Esophageal cancer is the 7th leading cause of cancer deaths worldwide. While squamous cell carcinoma is the most prevalent histology internationally, adenocarcinoma of the distal esophagus accounts for nearly 50% of cases in developed countries due to the differences in etiologic factors such as gastroesophageal reflux disease (GERD) and obesity that predominate. While surgery is the mainstay of treatment of this disease, the utilization of chemoradiation, either used postoperatively or neoadjuvantly, has become a standard practice in the United States. What is the optimal management approach is still an area of contention, however, and may be different in different regions around the world. This article reviews some of these controversies, including the role for surgery in patients treated with definitive chemoradiation. At the end, we will also outline recommendations regarding radiotherapy procedures and techniques.

**Key words:** Esophageal cancer, stage, combined modality treatment, radiation technique

### Epidemiology and Risk Factors

Esophageal cancer is a serious and deadly cancer and is the seventh leading cause of cancer deaths worldwide. The incidence of esophageal cancer varies depending on the regions of the world, with rates from 30 cases to as high as 800 cases per 100,000 persons. Highest incidence occurs in areas such as northern Iran, southern Russia, and northern China. While squamous cell carcinoma accounts for 95% of the pathology of esophageal cancers worldwide, adenocarcinomas are becoming an increasing and common entity in the western world. For instance in the 1970’s squamous cell carcinoma accounts for the majority of cases in the United States. However adenocarcinomas of the distal and gastroesophageal junction achieved the status of being the fastest growing incidence rate of all cancers in the United States, and have now exceeded the incidence of squamous cell carcinomas.

The reason for the shift in the epidemiology of esophageal cancers in the Western world has to do with the causative factors for esophageal cancers. Squamous cell carcinoma is strongly associated with smoking and alcohol consumption, genetic risk factors such as Tylosis and Plummer-Vinson Syndrome, and environmental exposures to lye ingestion and therapeutic irradiation. Smoking and alcohol are synergistic in contributing to the development of squamous cell carcinomas of the esophagus. Adenocarcinomas of the esophagus most often arise from the distal portions of the esophagus and are associated with Barrett’s esophagitis, a metaplasia that occurs at the distal gastroesophageal junction due to chronic irritation from GERD. Obesity, whether related to the development of GERD or to the consumption of western diet poor in vitamins, vegetables, fruits, fish and poultry, is also a strong risk factor in the development of adenocarcinoma of esophagus.

### Anatomy, pathology, and patterns of spread

The esophagus is an approximately 25 cm muscular tube that spans from the cricopharyngeus at the cricoid cartilage above to the gastroesophageal sphincter below. It is served by a rich network of lymphatic channels and nodes that traverse throughout the mediastinum. The esophagus is drained by a submucosal lymphatics draining to regional lymph nodes in the cervical, mediastinal, paraesophageal, gastric, and celiac regions. The esophagus has four layers (mucosa, submucosa, muscularis propria, and adventitia) but unlike other gastro-intestinal (GI) organs below the diaphragm, the esophagus doesn’t have a serosa layer. Therefore local extension of disease to adjacent structure is common due to lack of barrier to locoregional spread. Common areas of local spread include adjacent structures
such as the pericardium, heart, trachea, vertebral body, and lung. Besides locoregional spread, hematogenous spread to distant sites is common, especially for adenocarcinoma. The most common sites of spread are the lungs, liver, and bone.

**Diagnosis and workup**

Most patients with esophageal cancers present in their 5th and 6th decade of life. The most common presenting symptoms of patients with esophageal cancers are dysphagia and weight loss, occurring in nearly 90% of patients. The dysphagia is typically described as a progressive dysphagia from solids initially to liquids due to the tumor obstructive process. Other symptoms include odynophagia, hoarseness, cough, chest pain, melena, and sequel of locally advanced disease and distant areas of spread of disease. Over 75% of patients will have lymph node involvement at the time of presentation. After a complete history detailing duration and severity of symptoms will be important to determine if nutritional intervention through feeding tube will be necessary. Physical examination is often unrevealing, except for the occasional instance where a cervical or supraclavicular lymph node will be apparent. A barium swallow study can be done to visualize a filling defect that distinguishes obstructive causes of dysphagia from neurogenic ones. An esophagogastroduodenoscopy (EGD) is the most direct way to visualize the size and the circumferential and linear extent of the disease, as well as for the tumor to be biopsied. An endoscopic ultrasound (EUS) is the only way to definitively stage the tumor, since the American Joint Commission on Cancer (AJCC) TNM staging system relies on the depth of invasion (T) and nodal involvement (N). Often suspicious nodes seen by EUS can be biopsied by fine needle aspiration (FNA). For those nodal areas within the mediastinum that is not easily accessible by EUS, an endobronchial ultrasound (EBUS)-guided FNA of suspicious nodal areas could be used. Contrast enhanced computed tomography (CT) scan of the chest and abdomen will be at the minimum necessary to rule out potential distant metastatic disease, however fluorodeoxyglucose-postron emission tomography (FDG-PET)/CT is useful for initial staging workup but also as a baseline study to determine the response to therapy, whether that will be induction chemotherapy or chemoradiation. Many studies have demonstrated the utility of PET as a gauge of treatment response, with tumors that demonstrate response on FDG-PET to have a better prognosis. PET scan also has far better sensitivity and specificity than a CT scan, and therefore is able to detect occult metastasis in 15% of cases.

