010 is investigating the addition of Trastuzumab to neoadjuvant chemoradiation. The LoGIC trial is examining the effect of Lapatinib (an oral inhibitor of ErbB1 and ErbB2) added to capecitabine and oxaliplatin in HER2/Neu-overexpressing, locally advanced or metastatic esophageal, GEJ, or gastric adenocarcinoma.

Other pathways of interest for molecularly-targeted therapies include EGFR and VEGF, though recent data on agents that target EGFR have been disappointing. The SCOPE-1 phase II/III trial[60] randomized 258 patients with stage I-III esophageal carcinoma to receive definitive chemoradiation with or without Cetuximab (an antibody directed against the EGFR receptor). Cetuximab was given as a loading dose on day 1 and then weekly. Chemoradiation consisted of four cycles of cisplatin on day 1, with oral capecitabine given twice daily on days 1-21, with the third and fourth cycle given concurrently with radiation to a total dose of 50 Gy. The trial was halted in the phase II stage because the addition of Cetuximab led to worse outcomes with higher toxicity. The primary endpoint of freedom from treatment failure at 24 weeks was 66.4% in the Cetuximab arm compared to 76.9% in the no Cetuximab arm. Overall survival was worse in patients who received Cetuximab (adjusted HR of 1.53 with 95% CI 1.03-2.27), which was attributed to more patients in the Cetuximab arm prematurely stopping their therapy due to cardiac, dermatologic, and metabolic toxicities. The ongoing RTOG 0436 trial is investigating the effect of Cetuximab added to cisplatin and paclitaxel with radiation therapy in patients who are not undergoing surgery in the United States.

The EXPAND[61] phase III trial investigated the addition of Cetuximab to cisplatin and capecitabine in 904 patients with previously untreated, unresectable or metastatic gastric adenocarcinoma, with a primary endpoint of progression free survival. Cetuximab was given as a loading dose on day 1 followed by weekly doses. Chemotherapy was given as three-week cycles of capecitabine daily on days 1-14, and cisplatin on day 1. No significant difference in progression-free survival was seen in the two groups, with a median progression-free survival of 4.4 months in those who received Cetuximab, compared to 5.6 months in those who did not. Toxicities from Cetuximab included diarrhea, electrolyte abnormalities, rash, and hand-foot

syndrome. The authors postulated that the results may have been hampered by the choice of chemotherapy backbone.

The phase III REAL-3 trial investigated the effect of adding Panitumumab (another antibody directed against EGFR) to ECX as first-line therapy in locally advanced, inoperable or metastatic esophageal, GEJ, or gastric adenocarcinoma[62]. 553 patients were randomized to either the REAL-2 ECX regimen or to Panitumumab on day 1 with modified ECX. The trial was halted early at a planned interim analysis as median overall survival was significantly decreased in patients who received Panitumumab (8.8 months) compared to those who did not (11.3 months) with a Hazards Ratio of 1.37, 95% CI 1.07-1.76. Possible explanations were decreased dose intensity of the chemotherapeutic agents, interaction between Panitumumab and one of the chemotherapies, and non-selection of patients for Panitumumab treatment based on K-ras mutation status. Toxicities in the Panitumumab patients included an increased rate of diarrhea, rash, mucositis, and hypomagnesemia.

Results from targeting the VEGF pathway have been more encouraging. The AVAGAST trial combined Bevacizumab (an antibody directed against the VEGF ligand) with cisplatin and capecitabine as first-line therapy in patients with unresectable or metastatic GEJ or gastric cancer[63]. 774 patients were randomized to receive cisplatin on day 1 and capecitabine twice daily on days 1-14 every three weeks, with or without Bevacizumab 7.5 mg/kg on day 1. Median overall survival was not significantly different but favored patients who received Bevacizumab (12.1 months) versus those who did not (10.1 months). Progression-free survival (6.7 months) and tumor response (46%) were significantly improved in patients who received Bevacizumab compared to those who did not (5.3 months and 37%, respectively). The ongoing MAGIC-B trial is investigating the addition of Bevacizumab to 6 perioperative cycles of ECX in patients with resectable GEJ (Siewert III) or gastric adenocarcinoma.

