Multimodality Treatment of Esophageal Cancer: A Review of the Current Status and Future Directions

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Surgical resection will cure only 15% to 20% of patients with seemingly localized esophageal cancer. Multimodality therapy has the potential to increase the cure rate by improving locoregional control and preventing systemic relapse. Randomized trials demonstrate that chemoradiation followed by surgery decreases local relapse as compared with surgery alone; however, the effect on overall survival remains uncertain. The additional impact of surgery following chemoradiation also remains unclear, with two randomized trials demonstrating an improvement in locoregional control without a benefit in survival. Morbidity and mortality of trimodality therapy have limited potential gains. Incorporation of docetaxel, irinotecan, and oxaliplatin into chemotherapy regimens prior to chemoradiation or as adjuvant therapy may decrease systemic recurrence. New radiation sensitizers may improve locoregional control. Biologic agents, such as cetuximab, trastuzumab, erlotinib, and bevacizumab, may enhance chemoradiation and target systemic micrometastases. Advances in radiation oncology and surgery may decrease morbidity and mortality from trimodality therapy, improving patient outcome.

Introduction

In this review, sentinel phase III studies comparing multimodality therapy to surgery alone for esophageal cancer are summarized. The current state and controversies surrounding the standard use of preoperative chemotherapy, chemoradiation, and adjuvant therapy are described. Emphasis is placed on novel approaches that are in early trials. These include the incorporation of more effective chemotherapy agents, radiation sensitizers, and molecular agents that target crucial genetic alterations that are critical to the pathobiology of esophageal cancer. Promising strategies that in the next 5 to 10 years may demonstrate survival benefit are detailed.

Multimodality Therapy: Phase III Studies

Modern surgical series demonstrate that 80% to 85% of patients with seemingly localized esophageal cancer will relapse and die of their disease following surgical resection [1••,2,3]. Neoadjuvant and adjuvant chemotherapy and radiation are intended to eliminate residual microscopic disease and improve survival. Multiple phase II studies have demonstrated that neoadjuvant chemoradiation followed by surgery is feasible [4,5]. However, the impact of current chemoradiation regimens on survival remains controversial.

Walsh et al. [6••] randomly assigned 113 patients with adenocarcinoma of the esophagus to surgery alone or two courses of 5-fluorouracil (5-FU) and cisplatin with concurrent radiation followed by surgical resection. Patients received chemotherapy on weeks 1 and 6 with radiotherapy, 40 Gy administered in 15 fractions, over a 3-week period, beginning concurrently with the first course of chemotherapy. Neoadjuvant chemoradiation was associated with a statistically significant increase in median survival (16 months vs 11 months) and 3-year survival (32% vs 6%). However, the results of surgery alone in this trial were inferior to the expected results with surgery and raised questions about the adequacy of pretreatment staging. Staging in this study was performed by chest radiography and abdominal ultrasound. Computerized tomography scanning was not required. Preoperative therapy appeared to downstage tumors. At the time of surgery, 42% of patients who underwent multimodality therapy had involved lymph nodes, whereas 82% of patients who underwent surgery had involved lymph nodes. A pathologic complete response was demonstrated in 25% of patients.

Urba et al. [7•] from the University of Michigan randomized 100 patients with esophageal cancer to preoperative cisplatin, 5-FU, vinblastine, and 45 Gy of radiation followed by transhiatal esophagectomy versus surgery alone. A complete pathologic response was demonstrated in 28% of patients. Trimodality treatment did not reduce distant metastases. However, a statistically significant reduction was apparent in locoregional recurrence with trimodality therapy (19% vs 42%). No difference was seen in median survival (16.9 months vs 17.6 months for multimodality therapy and surgery alone, respectively). However, there was a trend for improvement in 3-year survival favoring the trimodality therapy (3% vs 16%). The survival difference was not statistically significant; however, this small trial had limited power to detect a modest survival benefit.

The European Organization for Research and Treatment of Cancer (EORTC) randomly assigned 282 patients with squamous cell cancer of the esophagus to surgery alone or preoperative cisplatin and split-course radiation followed by surgery [8•]. Preoperative treatment was associated with a higher frequency of curative resection, a significantly longer disease-free survival and time to local failure, and a lower rate of cancer-related deaths. However, there was no difference in median survival and overall survival. The use of single-agent cisplatin and split-course radiation may have reduced the effectiveness of chemoradiation. Trimodality treatment was associated with a significantly higher postoperative mortality (12.3% vs 4%). Reductions in toxicity of trimodality therapy are needed to improve survival.

