Chemoradiotherapy for Esophageal Cancer

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ABSTRACT

Radiotherapy and surgery have both played prominent roles in the treatment of esophageal cancer since the beginning of the 20th century. Although the use of radiotherapy alone to treat esophageal cancer has a long history, it has not demonstrated improved outcomes compared with surgery alone. The disappointing rates of survival and local control associated with single-modality therapy and the need for effective nonsurgical management led to the development of definitive chemoradiotherapy paradigms for esophageal cancer. Adding cytotoxic chemotherapy to radiotherapy for additive or synergistic effect was described as early as 1968, and over time, treatment has shifted from single-modality therapy toward combined-modality therapy using chemotherapy and radiotherapy. This approach eventually demonstrated superior outcomes in patients with esophageal cancer when compared to radiotherapy alone. Maximum benefit of this therapy depends on the appropriate addition of surgery and the optimization of radiosensitizing chemotherapy. A burgeoning area of research has focused on improving definitive chemoradiotherapy strategies through the incorporation of newer chemotherapeutic agents and targeted biologic agents. An overview of the history of chemoradiotherapy in the treatment of esophageal cancer is presented, as well as a discussion of ongoing studies and future areas of promising research.

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The treatment of esophageal cancer remains a therapeutic challenge. Despite an 11% improvement in survival over the past 30 years, 5-year survival rates for patients with localized and regional involvement remain low at 33.7% and 16.7%, respectively.[1] In this time period, treatment evolved away from single-modality therapy as combined-modality therapy using chemotherapy and radiotherapy found success as a treatment paradigm in sites such as anal cancer. This approach eventually demonstrated superior outcomes in patients with esophageal cancer when compared to radiotherapy alone.[2,3] Recent and ongoing research has focused on the optimization of chemoradiotherapy regimens through the use of induction chemotherapy, the addition of surgery, the alteration of radiation delivery, and the incorporation of novel chemotherapeutics and targeted agents.

HISTORY OF TREATMENT

Radiation and surgery have both played prominent roles in the treatment of esophageal cancer since the beginning of the 20th century. The first cervical esophageal resection for carcinoma in a human was performed by Czerny in 1897 and transthoracic approaches for resection were developed soon after.[4–6] A review of surgical series done before 1978 showed a disappointing 5-year overall survival rate of 9.6%.[7] Unfortunately, surgery as a primary treatment modality can only be used in a minority of patients. Up to 50% of patients presenting with localized esophageal cancer are inoperable and, of the remaining patients, 20% will have unresectable disease and only 36% will undergo a potentially curative surgery.[8]

Radiotherapy alone for esophageal cancer has a long history but has not demonstrated improved outcomes compared with surgery alone. Exner first described the treatment of esophageal cancer with radium in 1904.[9] Several series using radiotherapy alone in the treatment of esophageal cancer since that time have shown disappointing 5-year survival rates on the order of 0 to 5%.[3,10] Other research demonstrated a 77% local recurrence rate in patients treated with radiotherapy alone to 51–61 Gy.[11] However, modern trials comparing radiotherapy alone to chemoradiotherapy have demonstrated an improvement in outcomes with the addition of radiosensitizing chemotherapy. Several of these trials are listed in Table 1.

DEFINITIVE CHEMORADIOTHERAPY

The disappointing rates of survival and local control associated with single-modality therapy and the need for effective nonsurgical management led to the development of definitive chemoradiotherapy paradigms for esophageal cancer. Adding cytotoxic chemotherapy to radiotherapy for additive or synergistic effect was described

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Table 1. Phase-III trials comparing chemoradiotherapy to radiotherapy alone

Trial	No. patients	Chemotherapy	Radiation dose	5-Year survival (%)
Araujo et al.[85]				
RT	28	5-FU, MMC,	50	6
chemoradiotherapy	31	Bleomycin	50	16
Slabber et al.[86]				
RT	34		40 SC	6 months†
chemoradiotherapy	36	5-FU	40 SC	5 months
*Smith et al.[87]				
RT	62		40-60	7
chemoradiotherapy	65	5-FU, MMC	40-60	9
Wobbes, et al.[88]				
RT	111		40 SC	7.9 months†
chemoradiotherapy	110	Cisplatin	40 SC	9.6 months
Herskovic et al.[3]				
RT	62		64	0
chemoradiotherapy	61	Cisplatin, 5-FU	50	26
Zupanc. et al.[89]				
RT	52		60 non-SC	14.5
chemoradiotherapy	55	Cisplatin, 5-FU	40 SC	24.5