The recently published REGARD trial[64] demonstrated an overall survival benefit for using Ramucirumab (an antibody against the VEGFR2 receptor) as compared to best supportive care as second-line therapy in metastatic gastroesophageal or gastric cancer. Side effects of Ramucirumab included hypertension, anemia, abdominal pain, ascites, fatigue, anorexia, and hyponatremia. Based on these results, the FDA has designated Ramucirumab for priority review. Preliminary results from the RAINBOW trial with 655 patients were recently presented at the 2014 GI Cancers Symposium. The addition of Ramucirumab to Paclitaxel increased median overall survival to 9.6 months as compared to 7.4 months with Paclitaxel alone as second-line therapy in locally advanced or metastatic GEJ or gastric tumors that progressed on a fluoropyrimidine and platinum containing regimen.

Emerging Concepts

An alternative approach for managing esophageal cancer is preventing the malignant progression of precursor lesions, squamous dysplasia in squamous cell carcinoma or Barrett's esophagus in adenocarcinoma. In Barrett's esophagus, this is an attractive strategy as Barrett's epithelium has a characteristic appearance on endoscopy, the histopathologic changes are readily diagnosed by pathologists, and a malignant progression sequence through low and high-grade dysplasia and transformation into invasive adenocarcinoma is well-defined.

Barrett's esophagus, the metaplastic change of the stratified squamous epithelium lining the distal esophagus to columnar epithelium, is thought to be an adaptive response to chronic injury from gastroesophageal reflux[65]. With continued exposure to acid and bile salts, Barrett's epithelium can acquire an increasing number of genetic alterations leading to development of

concomitant dysplasia. It is estimated that the risk for developing esophageal adenocarcinoma in patients with Barrett's esophagus without dysplasia is between 0.12% and 0.33% per year[66,67]. This increases to a 0.44% annual incidence rate in patients with Barrett's esophagus and low-grade dysplasia and to roughly a 6% annual incidence rate in those with Barrett's esophagus and high-grade dysplasia[68,69]. Given that this risk is cumulative, patients with Barrett's esophagus and high-grade dysplasia would, in the past, undergo prophylactic esophagectomy. In 2009, radiofrequency ablation was shown to be an effective endoscopic method to eradicate dysplasia and prevent progression[70]. Among 63 patients with Barrett's esophagus and high-grade dysplasia, 81% had complete eradication of their dysplasia and the risk of progression was reduced from 19% to 2%. Among 64 patients with Barrett's esophagus and low-grade dysplasia, 91% had complete eradication of their dysplasia and the risk of progression was reduced from 14% to 5%. A recent study, conducted in the Netherlands, in 136 patients with Barrett's esophagus and low-grade dysplasia found that radiofrequency ablation reduced the risk of progression to either high-grade dysplasia or adenocarcinoma from 26.5% to1.5% and to adenocarcinoma from 8.8% to 1.5%[71]. In this more recent trial, the diagnosis of low-grade dysplasia had to be confirmed by an expert panel of pathologists. Whether this would be feasible in the United States is unclear.

Despite the success of radiofrequency ablation, these studies demonstrate that a subset of patients still progress to esophageal adenocarcinoma. Further, the development of subsquamous intestinal metaplasia following radiofrequency ablation has been recognized[72]. Subsquamous intestinal metaplasia is found buried below healed neosquamous epithelium and requires random biopsies to diagnose as it cannot be visualized endoscopically. In theory, this subsquamous intestinal metaplasia has the same risk of malignant progression as the original Barrett's epithelium.