Randomized trials of trimodality therapy versus surgery alone in esophageal cancer have generally enrolled 100 to 300 patients and have had limited power to detect improvements in survival. The Cancer and Leukemia Group B (CALGB) attempted to complete a large definitive trial of cisplatin, 5-FU, and radiation followed by surgery versus surgery alone. This trial was closed due to slow accrual, but final analysis is pending. Two meta-analyses have compared neoadjuvant chemoradiation followed by surgery with surgery alone. The meta-analysis included 1116 patients enrolled on nine trials [9•,10]. Trimodality therapy was associated with an improvement in 3-year survival and reduction in locoregional recurrence and complete (R0) resection. There was a nonsignificant trend toward increased treatment mortality with neoadjuvant chemoradiation. Concurrent administration of neoadjuvant chemoradiation was superior to sequential chemotherapy and radiation.

Chemoradiation Regimens Using Taxanes, Irinotecan, and Oxaliplatin

Phase III trials of multimodality treatment in esophageal cancer have used cisplatin, 5-FU, and concurrent chemoradiation. Paclitaxel, irinotecan, and oxaliplatin have been incorporated in phase II studies and represent acceptable alternative regimens.

Paclitaxel has important single-agent activity in squamous cell carcinoma and adenocarcinoma of the esophagus [11]. Paclitaxel is an important radiation sensitizer [12]. Multiple phase II studies have evaluated paclitaxel-based chemoradiation in esophageal cancer [13,14]. These trials have demonstrated similar complete response rates and survival to those of cisplatin, 5-FU, and radiation. In our original phase II study incorporating paclitaxel into a neoadjuvant regimen for esophageal cancer, patients received paclitaxel, 60 mg/m^2, and cisplatin, 25 mg/m^2, with concurrent radiation [13]. Prophylactic feeding tubes were not used. Forty-one patients were entered with a mean age of 64 years (range, 43–83). Twenty-nine had adenocarcinomas of the gastroesophageal junction, and 12 had squamous cancers. Ten patients had adenopathy, including six with celiac or periportal nodes. The most frequent toxicity was hematologic, with five patients (12%) having grade 4 hematologic toxicities. Only two patients (5%) experienced grade 4 esophagitis, defined as the need for enteral or parenteral nutritional support. Patients who refused surgery and received the chemoradiation boost did not experience additional toxicity. The pathologic complete response rate was 29%. The 2-year progression free and overall survival rates were 51% and 54%, respectively. The phase II studies from the Brown University Oncology Group and Memorial Sloan-Kettering demonstrate substantially less esophagitis with the regimen of cisplatin, paclitaxel, and radiation than in the traditional regimen of cisplatin, 5-FU, and radiation without the need for prophylactic enteral feeding tubes [13,14]. Weekly paclitaxel/cisplatin/radiation regimens do not require central venous catheter devices when paclitaxel is administered by weekly 1-hour infusion, compared with continuous-infusion 5-FU–based regimens. Investigations of three-drug regimens of paclitaxel, cisplatin, and 5-FU with concurrent chemoradiation have also demonstrated substantial activity [15,16]. However, there is increased esophagitis with these three-drug regimes without a clear clinical benefit in overall survival. Paclitaxel-based chemoradiation has been the framework for the recent Radiation Therapy Oncology Group (RTOG) trials in esophageal cancer. RTOG-0113 and RTOG-0246 have each demonstrated that paclitaxel can be safely incorporated into therapy in a cooperative group setting.

Chemoradiation regimens with irinotecan, cisplatin, and concurrent chemoradiation have also been described [17,18]. In phase II studies, a regimen of irinotecan, cisplatin, and radiation appears to have similar activity and toxicity to paclitaxel, cisplatin, and radiation. The Eastern Cooperative Oncology Group (ECOG) recently completed a randomized phase II trial of preoperative chemoradiation comparing paclitaxel, cisplatin, and radiation to irinotecan, cisplatin, and radiation. Results from this trial are pending. Another promising chemoradiation strategy is to evaluate oxaliplatin in combination with protracted-infusion 5-FU and radiation. In a report

by Khushalani et al. [19], 38 patients completed treatment with this regimen on a phase II study. After completion of chemoradiation, 81% of patients had no cancer in the esophageal mucosa, and five of 13 patients undergoing resection had pathologic complete responses. Further evaluation of oxaliplatin-based chemoradiation is ongoing in the Southwest Oncology Group (SWOG).