* Surgery allowed after 40 Gy
† Median Survival
Abbreviations: RT = radiotherapy; 5-FU = 5-fluorouracil; MMC = mitomycin C; SC = split course

as early as 1968.[12] Thereafter, investigators began incorporating several agents including 5-fluorouracil (5-FU), cisplatin, and mitomycin C (MMC) into chemoradiotherapy regimens that would ultimately prove clinically beneficial.

5-Fluorouracil exerts its radiosensitizing effect through the disruption of DNA repair and synthesis as well as RNA synthesis through multiple mechanisms.[13] When combined with radiotherapy, these effects are enhanced by decreases in DNA damage repair and the buildup of toxic metabolites.[12,14–16] Also a potent cytotoxin and radiosensitizer, cisplatin exerts its effects by binding DNA and causing cross-links in the double helix. When combined with radiotherapy, the differential DNA damage of the combined modalities overwhelms DNA repair mechanisms for synergistic cytotoxicity, even in radioresistant hypoxic cells.[17–19] Mitomycin C (MMC) is a naturally occurring antitumor agent that is reduced to its active form under hypoxic conditions that causes DNA damage through the formation of guanine-guanine cross links.[20] Nigro and colleagues devised an effective anal cancer chemoradiotherapy regimen using MMC, 5-FU and radiotherapy in the early 1970s.[2] The efficacy of combining cisplatin with radiotherapy was first demonstrated in patients with non–small-cell lung cancer.[21] Success of these agents in other cancer sites led investigators to incorporate them into chemoradiotherapy paradigms for esophageal cancer.

Coia and associates conducted a phase II trial examining chemoradiotherapy in both definitive and palliative regimens.[22] Definitive treatment consisted of 60 Gy external beam radiation (EBRT) given over 6–7 weeks combined with 5-FU and MMC. Palliative treatment consisted of the same chemotherapy regimen but with a reduced radiation dose of 50 Gy. These regimens were well tolerated, with severe acute and chronic toxicity rates of only 12.2% and 3.3%, respectively. However, much of the severe toxicity was related to a 10% rate of severe esophagitis requiring hospitalization. Overall median survival for those treated definitively was 18 months, and the 5-year actuarial survival was 18%, which was a significant improvement over historical data. Although MMC-based regimens such as this one have shown clinical efficacy, the use of MMC in esophageal cancer has waned because of its associated significant hematologic toxicity and possibly decreased efficacy as compared to other agents.[22–24]

One of the most important initial experiences with chemoradiotherapy for esophageal cancer was described by Herskovic and colleagues.[25] Their protocol delivered radiation to a large field in 2-Gy fractions to a total dose of 30 Gy along with concomitant 5-FU/cisplatin chemotherapy, followed by a 20 Gy small field boost given with MMC and bleomycin. The investigators ultimately eliminated MMC/bleomycin because of pulmonary toxicity and marginal recurrences and gave four cycles of cisplatin/5-FU to the remaining patients. This regimen achieved an encouraging median survival of 22 months in the 22 patients treated; 6 of these patients were alive and disease free at 40 to 46 months.

Based on these data, the Radiation Therapy Oncology Group (RTOG) conducted a seminal phase III trial, RTOG 8501, which compared concurrent chemoradiotherapy to radiotherapy alone.[3] Patients with adenocarcinoma or squamous cell cancer were included, though more than 80% of these patients had SCC. Patients in the combined-modality arm received 30 Gy to the entire length of the esophagus and 20 Gy to a boost target 5 cm above and below the known tumor extent. Radiation was delivered in 2-Gy fractions over 5 weeks, and chemotherapy consisted of 5-FU and cisplatin given in four cycles every four weeks. Patients receiving radiotherapy alone were prescribed a higher dose of 64 Gy in 2-Gy fractions over 6.4 weeks, allocated as 50 Gy to the regional field and 14 Gy to the boost field.