**Cancer staging**

The 7th Edition AJCC Cancer Staging Manual has made several revisions to the previous staging system for esophageal cancers. The most notable change is in the nodal staging where a more surgical staging system is in place to give prognostication for the number of lymph nodes (N1 = 1–2 nodes, N2 = 3–6 nodes, and N3 = greater than or equal to 7 nodes). Stage grouping is giving weight to the grade of the cancer which was not done in the past, as well as adding a separate stage grouping for squamous cell carcinoma of the esophagus, recognizing the differences in the prognosis of the cancer depends on the tumor location (with lower location being slightly better in prognosis due to resectability of these tumors). The M staging has also undergone changes, with the elimination of the M1a designation that was reserved for nodal involvement in the celiac axis (for distal esophageal tumors) or supraclavicular area (for cervical esophageal and upper thoracic). Now nodal involvement in these areas are still given the N staging designation, while distant nodal (cervical, paraaortic) and organs (lung, liver, bone) to be strictly designated as M1. A summary of 7th Edition staging system for adenocarcinoma of the esophagus is in Table 1. Table 2 summarizes a new addition to the staging system accounting for the difference seen for squamous cell carcinoma of the esophagus.

**Management**

The goals in managing esophageal cancers are not only to treat the underlying disease but also to relieve obstructive symptoms. Except for the earliest stage of cancers, a multidisciplinary approach utilizing all three disciplines of cancer management (surgery, radiation, chemotherapy, or “trimodality”) should be employed for best outcomes. However, surgery is the mainstay of treatment for all stages of esophageal cancers, with a 5-year overall survival for all comers to be 20%–25% [4,5]. The most common surgical approach is esophagectomy, either using transthoracic or transhiatal approaches for dissection. Transhiatal esophagectomy is a less morbid procedure that is good for removal of distal tumors but has poorer visualization for upper/middle thoracic tumors giving the more limited dissection that can be performed. Transthoracic approach using a right thoracotomy (Ivor-Lewis) or left thoracotomy allow great exposure an dissection of the lymph nodes, however the Ivor Lewis is generally the preferred approach for most surgeons given the fact that it allows great exposure of all levels of the esophagus (and therefore a better lymph node dissection) whereas the left thoracotomy may provide access to only
the distal esophageal tumors. The drawback for transthoracic approach is the potential of greater postoperative morbidity, while anastomotic leakage rate is lower than the transthiatal approach. The surgical morbidity and mortality is strongly related to the experience of the surgeons, with much lower complication rates in high volume centers. A large meta-analysis examining the differences in the outcomes of the two surgical approaches find no difference in the survival outcomes (both range in the order of 20%–25% in the 5-year overall survival rate)\(^6\). Despite the importance of surgery in the management of esophageal cancers, the local control rates remains poor for locally advanced disease if used alone, with local failure rates around 19%–57% depending on the stage of disease and resection margin status.

Radiation is an important component in the management of esophageal cancers, although when used alone it tends to have poor outcomes. Radiation alone is however done in the palliative setting to help relieve bleeding or obstruction in patients who are unresectable and in a poor medical condition. The role of radiation therapy after esophagectomy remains controversial. One randomized study indicated that post-operation radiotherapy improved local control and survival for patients with positive lymph nodes but other randomized studies showed no survival benefit\(^6\). Intergroup adjuvant gastric cancer trial 0116 in the United States that included a subset of tumors (~25%) in esophageal/gastroesophageal junction cancers indicated that post-operation concurrent chemotherapy/radiotherapy improved survival and should be considered\(^9\). For curative intent, radiation should be administered with chemotherapy, either preoperatively or definitively. Details of the evidence in support of these approaches are given below.

Combination chemotherapy, typically in the form of cisplatin, 5-fluorouracil, or docetaxel, is either given alone in...
patients with distant metastasis, together with radiation to enhance radiotherapy efficacy, or perioperatively with or without radiation. More recently, targeted agents utilizing antagonists against epidermal growth factor receptor or other biologic agents, are added to conventional cytotoxic chemotherapy in experimental studies[9].

**Early stage (T1aN0 or T1bN0)**

The standard approach for the treatment of early stage esophageal cancers is esophagectomy, however local excision techniques such as endoscopic mucosal resection (EMR) are good options for patients with localized high grade dysplasia, carcinoma-in-situ, or mucosal disease (Tis-T1a). EMR involves the submucosal injection of saline to lift and separate the lesion from the underlying muscular layer, with resection carried out by suction trapping the lesion into a cylinder device. Patients should be selected to undergo this procedure, such as tumors less than 2 cm, or well to moderately differentiated without invasion beyond the mucosal layer, ulceration, and lymph vascular invasion (LVI). In the best selected patients to undergo this procedure, the outcomes are often excellent. In the single institution study from Germany involving 100 consecutive patients with 147 resections, the 5-year survival is 98% (two patients died from other non-cancer related causes), with recurrent or metachronous lesions in 11% of the patients with repeat EMR salvaged successfully. The only complication is minor bleeding from the procedure[11].