Novel Radiation Sensitizers

Paclitaxel poliglumex (PPX; Xyotax, Cell Therapeutics, Inc., Seattle, WA) is a drug conjugate that links paclitaxel to a biodegradable polymer, poly-l-glutamic acid [20]. Preclinically, poly–(l-glutamic acid)–paclitaxel (PPX) has demonstrated tumor tissue radiation enhancement factors from 4.0 to 8.0 as compared with 1.5 to 2.0 for paclitaxel [21]. The macromolecular structure of PPX may underlie its improved radiation enhancement. PPX has a molecular weight of 40,000 as compared with 854 for paclitaxel [20]. Solid tumors are more permeable to macromolecules than normal tissue due to altered capillary endothelium. Radiation increases the vascular permeability of solid tumors further, increasing PPX uptake. These preclinical findings support the hypothesis that the supra-additive effect of combined PPX and radiation is due to the modulation of the enhanced permeability and retention effect of macromolecules by radiation.

We have completed a phase I trial of PPX and radiation for patients with esophageal and gastric cancer. Twenty-one patients were enrolled over five dose levels [22]. Sixteen patients had esophageal cancer, and five had gastric cancer. Twelve patients received PPX and radiation as definitive locoregional or neoadjuvant therapy, four patients had undergone resection and received adjuvant PPX and radiation, and five patients had metastatic disease and received PPX and radiation for palliation of dysphagia. Dose-limiting toxicities of gastritis, esophagitis, neutropenia, and dehydration developed in three of four patients treated at the 80-mg/m^2 dose level. Four of 12 patients (33%) with locoregional disease had a complete clinical response. We are currently evaluating PPX in combination with cisplatin. Based on the preclinical activity, PPX may be a more effective radiation sensitizer than paclitaxel and may improve locoregional control in esophageal cancer.

Induction Chemotherapy Prior to Chemoradiation

The randomized studies of trimodality therapy versus surgery alone and the meta-analysis suggest that the primary benefit of concurrent chemoradiation is to decrease locoregional recurrence. To further improve survival, effective chemotherapy is needed to prevent systemic recurrence. Randomized trials of chemotherapy and surgery compared with surgery alone have demonstrated conflicting results.

The US Intergroup trial 0113, led by Kelsen et al. [1••] and the RTOG, randomly assigned 467 patients with resectable esophageal cancer to surgery alone or three cycles of preoperative and two cycles of postoperative cisplatin and 5-FU. Surgery was performed 2 to 4 weeks after the completion of the third cycle. A complete pathologic response rate was noted in only 2.5% of patients. There was no difference in treatment-related mortality or the rate of complete resection. There were no differences in median and overall survival. The median survival was 14.9 months for patients receiving preoperative therapy and 16.1 months for those undergoing immediate surgery (P=0.53). There was no change in the rate of recurrence or locoregional or distant recurrence.

Contrasting results were reported by the Medical Research Council (MRC) in the United Kingdom, which evaluated 802 patients with operable esophageal cancer [23••]. Patients were randomized to resection alone or two cycles of cisplatin and 5-FU followed by resection. Preoperative chemotherapy was associated with significantly greater overall survival (hazard ratio 0.79; 95% CI, 0.67–0.93) and median survival (16.8 vs 13.3 months). The frequency of locoregional recurrence was similar in both arms, suggesting that the benefit of chemotherapy was to decrease systemic recurrence. It is not clear why the MRC and Intergroup 0113 trials, both with very similar designs, revealed conflicting results. In the MRC trial, clinicians could choose to give preoperative radiation to all their patients regardless of their randomization. Because only 9% of were randomized, it is unlikely that this resulted in the treatment effect. There was no increase in surgical mortality following preoperative chemotherapy in both Intergroup 0113 and the MRC trial. These findings contrast with those for preoperative chemoradiation, in which a trend toward increase in mortality has been demonstrated.