After an interim analysis showed a survival benefit in the combined-therapy arm, randomization was suspended and all remaining 73 patients were given chemoradiotherapy. Five-year survival rates for chemoradiotherapy vs. radiotherapy were 26% and 0%, respectively, and 22% of the chemoradiotherapy group survived at least 8 years.[26] Despite a dramatic improvement in survival, chemoradiotherapy was associated with persistent disease or local recurrence in more than 50% of patients. In addition, this 5-FU based chemoradiotherapy regimen was associated with significant toxicity; acute severe and life threatening toxicities were 44% and 20%, respectively, and resulted in one treatment-related death in the chemoradiotherapy arm. These toxicities may have been

partially related to the large radiation fields used in this study.

Shortly thereafter, taxane-based chemoradiotherapy regimens were investigated as a less toxic alternative to 5-FU–based regimens. The taxanes had been identified as potential radiosensitizers when preclinical data revealed their lethal effects of inhibiting mitosis, interfering with the cell cycle, and encouraging apoptosis.[27–31] Paclitaxel was shown to have significant activity in patients with regional or metastatic esophageal cancer in the early 1990s.[32] Multiple phase II studies have evaluated paclitaxel-based chemoradiotherapy regimens in esophageal cancer. These studies and other retrospective analyses support the conclusion that paclitaxel-based regimens result in complete response rates and survival comparable to those attained using 5-FU–based regimens.[33–35] In addition, data show that rates of grade 4 esophagitis in these regimens are 5% or less, effectively obviating the need for prophylactic enteral feeding tubes.[36–38] The improved therapeutic ratio of paclitaxel-based regimens has led to their incorporation into the framework of several recent RTOG trials investigating the nonsurgical management of esophageal cancer.

CHEMORADIOTHERAPY OPTIMIZATION

Radiation Dose Escalation

The rates of persistence of disease and local recurrence seen in RTOG 8501 and other trials sparked an effort to improve response through modulation of the radiotherapy schemas used in esophageal cancer. Intergroup trial 0123 investigated basic radiation dose escalation as a way to improve local control and survival. Prior to the initiation of this study, modifications had to be made to the original RTOG 8501 design to account for the expected increased toxicity of dose escalation. Therefore, the daily radiation dose was decreased from 2.0 Gy/day to 1.8 Gy/day, and most importantly, the initial radiation treatment fields were reduced to 5 cm proximal and distal to the tumor volume with a 2 cm radial margin. The chemotherapy regimens remained essentially the same in both studies. The randomization of this study was between 64.8 Gy and 50.4 Gy, both given in 1.8-Gy fractions.[39]

A planned interim analysis revealed 11 (10%) treatment-related deaths in the high-dose arm compared with 2 (2%) in the low-dose. The study was then terminated early after further analysis revealed a low probability of finding a statistically significant benefit in the high-dose arm. Unfortunately, 2-year and median survivals yielded disappointing results showing no difference between the high-dose and standard-dose arms (31% vs. 40% and 13 months vs. 18.1 months, respectively). Two-year local failure remained unchanged by dose escalation, with rates of 56% and 52% in the high-dose and standard-dose arms, respectively. Upon closer examination of the treatment deaths in the high-dose arm, seven deaths occurred at or below 50.4 Gy. As such, dose escalation should not be interpreted to be associated with higher mortality. Nevertheless, the dose of 50.4 Gy remains the standard of care for combined-modality therapy.