For patients with submucosal involvement (T1b), the risk for nodal metastasis and lymphovascular invasion is substantially higher than those with earlier stage disease[12]. The standard of care is esophagectomy, with 5-year survival of ~70% and disease-free survival of 80%. However patients with LVI or nodal metastasis tend to do much worse than those without, with 5-year survival rates that is nearly equal to those in the more advanced setting (<37%)[11]. Patients with LVI or nodal metastasis that undergo esophagectomy have a relapse rate of 16%[11]. There is still a need to improve the outcomes of patients in this category and is currently an area of active research, particularly in Japan where the utilization of definitive chemoradiation has been employed as a way for possible organ preservation. However, the 4-year recurrence-free survival is 52.8% and the 4-year survival is 80%[13]. Many of the patients could be salvaged using endoscopic approaches, but those patients with nodal failures tend to be unsalvageable. Currently, a phase-II trial (JCOG0508) is testing the role of EMR in combination with chemoradiation as a management of patients with stage-I esophageal cancers[14].

**Locally advanced cancer (T2–4N0 or N+)**

For patients with T2+ or N+ disease, the optimal management is controversial and standard therapy could vary depending on the region of the world. Surgery is still the mainstay of treatment, but since the 5-year overall survival is only 20%–25% and the local recurrence risk is fairly high (around 50%), adding additional therapies postoperatively or upfront prior to surgical resection may help to improve outcomes. Postoperative therapies incorporating radiation alone, chemoradiation, or chemotherapy alone have been tested in multiple randomized trials. In general, radiation or chemotherapy alone is not indicated but the issue of post-operation radiotherapy remains controversial. However for distal esophageal and gastroesophageal junction tumors, postoperative chemoradiation may be indicated based on the United States. Intergroup 0116 study that randomized 556 patients with gastric (80%) or gastroesophageal junction (20%) tumors, stage lb or greater (except those with T2aN0 disease) to surgery alone or postoperative chemoradiation using 5-FU and leucovorin[9]. The study demonstrated improved median overall survival in the chemoradiation group (36 months versus 27 months, \( P = 0.005 \)) and a 3-year absolute survival benefit of ~10% using chemoradiation[9]. More studies to date have incorporated the use of preoperative treatment in the management of esophageal cancers, but the standard regimen differs internationally. In the United States, the standard approach is preoperative chemoradiation, but in the United Kingdom (or possibly in Europe as well) the standard may be perioperative chemotherapy.

**Preoperative chemotherapy**

In the United States, the use of neoadjuvant chemotherapy was largely abandoned based on the United States Intergroup 0113 study that randomized 467 patients with squamous (46%) or adenocarcinoma (54%) of the esophagus to surgery alone or to preoperative (3 cycles cisplatin/5-FU) and postoperative chemotherapy (2 cycles cisplatin/5-FU). The pathologic complete response (pCR) rate to chemotherapy was 2.5%, but there were no differences in R0 resection or survival between the treatment groups (4-year overall survival 23% versus 26%, median survival 15 months versus 16 months, respectively)[15,16]. These results could not have been more different in the trials done in the United Kingdom with the Medical Research Council (MRC) trials, OE02 and Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC). MRC OE02 is a prospective randomized study that randomized 802 patients with esophageal adenocarcinoma (66%) or squamous cell carcinoma (31%) to preoperative chemotherapy using 2 cycles of cisplatin/5-FU or surgical resection alone[17]. The investigators found that preoperative chemotherapy group yielded a better R0 resection rate (60% versus 54%, \( P < 0.001 \)) and better survival (2-year overall survival 43% versus 34%, median survival 16.8 months versus 13.3 months, \( P = 0.004 \))[17]. In the MAGIC trial, 503 patients with gastric (74%), GEJ (11%), or distal esophageal (15%) adenocarcinomas were randomized to perioperative
Epirubicin/cisplatin/5-FU (ECF) for 3 cycles pre- and postoperatively or surgical resection alone\[^{[18]}\]. There was a significant downstaging using chemotherapy, with more T1 and T2 tumors (51.7% versus 36.8%) and smaller tumors (3 cm versus 5 cm) in the chemotherapy arm. This yielded a better 5-year overall survival (36% versus 23%, \(P < 0.009\)) and disease-free survival (HR 0.66). The toxicities were similar between the two groups\[^{[18]}\].