The MAGIC trial (MRC Adjuvant Gastric Infusional Chemotherapy), also conducted by the MRC, further supports the use of neoadjuvant chemotherapy. This study was intended to evaluate the effect of three cycles of preoperative and three cycles of postoperative epirubicin, cisplatin, and 5-FU (ECF) compared with surgery alone in patients with resectable gastric cancer [24]. Twenty-five percent of patients on this study had distal esophageal or gastroesophageal junction adenocarcinoma. An improvement in survival was shown for patients randomized to ECF; however, the applicability of these findings to esophageal cancer is unclear.

Induction chemotherapy followed by concomitant chemoradiotherapy has been explored at the University of Texas M.D. Anderson Cancer Center and the Memorial Sloan-Kettering Cancer Center [17,25,26]. Swisher et al. [25] reported the long-term outcome of 38 patients treated with two cycles of neoadjuvant paclitaxel, 5-FU, and cisplatin followed by chemoradiation with cisplatin and 5-FU. A pathologic complete response rate was noted in 23% of patients. The 5-year disease-free survival rate

was 51%, and the 5-year overall survival rate was 39%. Ajani et al. [26] have also evaluated induction irinotecan and cisplatin chemotherapy followed by chemoradiation with 5-FU, cisplatin, and 45 Gy of radiation [18,26]. The pathologic complete response rate was 28%, and the median survival was 22 months. Ilson et al. [17] reported a similar 32% pathologic complete response rate with induction irinotecan and cisplatin followed by concurrent cisplatin, irinotecan, and radiation followed by resection [17]. Another approach is to give induction chemoradiation followed by surgery followed by adjuvant chemotherapy [27].

Incorporation of New Agents into Induction Chemotherapy

The V325 study demonstrated that docetaxel increased survival in patients with metastatic gastric cancer and adenocarcinoma of the gastroesophageal junction [28]. This trial randomized 457 patients to docetaxel, cisplatin, and 5-FU (DCF) or cisplatin and 5-FU (CF). Time to progression was longer with DCF (5.6 months) as compared with CF (3.7 months) (P=0.004). A statistically significant increase in response rate (36% vs 25%) and survival was reported with the addition of docetaxel. Median survival increased from 8.6 months to 9.2 months. One- and 2-year survival rates were 40.2% and 18.4% with DCF as compared with 31.6% and 8.8% with CF. These results suggest that incorporation of docetaxel into induction chemotherapy regimens for esophageal cancer represents a promising strategy.

Substantial toxicity was reported with DCF, with 81% and 75% of patients having grade 3 and 4 nonhematologic toxicities in DCF and CF respectively. Furthermore, over 80% of patients on the DCF arm experienced grade 3 and 4 hematologic toxicities. The Brown University Oncology Group has attempted to modify this regimen to decrease toxicity and improve patient convenience while retaining activity. We recently reported a phase I study of weekly docetaxel, carboplatin, and 10-day capecitabine [29]. The maximum tolerated dose of this regimen was docetaxel, 35 mg/m^2, and carboplatin area under the curve (AUC) = 2, weeks 1 and 8 with capecitabine, 1500 to 2000 mg/m^2 for 10 days in a 21-day cycle. The overall response rate of this regimen in 26 evaluable patients was 46%, and 10 of 15 patients (67%) at the final dose level responded.

Oxaliplatin may also play an important role in induction chemotherapy regimens in esophageal cancer. Response rates of 38% to 54% have been reported with oxaliplatin and 5-FU regimens in patients with advanced gastroesophageal cancer [30,31]. Preliminary data from the REAL-2 trial suggest that response rates in gastric cancer may be improved by the substitution of cisplatin with oxaliplatin and the substitution of 5-FU with capecitabine [32]. In a preliminary analysis following the first 204 patients, the response rate of epirubicin, oxaliplatin, and 5-FU (EOX) was 38% as compared with 31% with epirubicin, cisplatin, and 5-FU (ECF). Furthermore, the response rate of epirubicin, oxaliplatin, and capecitabine was increased to 48%. Survival data are pending. This trial is continuing to a total accrual of 1000 patients.