Inhibiting molecular signaling pathways that induce columnar metaplasia could be an important adjunct to radiofrequency ablation and serve as a molecularly targeted chemopreventative or therapeutic strategy for Barrett's esophagus and esophageal adenocarcinoma. Recognizing that the embryonic esophagus is initially lined by a columnar epithelium that undergoes squamous differentiation and stratification (simplistically "Barrett's esophagus in reverse"), we have taken a developmental approach to identify novel pathways involved in Barrett's metaplasia pathogenesis. One pathway that is highly expressed during the columnar phase of mouse embryonic esophageal epithelial development and then is extinguished when the epithelium becomes stratified squamous is the Hedgehog signaling pathway. We have shown that in the normal adult human esophageal squamous epithelium Hedgehog signaling is absent. However, Hedgehog signaling can be reactivated with acid and bile exposure and is found in Barrett's esophagus, Barrett's esophagus with dysplasia, and esophageal adenocarcinoma tissues[73]. Hedgehog signaling can induce phenotypic changes characteristic of Barrett's epithelium in human squamous esophageal epithelial cells, including induction of both columnar genes and genes associated with intestinal mucin production. In primary and established esophageal adenocarcinoma cell lines, we have demonstrated that Hedgehog signaling is upregulated following chemotherapy treatment (mediating chemoresistance) and that inhibiting Hedgehog signaling decreases proliferation in these cells. A phase Ib clinical trial with a Hedgehog inhibitor in combination with chemotherapy in patients with metastatic gastroesophageal cancer is ongoing and the results are pending.

Treatment Recommendations for Patients with Esophageal Cancer

1) Once diagnosed with esophageal cancer, patients should undergo staging with a PET/CT scan and endoscopic ultrasonography. Bronchoscopy should be performed for tumors at the level of the carina or higher. Staging laparoscopy should be done as part of the initial staging evaluation, or at the time of planned esophageal resection.

2) Patients should be managed by a multidisciplinary team of experts and enrollment in clinical trials should be prioritized.

3) For patients with stage IA disease, endoscopic eradiation therapy is an acceptable alternative to esophagectomy.

4) For patients with stage IB-III disease, neoadjuvant chemoradiation (RTOG 8501 or CROSS trial regimens) followed by esophagectomy is preferred. Acceptable alternatives are peri-operative chemotherapy (MAGIC trial regimen) and esophagectomy OR definitive chemoradiation (RTOG 8501 regimen) for non-surgical candidates.

5) Esophagectomy should be performed in a specialized, high volume center by a surgeon experienced in esophageal cancer surgery.

6) For patients who have surgery without prior neoadjuvant therapy, adjuvant chemoradiation (INT 0116 regimen) should be offered.

7) For patients with metastatic adenocarcinoma, the tumor should be tested for HER2/Neu amplification. If positive and the patient is a chemotherapy candidate, a Trastuzumab-containing regimen should be used (ToGA regimen). If negative and the patient is a chemotherapy candidate, a multi-agent chemotherapy regimen (REAL-2 regimens) should be chosen based on the patient's performance status.

8) Palliative adjuncts such as radiation therapy or stent placement should be considered by members of the multidisciplinary treatment team.

Issues for Primary Care Physicians

Patients who receive chemoradiation can develop severe esophagitis. If patients are at nutritional risk, a percutaneous feeding tube should be considered prior to the initiation of therapy. For patients who undergo esophagectomy and gastric pull-up, they will need to eat 5-6 small meals throughout the day and remain on proton pump inhibitors life-long. A normal digestive routine will take approximately 12 months to establish. Patients will undergo surveillance with oncology clinic visits and imaging every 3 months for the first two years, every 6 months for the next two years, then annually. After 5 years, patients may opt to follow with their primary care physicians only. Patients with metastatic disease can develop a tracheoesophageal fistula, which can be treated with a wall stent. This should be suspected if a patient develops chronic cough, recurrent pulmonary infections, or unexplained fever.

Patients with Barrett's esophagus without dysplasia should undergo surveillance endoscopies every 3-5 years with four quadrant biopsies taken every 1-2 cm of visualized Barrett's esophagus[74]. For patients with low-grade dysplasia, endoscopies should be performed every 6-12 months and for patients with high-grade dysplasia every 3 months[74]. Four quadrant biopsies should be taken every 1 cm in patients with dysplasia.

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