**Preoperative chemoradiation**

Preoperative chemoradiation, although a standard practice in the United States for the management of esophageal cancers, is not without its controversies. The seminal study that is often cited as proof for the standard of care in the United States is based on an Irish study that randomized 113 patients with adenocarcinomas of the esophagus to 2 cycles of preoperative cisplatin/5-FU and concurrent radiation to 40 Gy in 15 fractions or to surgical resection alone\[^{[16]}\]. The pCR rate for preoperative chemoradiation was 25%. There was a significant improvement in the 3-year overall survival (32% versus 6%) and median survival (16 months versus 11 months) (\(P = 0.01\)) for the preoperative chemoradiation group. Many with a pCR (85%) were alive and disease-free at 2 to 43 months. However, the surgical resection group had an unusually poor 3-year survival rate of 6%, especially when historical surgical series demonstrate a 3-year survival of 20%–25%. Many would argue that preoperative chemoradiation made up for the poor outcomes of surgery in this series of patients. At around the same time, Arlene Forastiere and colleagues in the United States were also studying the role of preoperative chemoradiation, first as a phase-II study that demonstrated promising results compared to historical controls of surgery alone\[^{[20]}\], and later as a prospective randomized study of 100 patients\[^{[21]}\]. This latter study randomized patients to preoperative chemoradiation with 5-FU/cisplatin/vinblastine plus radiation (45 Gy) or surgery alone. The pCR rate was 28%. There was an improved local control rate in the chemoradiation group (81% versus 60%, \(P = 0.04\)), but because of the small size of the study, there was only a trend to improved survival for the chemoradiation group (30% versus 16%)\[^{[21]}\]. Although being technically a negative study, this trial is largely viewed as a positive trial demonstrating the superiority of preoperative chemoradiation since the survival rate in the neoadjuvant group is similar to the study by Walsh et al.\[^{[23]}\] and that the surgery alone arm had survival rates that was largely equivalent to historical rates. These results were further corroborated by the recent publication of the results of CALGB 9781, a phase-III study that closed to poor accrual with only 56 patients enrolled out of the planned 475 patients\[^{[23]}\]. Patients were randomized to preoperative cisplatin/5-FU and radiation to 50.4 Gy or surgery alone. The pCR rate was 40%, and the median survival was better in the chemoradiation group (4.5 years versus 1.8 years) as well as the 5-year overall survival (39% versus 16%). However, trials done through the EORTC (Europe) and the TTOG (Australia) testing the role for preoperative chemoradiation have been largely negative studies, with only a benefit of disease-free survival but not overall survival for patients treated with preoperative chemoradiation\[^{[21, 24]}\]. A meta-analysis of 10 randomized trials comparing preoperative chemoradiation versus surgery (1209 patients) and 8 trials comparing preoperative chemotherapy versus surgery (1724 patients) actually found that both approaches are potentially beneficial\[^{[25]}\]. For the preoperative chemoradiation studies, the meta-analysis found better hazard-ratio for mortality (0.81), corresponding to a 13% absolute 2-year survival benefit. The benefit was seen for both squamous and adenocarcinoma histologies\[^{[26]}\]. Analysis of the preoperative chemotherapy trials also found a better hazard-ratio of 0.90, corresponding to a 7% of absolute 2-year survival benefit (\(P = 0.05\)). But for preoperative chemotherapy, it appears that only adenocarcinomas seemed to benefit. There is a paucity of data that directly compares preoperative chemotherapy to chemoradiation. One prospective randomized trial comparing preoperative chemotherapy with preoperative chemoradiation was recently published by the German Esophageal Cancer Study Group\[^{[27]}\]. The study was closed early due to poor accrual after only 126 patients were enrolled out of 354 planned. All patients had T3–4NxM0 adenocarcinoma of the gastroesophageal junction or gastric cardia. They were randomized to preoperative chemotherapy (2.5 cycles 5-FU/cisplatin/LV) or preoperative chemoradiation consisting induction chemotherapy for 2 cycles, followed by preoperative chemoradiation using cisplatin/etoposide and 30 Gy radiation. The study can be criticized for the use of induction chemotherapy, which is known to potentially increase toxicity and decrease tolerance to preoperative chemoradiation, the use of unconventional concurrent chemoradiation, and the relatively low radiation dose. Despite these limitations, the pCR rate was higher in the chemoradiation arm (15.6% versus 2.0%) with a trend to improved overall survival (3-year overall survival 47.4% versus 27.7%, \(P = 0.07\)). The postoperative mortality rate is slightly increased in the chemoradiation group, but not significantly (10.2% versus 3.8%, \(P = 0.26\)).

At University of Texas M. D. Anderson Cancer Center, our standard of care protocol is the trimodality approach, using preoperative chemoradiation followed by surgical resection. This is based not only on the evidence from the United States studies and the meta-analysis, but also from our own experience treating patients using the trimodality approach compared to surgery alone. For stage-II and -III
patients treated at our institution, the 3-year overall survival is 45% compared to 37% treated with surgical resection or with preoperative chemotherapy ($P = 0.02$). For patients with clinical stage-III disease, the difference is even more pronounced, with a 3-year survival of 45% for preoperative chemoradiation versus 29% for surgical resection alone ($P < 0.001$) (unpublished).