Bevacizumab in Multimodality Therapy

New blood vessel growth is required for solid tumors to expand [33]. Vascular endothelial growth factor (VEGF) is a potent factor in stimulating new blood vessel formation [34]. VEGF produces a number of biologic effects, including endothelial cell mitogenesis and migration, induction of proteinases leading to remodeling of the extracellular matrix, increased vascular permeability, and maintenance of survival for newly formed blood vessels [34]. VEGF is overexpressed in 30% to 60% of patients with esophageal cancer and has been correlated with advanced stage and poor survival in patients undergoing esophagectomy in some but not all studies [35,36].

Bevacizumab (recombinant humanized monoclonal anti-VEGF antibody [rhuMAb VEGF]) is a humanized monoclonal antibody to VEGF [37]. Hurwitz et al. [37] reported a dramatic survival benefit for patients with metastatic colon cancer randomized to irinotecan/5-FU/leucovorin (IFL) with bevacizumab or placebo. Bevacizumab increased survival from 15.6 months with IFL and to 20.3 months with IFL and bevacizumab (P=0.00004). An increase in gastrointestinal perforations appeared to be present from the addition of bevacizumab. Six perforations (0.8%) were reported in the IFL/bevacizumab arm and no perforations in the IFL control arm. In one patient the perforation resulted in death. Investigators at Memorial Sloan-Kettering reported a phase II study of irinotecan, cisplatin, and bevacizumab in 20 patients with unresectable or metastatic gastric cancer or gastroesophageal adenocarcinoma. Shah et al. [38] reported that 87% of patients had partial response or stable disease. In 10 patients with measurable disease who had completed at least two cycles of therapy there were five partial responses (50%), four minor responses (40%), and one instance of stable disease. However, one of the patients had a gastric perforation and another had a near perforation. Rapid tumor response may be the cause of perforation. Trials of bevacizumab as induction therapy in gastrointestinal malignancies, when the primary tumor is present and transmural, should proceed cautiously due to the risk of gastrointestinal tract perforation.

Targeting the HER Family: HER2

Novel therapies are needed to block aberrant growth factor signal transduction pathways that stimulate esophageal cancer progression and metastasis. These gene alterations may serve as specific targets for molecular-based therapies [39]. The human ErbB receptors belong to the type 1 receptor

tyrosine kinase family. The ErbB receptor family consists of four transmembrane glycoproteins (ErbB1-ErB4) [40].

ErbB2 (HER2) is the preferred dimerization partner of the other ErbB family members [39]. The *HER2* gene encodes a transmembrane glycoprotein receptor, $p185^{HER2}$, that is targeted by the humanized anti-$p185^{HER2}$ monoclonal antibody trastuzumab [41]. Trastuzumab dramatically reduces disease recurrence when administered as part of adjuvant treatment in HER2-overexpressing breast adenocarcinoma [41,42]. Small series have suggested that the rate of HER2 expression by immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) in esophageal adenocarcinoma is similar to that of breast cancer [43•,44]. Therefore, we investigated trastuzumab for HER2-overexpressing esophageal cancer.

The Brown University Oncology Group has completed a phase I/II study of trastuzumab, paclitaxel, cisplatin, and radiation. Patients with adenocarcinoma of the esophagus without distant organ metastases and 2+/3+ HER2 overexpression by IHC were eligible. One third of screened patients with esophageal adenocarcinoma overexpressed HER2 by DAKO IHC (Copenhagen, Denmark) [43•]. All patients received cisplatin, 25 mg/m^2, and paclitaxel, 50 mg/m^2 weekly for 6 weeks with radiation, 50.4 Gy. Patients received trastuzumab at dosages of 1, 1.5, or 2 mg/kg weekly for 5 weeks after an initial bolus of 2, 3, or 4 mg/kg.

Nineteen patients were entered; seven (37%) had celiac adenopathy, and seven (37%) had retroperitoneal portal adenopathy or scalene adenopathy. Fourteen of 19 patients (74%) had either 3+ HER2 expression by IHC or an increase in *HER2* gene copy number by *HER2* gene amplification or high polysomy by FISH. No decline in left ventricular ejection fraction was detected as determined by serial echocardiograms. Further evaluation of trastuzumab in HER2-overexpressing esophageal cancer is indicated.