**Definitive chemoradiation for patients with unresectable esophageal cancers**

For patients who are medically or technically inoperable (especially for those with proximally-located tumors), definitive chemoradiation should be the standard of care since around one-fifth of the patients can be cured using this regimen. RTOG 8501 determined this in 121 patients with unresectable esophageal cancers randomized to either radiation alone (64 Gy) or chemoradiation (50 Gy) [27,28]. Because of early stoppage rules, the trial close early after the chemoradiation arm demonstrated superior outcomes. The median survival is 12.5 months in the chemoradiation group and 8.9 months in the radiation alone arm ($P = 0.001$). In the most recent update, the 5-year overall survival is 26% in the chemoradiation group compared to 0% in the radiotherapy alone group. The survival essentially plateaued at the 3-year time point. There was also a benefit for local recurrence and distant metastatic rates. In a second non-randomized group of patients separated from the main study, the 5-year survival was 14% versus 9%, respectively. There were more grade-3 and -4 toxicities seen in the chemoradiation group.

The question of whether escalating the dose beyond 50 Gy using concurrent chemotherapy produced additional benefit was tested in RTOG 9405 (Intergroup 0123) [29]. This trial randomized 236 patients with unresectable T1-4, N0/1, M0 squamous cell or adenocarcinoma of the esophagus to standard dose (50.4 Gy) or high radiation dose (64.8 Gy) with concurrent chemotherapy (2 cycles during and 2 cycles after with 5-FU (1000 mg/m² for 4 days) and cisplatin (75 mg/m² on day 1). The trial closed early owing to no benefit of the high dose arm, with a trend to worse survival in the high dose arm (13 months versus 18 months, 2-year overall survival of 31% versus 40%). Although there were 11 patient deaths coded as treatment-related in the high dose versus only 2 in the low dose group, 7 of the 11 deaths occurred before reaching 50.4 Gy. There was no good explanation for this, but regardless the standard dose has been fixed at 50.4 Gy ever since. For cervical or proximal squamous cell carcinoma of the esophagus, achieving a dose typically used for cancers of the head and neck will be desirable. Case series from M. D. Anderson Cancer Center using intensity-modulated radiation therapy (IMRT) plus cisplatin/5-FU and from Australia show that achieving doses towards 70 Gy (60–66 Gy) demonstrates good local control and response rates (88% local control, 5-year survival of 55% from Burmeister et al. series) [30,31]. However such doses to the esophagus can have high rates of fibrosis, stricture, and fistula formation that diminishes the quality of life for these patients [32].

**Is adding surgery necessary after chemoradiation?**

Since esophageal cancers often afflict those who are not the best candidates for surgery (obesity, diabetes, extensive smoking and alcohol history), esophagectomy after preoperative chemoradiation can often carry substantial morbidity and mortality. Is an esophagectomy necessary for all patients following preoperative chemoradiation? The importance of surgery was addressed in two clinical trials. First is a randomized trial based in Germany that randomized 172 patients with locally advanced squamous cell carcinoma of the esophagus to either induction chemotherapy, followed by neoadjuvant chemoradiation to 40 Gy and surgery versus induction chemotherapy followed by definitive chemoradiation to 65 Gy or above. Induction chemotherapy utilized 3 cycles of bolus 5-FU/LV/ cisplatin/etoposide and concurrent chemotherapy was cisplatin/etoposide [32]. The pCR rate after preoperative regimen was 35%. Although the study demonstrated a better local progression-free survival after surgery (2-year progression-free survival rate 64.3% versus 52.1%, $P = 0.03$), there was no difference in 2-year overall survival (39.9% surgery versus 35.4% chemoradiation, log-rank test for equivalence $P = 0.007$). This was due to the fact that although patients in the surgical arm were less likely to die from cancer, they had significantly higher risk of treatment-related deaths compared with patients who didn’t get surgery (12.8% versus 3.5%, $P = 0.03$). A second trial was a French study that randomized 444 patients with T3N0–1 of mostly squamous cell carcinomas (89%) to initially 2 cycles of 5-FU/cisplatin and 46 Gy of radiation [33]. Patients were evaluated for response after treatment 38–41 days posttreatment. If patients had an objective clinical response defined by an improvement (either complete or partial) in dysphagia and of visible tumor on esophagogram (partial response is a decrease of > 30%) and were still good candidates for surgery, they were randomized to either surgery or to continuation of chemoradiation for an additional 20 Gy (total of 66 Gy). The local control rate was better for surgery (66.4% versus 57%, $P < 0.001$). Like the German trial, there was again no difference in 2-year overall survival (34% surgery versus 40% chemoradiotherapy, $P = 0.14$), probably due to a greater 3-month mortality rate in the surgery arm (9.3% versus 0.8%, $P = 0.002$).

It is clear from the above two studies, the local control benefit of surgery is undisputed, and the survival benefit from adding surgery to chemoradiation could have been seen if the postoperative mortality rates were kept low. We have evaluated our experience with either definitive chemoradiation or with preoperative chemoradiation in...
patients treated at M. D. Anderson Cancer Center between 1990 and 1998[34]. In a retrospective review of 132 consecutive patients with clinical stage II or III esophageal cancers, half (60) underwent esophagectomy 6–8 weeks after chemoradiotherapy. The median dose of radiation was 50 Gy in the definitive chemoradiation group, and 45 Gy in the preoperative group. Compared to the definitive chemoradiation group, there were far more patients in the preoperative group who were younger (median 59 versus 66 years old, \( P < 0.001 \)), had better KPS (88% versus 83%, \( P = 0.003 \)), had more T4 tumors (16% versus 3%, \( P = 0.03 \)), and had more tumors in the distal esophagus/GE junction (72% versus 33%, \( P < 0.001 \)). Patients treated with preoperative chemoradiation had better 5-year locoregional control (67.1% versus 22.1%, \( P < 0.001 \)), disease-free survival (40.7% versus 9.9%, \( P < 0.001 \), 5-year overall survival (52.6% versus 6.5%, \( P < 0.001 \)) and median survival (62 months versus 12 months). However, there was no statistically significant difference in the rate of distant metastatic disease between the two groups (67.5% versus 65.8%, \( P = 0.3 \)). On univariate and multivariate analysis, surgical resection of the tumor was an independent predictor of improved loco-regional control and overall survival. To reduce the potential selection bias in the surgery arm, 34 patients from each group that were matched for pretreatment characteristics were compared. Again the results demonstrated a better disease-free survival, locoregional control, and overall survival. Although not reported in this study, the impact of induction chemotherapy and preoperative chemoradiation on operative morbidity and mortality in 71 consecutive patients with gastric or gastroesophageal junction cancers treated at M. D. Anderson Cancer Center was reported in an overlapping but separate cohort of patients treated between 1997 and 2004[38]. The overall morbidity (defined as complications from anastomotic leak, abdominal abscess, wound infection/dehiscence, bowel obstruction, pleural effusion, pneumonia, sepsis, urinary tract infection, cardiac failure, and respiratory failure requiring mechanical ventilation) was 38%, but the operative mortality rate (defined as deaths from any cause within 30 days of surgery or during same hospital stay) was 2.8%. It is therefore our conclusion from these experiences that preoperative therapies could be delivered with acceptable operative morbidity and low operative mortality[36,37]. Since the potential benefit of adding surgery is high to improve locoregional control and survival, we will typically recommend surgery after chemoradiation for patients with adenocarcinoma of the mid to distal esophagus and gastroesophageal junction. For more proximal tumors, the increased morbidity and mortality rates due to pulmonary complications are higher than those for the tumors in other sites which may outweigh the benefit of surgery in these locations[36]. For these cases, surgical recommendations are made on a case-by-case basis.

Selecting patients for definitive chemoradiation without surgery

It’s a fact that not all patients require surgery after a full course of chemoradiation since it alone can cure about one-fifth of patients as demonstrated by the RTOG 8501[39]. It is no coincidence that the pCR rate is also around 25% after preoperative chemoradiation, and studies have demonstrated that pCR is one of the strongest predictor of long-term survival after preoperative chemoradiation[39]. If one can predict which patients will have a complete response to chemoradiation, these will be the patients that would not need surgical resection. Posttreatment EGD biopsy tends to be a poor predictor of pathologic response rate. Clinical predictors of response to preoperative chemoradiation using FDG-PET or CT based response assessment have found correlation to better outcomes in the patients who have demonstrated clinical complete response in contrast to those who only attain an incomplete response, but none of the modalities can rule out residual disease[40,41]. In the M. D. Anderson Cancer Center series of 83 patients with resectable esophageal cancers who underwent preoperative chemoradiation, the pCR rate was 31% [40]. When the FDG-PET response before and 4–6 weeks after chemoradiation was determined for each of the patients and compared with the pathologic response, the post treatment FDG-PET SUV maximum response did correlate with pCR (\( P = 0.03 \)) and the post treatment SUV \( \geq 4 \) is the only preoperative factor that correlated with decreased survival (2-year overall survival 33% versus 60% in tumor with a post treatment SUV maximum < 4, \( P = 0.01 \)). However the FDG-PET could only predict for residual disease that were greater than 10%. FDG-PET was not sensitive enough to detect viable disease < 10% of the esophagectomy specimen. Understanding the molecular biology of the tumors may be a more sensitive way to determine which tumors are likely to respond to treatment and which would be resistant. Gene expression profiling to predict for clinicopathologic response using tissues from pretreatment endoscopic biopsies from 19 patients were performed in one study [42]. Unsupervised hierarchical clustering analysis segregated the cancers into two molecularly distinct subtypes, with each consisting of 10 and 9 specimens. Five of the 6 tumors that had a pCR clustered in molecular subtype I. It appears that expression levels of PERP, S100A2, and SPRR3 allowed discrimination of pCR from <pCR with high sensitivity and specificity. Pathway analysis demonstrated that downregulation of apoptotic pathways predicted for <pCR in the molecular subtype II tumors [43]. NF-kappaB activation has also come to the fore as a possible predictor for pCR after neoadjuvant chemoradiation. NF-kappaB activation predicts for more aggressive tumors, more advanced stage tumors, and
poorer outcomes in patients receiving surgical resection alone\[44, 47\]. NF-kappaB activation also predicts for a poorer response to neoadjuvant therapy (18% achieving major CR) compared to tumors with negative NF-kappaB expression (75% achieving major CR)\[46\]. Recently, a system biology approach was used to identify a gene predictor model for intrinsic radiation sensitivity in in vitro cell culture models and validated using clinical data sets\[47\]. In the future, likely a combination of various biomarkers will improve the accuracy of predicting pCR in patients who undergo neoadjuvant chemoradiation and help to identify patients who may be spared the morbidity and potential mortality of an esophagectomy.