Targeting the HER Family: HER1

Epidermal growth factor receptor (EGFR, HER1) is a tyrosine kinase cell surface receptor encoded by the c-erbB-1 protooncogene [39]. Among the known natural ligands of the EGFR are epidermal growth factor (EGF) and transforming growth factor α (TGF-α), which activate the receptor by binding to the extracellular domain and inducing the formation of receptor homodimers or heterodimers, followed by internalization of the receptor/ligand complex and auto-phosphorylation. It is now accepted that the EGFR signal transduction network plays an important role in multiple tumorigenic processes, including cell cycle progression, angiogenesis, and metastasis, as well as protection from apoptosis [45].

The epidermal growth factor receptor is expressed in between 50% and 80% of all esophageal cancers [46], and its expression is associated with poor prognosis. Accumulating clinical evidence indicates that EGFR represents a viable target in the treatment of esophageal cancer. Phase II trials presented at the 2004 American Society of Clinical Oncology (ASCO) and the 2005 ASCO GI Cancer Symposium described the use of agents that target EGFR-associated tyrosine kinase for patients with metastatic esophageal cancer. Both gefitinib and erlotinib achieved response rates of 10% in esophageal carcinoma [47,48]. Erlotinib is being evaluated in phase II studies in combination with radiation for esophageal cancer.

Cetuximab, an IgG1 chimerized monoclonal antibody, binds specifically to EGFR on normal and tumor cells [39]. The Brown University Oncology Group and The University of Maryland Cancer Center have piloted the addition of cetuximab with chemoradiation for patients with carcinomas of the esophagus and stomach [49]. In this phase II trial, patients were required to have pathologically confirmed adenocarcinoma or squamous cell cancer of the esophagus, gastroesophageal junction, or stomach. They were allowed to have locally advanced disease and regional metastatic disease if it could be contained in a radiation field, including mediastinal, celiac, periportal, and regional gastric lymphadenopathy. Patients with distant organ metastases were not eligible.

Patients received cetuximab, 400 mg/m^2 in week 1, then 250 mg/m^2/week for 5 weeks, followed by paclitaxel, 50 mg/m^2/week and carboplatin, AUC = 2 weekly for 6 weeks with a concurrent 50.4-Gy dose of radiation. Prophylactic feeding tubes were not used. Thus far, 22 patients have been treated. The median age was 62 years (range, 35–88). Nineteen patients had esophageal cancer and three had gastric cancer. Of the patients with esophageal cancer, 12 had adenocarcinoma and seven had squamous cell cancers. Thus far, 19 patients have completed treatment. No grade 4 toxicities have been reported. Three patients had grade 3 esophagitis. All patients had skin reactions typical of cetuximab. All patients with esophageal cancer noted rapid improvement in their dysphagia or odynophagia related to their cancer within 2 weeks of treatment. Thus far, 10 of 16 patients have had clinical complete response.

Surgery After Chemoradiation

Chemoradiation alone can achieve disease-free survival in approximately 20% to 25% of patients. These results are similar to what can be expected with surgery alone and raise the question of the value of the addition of surgery after chemoradiation. Two randomized trials have not demonstrated a survival benefit to the addition of surgery but show an improvement in locoregional control.

In a trial from France, 455 patients with T3–4, N0–1, M0 (tumor, nodes, metastasis) esophageal squamous cell cancer or adenocarcinoma received two cycles of cisplatin, 5-FU, and radiation [50]. Patients with at least a partial response and who lacked a contraindication to

surgery (n=259) were then randomly assigned to continue chemoradiation or to undergo surgery. The median survivals were 19.3 months for chemoradiation alone and 17.7 months for trimodality therapy. The 2-year survival rates were 40% for chemoradiation and 34% for chemoradiation followed by surgery. There were nine deaths in the trimodality arm and one death in the surgery arm (P=0.002). Surgically treated patients were significantly less likely to require esophageal stents (13% vs 27%; P=0.005) or repeated dilation (22% vs 32%; P=0.07).

In a trial by Stahl et al. [51••], 177 patients were randomly assigned to three cycles of 5-FU, leucovorin, etoposide, and cisplatin followed by definitive chemoradiation alone with greater than 65 Gy of radiation, cisplatin, and etoposide or 40 Gy of radiation with cisplatin and etoposide followed by surgery. No significant difference in survival was noted with trimodality therapy (median survival, 16 months, 3-year survival, 28%) as compared with chemoradiation alone (median survival, 15 months and 3-year survival, 20%). However, a significant improvement in local control was reported with trimodality therapy. The 2-year local progression-free survival rate was 64% with trimodality and 40% with chemoradiation alone. Treatment-related mortality was higher in the trimodality arm (10% vs 4.3%).