**Treatment of recurrence disease or palliation**

Patients whose diseases recur after primary treatment of esophageal cancers depend on the site of recurrence and the type(s) of initial therapy. Patients who undergo primary surgical resection without neoadjuvant or adjuvant radiation therapy can be considered for salvage chemoradiation, palliative chemotherapy, surgical resection, or best supportive care depending on the patients’ performance status. Nodal recurrence superior to areas previously irradiated can be considered for definitive management using chemoradiation. Appropriate management needs to be evaluated on a case-by-case basis, and best determined in a multidisciplinary setting.

Patients who have metastatic disease at initial presentation should be considered for palliative local therapies at the site of primary disease since often these patients have symptomatic obstructive disease. Chemoradiation is very effective in relieving obstruction, which may occur 2 to 4 weeks after the start of treatment\[46\]. The dose used is the same as in definitive cases, to a dose of 50.4 Gy in 28 fractions with concurrent chemotherapy. However, immediate relief can be achieved with EGD mediated stent placement\[40, 51\], or consideration should be made for feeding tube placement prior to the start of palliative therapies.

**Radiation Therapy Techniques**

**General principles**

**Simulation**

CT-based planning is utilized for all esophageal cancer patients being treated with radiation. Four-dimensional (4D) CT simulation for tumor motion should be considered for all patients, although spiral CT or extended-time simulation (slow CT scanning) to acquire an “average” image of tumor at all phases of the breathing cycle can be performed if 4D-CT technology is not readily available.

Patients are immobilized by placing patient in the supine position with both arms up and stabilized with a wing-board and T-bar and the shoulders cradled in a Vac-lok bag conforming to the anatomy of the upper torso. The setup uncertainty is around 7 mm.

**Target delineation**

The gross tumor volume (GTV) is defined radiographically on the CT scan in conjunction with endoscopic reports and FDG-PET scan if available. If a PET is available, it should be fused with the simulation CT scans to delineate GTV\[50\]. If a 4D-CT simulation is performed, a maximal intensity projection (MIP) images are used to define the GTV (or internal motion GTV, or iGTV). MIP is created by combining the dataset of all possible respiratory positions of the target. The clinical tumor volume (CTV) accounts for the high propensity of submucosal spread of disease. In general, the CTV extends superiorly and inferiorly by 3 cm from the edge of the GTV. The pathologic evidence of microscopic extension in esophageal cancers as a corollary to the definition of CTV was reported by Gao et al.\[50\]. Sixty-six patients treated with surgery alone without neoadjuvant treatment were assessed for microscopic spread of disease both proximally and distally from the edge of the gross tumor. There was a difference in the extent of spread depending on the histology of the tumor. For squamous cell cancers, the mean microscopic spread of disease beyond the gross tumor was \(10.5 \pm 13.5\) mm proximally and \(10.6 \pm 8.1\) mm distally. For gastroesophageal junction adenocarcinomas, the proximal spread of disease was \(10.3 \pm 7.2\) mm and \(18.3 \pm 16.3\) mm distally. Taking all together, the authors concluded that the minimal CTV expansion to encompass 94% of cases is 3 cm, but for distal CTV margin for gastroesophageal junction adenocarcinomas, 5 cm was needed to cover 94% of the cases. Radially, the CTV should extend by 1 cm from the edge of the iGTV laterally, but respecting anatomic boundaries (vertebral body, pericardial sac, lung, and aorta), unless these structures are involved by disease. Automatic expansion of the CTV from the GTV using these parameters without adjustment on each cross sectional imaging is not an acceptable practice. The PTV expansion varies greatly depending on the day-to-day patients set up variation. If orthogonal portal imaging is taken once weekly to make alignments based on bony landmarks, a PTV expansion should be 7 to 10 mm. However if daily KV imaging are taken, a 5-cm PTV expansion is acceptable. The information about radiation target volume in post-operation setting is limited. One retrospective study indicated that it is not necessary to treat extensive field (the CTV encompassed the bilateral supraclavicular region, all mediastinal lymph nodes, the anastomosis site, the left gastric and pericardial lymphatic) and regional field (the CTV was confined to tumor bed and the lymph nodes in the immediate region of the primary lesion) should be considered\[55\].
Treatment delivery and dose

The standard is 3D-conformal radiation utilizing 3-field (AP/RPO/LPO) to six-field (AP/PA/LAO/RAO/RPO/LPO) beam arrangements. However, IMRT can further improve the conformality of the dose distribution by sparing adjacent normal structures that are often difficult to achieve with large tumors or nodal masses that abut adjacent structures such as the heart. We are increasingly incorporating technologies, such as proton beam therapy, to further improve the dosimetry and sparing of critical structures in these difficult cases.

The most standard daily dosing is at 1.8 Gy per fraction to a total dose of 45 to 50.4 Gy. This dosing allows delivery of treatment to areas where doses above this might be prohibitively toxic, such as the stomach and small bowel. For upper thoracic and upper cervical diseases which often require definitive treatment with chemoradiation, higher doses which is approaching to the dose used for the management of head and neck primaries would be desirable, generally in the range of 60–70 Gy. However, the consequence of the increased cure rates at these higher doses would be increased late toxicities such as esophageal strictures requiring dilation procedures, and possible dependency on feeding tubes.

Toxicities and normal tissue tolerance

Most common expected acute toxicities during chemoradiation are esophagitis, skin irritation, fatigue, and nausea/vomiting. Dysphagia, often caused by the primary tumors themselves, is often relieved during the course of treatment. Medical management of these side effects is important that includes narcotics for esophagitis, anti-emetics for nausea, and nutritional consultation and evaluation. Occasionally patients may need intravenous hydration due to dehydration from poor oral intake. Late toxicities include esophageal stricture, lung and esophageal fibrosis, radiation pneumonitis, pericarditis, pericardial effusion, and second cancers. Stricture rates may be minimized in patients whose irradiated portion of the esophagus is removed after preoperative chemoradiation.

During the radiation treatment planning process, it is important to observe common normal tissue constraints to minimize some of the late toxicities. These are summarized in Table 3. An example of a typical IMRT plan for treatment of esophageal adenocarcinoma is illustrated in Figure 1.

Follow-Up

Regardless of whether the patient is managed preoperatively or definitively with radiation, patients are to be evaluated with restaging scans with or without repeat EGD at 4–6 weeks after completion of treatment. If the patient continues to be eligible for surgery, surgical evaluation and recommendation for surgery will be made at this point, with surgery at 6–8 weeks after completion of preoperative treatment. Since the majority of esophageal cancers recur within 3 years from the time of the completion of cancer treatment, patients need to be followed up closely every 3–6 months for the first 3 years, every 6 months in years 3–5, and annually afterwards. At each visit, a complete history and physical examination is necessary to clinically assess the patient’s quality of life and need for intervention. Repeat EGD is performed if clinically indicated, as for laboratory studies. Some form of imaging may be necessary for restaging purposes. At a minimum, a contrast enhanced CT of the chest and abdomen will be needed, but a PET/CT or other imaging may be necessary if clinically indicated.

Table 3  Dose volume histogram dose constraints for radiation treatment planning

<table>
<thead>
<tr>
<th>Tissue</th>
<th>RT alone</th>
<th>Definitive chemo-RT</th>
<th>Preoperative chemo-RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal Cord</td>
<td>50 Gy MLD &lt; 20 Gy V20 &lt; 40%</td>
<td>45 Gy MLD &lt; 20 Gy V20 &lt; 35% V10 &lt; 45% V5 &lt; 65%</td>
<td>Same Same Same</td>
</tr>
<tr>
<td>Lung</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>V40 &lt; 50% Dmax &lt; 75 Gy V60 &lt; 50%</td>
<td>Same Dmax &lt; 75 Gy V55 &lt; 50%</td>
<td>Same</td>
</tr>
<tr>
<td>Esophagus</td>
<td>V20 &lt; 50% for both kidneys V20 &lt; 1/3 of one kidney if the other kidney is non-functional</td>
<td>Same</td>
<td>Same</td>
</tr>
<tr>
<td>Kidney</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>V30 &lt; 40%</td>
<td>Same</td>
<td>Same</td>
</tr>
</tbody>
</table>
Figure 1 Preoperative chemoradiation for a 66-year-old man with a T3N1M0 adenocarcinoma of the distal esophagus/gastroesophageal junction
A–D, axial, sagittal, and coronal views of the intensity-modulated radiotherapy (IMRT) plan. Note in Figure A to D that clinical tumor volume expansion respects anatomical boundaries. E, pretreatment fluorodeoxyglucose-positron emission tomography (FDG-PET) demonstrating hypermetabolic activity in the distal esophagus/proximal stomach, and in Figure F PET performed 4 weeks after completion of chemoradiation treatment. G, dose volume histogram analysis of the IMRT plan. Since the patient had a clinical complete response, both on PET and on esophagastroduodenoscopy biopsy, patient opted for surveillance rather than surgical resection.
References

[34] Liao Z, Zhang Z, Jin J, et al. Esophagectomy after concurrent chemoradiotherapy improves locoregional control in clinical stage II