Postoperative Treatment

For patients not undergoing preoperative treatment, adjuvant 5-FU and radiation should be considered based on the Intergroup Trial (INT-0116) led by the Southwest Oncology Group. Macdonald et al. [52•] randomized 556 patients with adenocarcinoma of the stomach and gastroesophageal junction to surgery alone or adjuvant 5-FU, 425 mg/m^2, + leucovorin, 20 mg/m^2 days 1 to 5 with 50.4 Gy of radiation followed by two cycles of 5-FU and leucovorin. Twenty percent of patients had proximal gastric/gastroesophageal junction tumors. This landmark trial showed a benefit of adjuvant therapy [52•]. The median survivals were 27 months for surgery alone and 36 months for patients undergoing chemoradiation followed by surgery.

Advances in Radiation Oncology

Recent advances in radiotherapy for esophageal cancer have sought to extend the therapeutic gains of trimodality therapy. The higher mortality rates seen in trials of preoperative chemoradiation were mostly related to increased postoperative pulmonary complications. These studies used conventionally planned radiotherapy portals, which often incorporate large lung volumes. Modern developments in three-dimensional planned radiotherapy (3D-RT) and intensity-modulated radiotherapy (IMRT) provide the capability to achieve more conformal dose distributions to the treated area and decrease dose to surrounding normal tissue. Dosimetric studies of IMRT have demonstrated that multibeam treatment plans reduce dose to the lung for treatment of locally advanced esophageal cancer [53,54]. Retrospective studies of patients undergoing IMRT as part of trimodality therapy have provided dosimetric parameters that predict for postoperative pulmonary complications [55]. These dose parameters, such as volume of lung receiving greater than 5 Gy, coupled with IMRT, may improve clinical outcomes, although no prospective trials have validated this strategy to date. Additionally, improved target delineation with pretreatment endoscopic ultrasound and ^{18}FDG–positron emission tomography may improve local disease control and allow for greater normal tissue sparing.

Advances in Surgery

The optimal surgical procedure for esophageal cancer continues to be controversial. The transhiatal esophagectomy (THE), popularized by Orringer et al. [56], involves laparotomy and a left cervical incision, thereby avoiding thoracotomy and its potential morbidity. Transhiatal esophagectomy may allow higher-risk patients to undergo esophagectomy. Detractors of this approach point out that THE does not allow for a complete thoracic lymphadenectomy as compared with the transthoracic esophagectomy (TTE). However, the addition of a right thoracotomy incision along with an intrathoracic anastomosis may result in higher morbidity and mortality for the TTE approach. Four randomized trials have compared TTE with THE [57,58]. In the largest trial, by Hulscher et al. [58], with 220 patients, significant differences in operative time, operative blood loss, intensive-care unit days, ventilator days, hospital days, and pulmonary complications favored THE. Operative mortality also favored THE (2% vs 4%) but did not reach statistical significance. However, 5-year disease-free survival (27% vs 39%) and overall survival (29% vs 39%) favored TTE over THE, but this did not reach statistical significance. Similar results were also found in a meta-analysis comparing THE with TTE [57]. It would seem that TTE might result in improved survival but with higher operative morbidity and mortality when compared with THE. Nevertheless, current data do not clearly indicate that one procedure is superior to the other.

Although THE and TTE are the procedures most widely performed and studied, there are advocates of an even more radical approach by en bloc esophagectomy with three-field lymphadenectomy. Such a procedure involves laparotomy, right thoracotomy, and cervical incision for three-field lymphadenectomy, esophagectomy with resection of pleura, diaphragm, pericardium, and thoracic duct en bloc. Altorki et al. [59] reported a series of 80 patients, among whom 16 had preoperative chemotherapy and four had preoperative radiation. The morbidity and mortality were 5% and 46%, respectively. Metastasis to cervical nodes was noted in 36%, and the overall survival at 5 years was a remarkable 51%. Again, it would seem that

improved survival might be at the expense of increased operative morbidity and mortality. The favorable outcomes of this series may be the result of careful patient selection. Therefore further studies are needed before such a radical procedure can be advocated widely.

Certainly, one of the keys to successful outcomes after trimodality therapy for esophageal cancer is minimizing the operative morbidity and mortality. In the randomized study by Bosset et al. [2] of 282 patients comparing chemoradiation followed by surgery (CRS) with surgery alone, a trend toward a higher operative complication rate (32.6% vs 26.3%, $P=0.249$) and a significantly higher mortality rate (12.3% vs 3.6%, $P=0.012$) was observed when chemoradiation was given prior to surgery. A meta-analysis by Urschel and Vasan [9•]. showed a higher rate of anastomotic leak, pulmonary complication, and mortality in the CRS group, but this did not reach statistical significance. However, in another meta-analysis, by Fiorica et al. [10], a statistically significant increase in operative mortality was found in the CRS group. This meta-analysis also showed a trend toward an increased postoperative complication rate in the CRS group. Preoperative chemoradiation may increase operative morbidity and mortality due to its adverse affects on the immune system, nutrition status, wound healing, and anastomotic healing. However, when these studies are examined in detail, it is the earlier randomized trials that show a higher operative mortality compared with the three more recent randomized trials, which show no difference in operative morbidity and mortality when preoperative chemoradiotherapy is given. It is likely that advances in perioperative care have decreased surgical morbidity and mortality even when the adverse effects of preoperative treatment are present. Optimization of preoperative nutritional status, improvements in anesthetic and operative techniques, and improvements in postoperative intensive care have all contributed.

Most recently, the use of thoracoscopy and laparoscopy for esophageal resection has evolved in the attempt to further minimize operative morbidity and mortality. Luketich et al. [60] reported on 222 patients undergoing minimally invasive esophagectomy, with 35.1% receiving preoperative chemotherapy and 16.2% receiving preoperative radiation. The mean operative time was 7.5 hours, with a conversion rate of 7.2%. The major morbidity was 32%, with mortality at 1.4%. Certainly the complexity of this procedure requires advanced skills. The learning curve is significant, as reflected by the long mean operative time and the types of technical complications. Longer follow-up on recurrence and survival is needed to determine the optimal role of minimally invasive esophagectomy as part of multimodality treatment of esophageal cancer.

To date no randomized studies have compared outcomes of various approaches for esophagectomy in the context of preoperative chemoradiation. Until such studies are performed, either THE or TTE is acceptable. The surgeon should choose the approach he or she is most familiar with and with which he or she obtains the best results. More studies examining the three-field en bloc esophagectomy or the minimally invasive esophagectomy are needed before these procedures can be recommended over THE or TTE.

Conclusions

Trimodality therapy has the potential to increase the cure rate of patients with esophageal cancer. Randomized trials have demonstrated that chemoradiation decreases locoregional recurrence. Thus far, a survival benefit has not been conclusively demonstrated, but randomized trials have been underpowered to demonstrate modest survival gains. The chemotherapy regimen most commonly used in randomized trials is cisplatin, 5-FU, and concurrent radiation. Chemoradiation regimens using paclitaxel/cisplatin, irinotecan/cisplatin, and oxaliplatin/5-FU are probably similar in efficacy to 5-FU and cisplatin but cause less esophagitis. A phase III trial comparing these commonly used chemoradiation regimens has not been performed and is unlikely to produce a meaningful survival difference. Preoperative chemotherapy has demonstrated a survival benefit in the MRC trial and the MAGIC trial but not in the US Intergroup Trial. More effective induction chemotherapy combinations, including agents such as oxaliplatin, docetaxel, and irinotecan, administered before chemoradiation, have the potential to decrease systemic recurrence and increase survival. Targeted therapies have considerable promise. Agents such as bevacizumab, trastuzumab, and cetuximab may be added to trimodality regimens without an appreciable increase in toxicity. An exception may be that bevacizumab may increase the risk of gastrointestinal tract perforation, and this will be investigated cautiously. Randomized trials of surgery after chemoradiation have shown reduced locoregional recurrence but have not demonstrated a survival benefit. Perioperative mortality has ameliorated the potential gains of resection. As modern radiation and surgical techniques improve, survival may increase, with reduction of morbidity and mortality from trimodality treatment.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

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