Dose Escalation Using Brachytherapy

By accessing the esophagus directly through a catheter-based system, a radiation source may be used to treat esophageal tumors while sparing normal tissues around the esophagus in a procedure known as intraluminal brachytherapy. Many institutions have used intraluminal brachytherapy in addition to external-beam radiotherapy as a method of achieving dose escalation.[40–42] RTOG conducted a multi-institutional phase I/II trial to test the safety and efficacy of intraluminal brachytherapy as a method of dose escalation in chemoradiotherapy regimens.[43,44] Only patients with thoracic esophageal tumors were included, and patients were excluded if they had involvement of the tracheobronchial tree or gastroesophageal (GE) junction. A 5-week regimen of 50 Gy of external-beam radiotherapy with concurrent 5-FU/cisplatin chemotherapy was administered prior to high dose rate (HDR) or low dose rate (LDR) brachytherapy starting on week 8. The HDR schedule consisted of a total dose of 15 Gy delivered in 5-Gy fractions at weeks 8, 9, and 10. If patients were to receive LDR brachytherapy, this was delivered as one 20 Gy dose during week 8. After several fistulas occurred in patients in the HDR group, the HDR brachytherapy dose was decreased to 10 Gy in two 5-Gy fractions given weeks 8 and 9.

Despite the increased dose, the local persistence/local recurrence rate (63%) was not improved when compared to historic phase III chemoradiotherapy data. Furthermore, even with the HDR dose adjustment, there were six (12%) treatment-related fistulas, which led to three deaths, and resulted in an overall 8% treatment-related mortality rate. The yearly estimate for fistula formation was 17.5% for those that received at least one fraction of brachytherapy. In contrast, institutions around the world using brachytherapy as a boost in definitive chemoradiotherapy paradigms have reported lower fistula rates.[45] These lower complication rates may be due to timing of the brachytherapy boost, lower doses per fraction, technique, and the therapeutic gain of experienced clinicians in high-volume centers.[42,45] However, even with improved technique and complication rates, dose escalation with brachytherapy has not been proven to increase local control or survival over external-beam–based chemoradiotherapy regimens.

Alteration of Radiation Dose Fractionation

Another technique for improving the radiation dose-response relationship is by altering the fractionation scheme. It is well known that an accelerated repopulation of tumor cells occurs late in a radiation-treatment course. Prolonging the treatment time may result in a decrease in the effective dose by 0.59 Gy per day in esophageal cancer.[24] Strategies to decrease treatment include the use of accelerated fraction schemes, which deliver an equivalent dose in a shorter treatment period, usually by giving multiple fractions per day. As late side effects are dependent on dose per fraction, altered fractionation can also be used to deliver a higher total dose. These paradigms theoretically maintain or lower late toxicity rates at the expense of higher acute toxicity, while diminishing the effects of accelerated repopulation.

The Cleveland Clinic described a phase II protocol that used induction cisplatin and 5-FU combined with a concurrent split course of accelerated radiation. Radiation was given twice daily in 1.5-Gy fractions to

a total dose of 45 Gy.[46] Chemoradiotherapy was followed by evaluation for surgical resection. Those patients found to have residual disease at the time of resection received an additional 24 Gy in 1.5-Gy fractions given twice daily. Seventy-two patients were enrolled in the trial. Ninety-three percent underwent surgical resection, which was associated with an 18% rate of perioperative death. The pathologic complete response (pCR) rate for induction chemoradiotherapy was 27% and the actuarial 4-year survival for the entire cohort was an encouraging 44%.

A phase I/II trial reported by Choi and associates examined an intensified chemoradiotherapy regimen consisting of cisplatin, 5-FU, and paclitaxel used concurrently with radiation therapy in 46 patients.[47] The radiation was delivered in 1.8 Gy per fraction to a total dose of 45 Gy with a concomitant boost of 1.5 Gy per fraction on days 1–5 and 29–32 to bring the total delivered dose to 58.5 Gy. Patients were offered surgery after chemoradiotherapy based on resectability. There was one death during induction therapy and two perioperative deaths. The rate of grade 3 and 4 esophagitis was 48% and 7%, respectively, and grade 4 neutropenia was 20%. Forty patients underwent surgical resection after chemoradiotherapy, and in all patients, the pCR rate was 39%. Median survival was 34 months, while the 5-year actuarial survival was 37%. While these studies are encouraging, they highlight the significant increase in acute treatment-related toxicity associated with altered fractionation regimens.

Induction Chemotherapy

Theoretically, tumor debulking and sterilization of early micrometastatic disease via induction chemotherapy should increase the efficacy of chemoradiotherapy and prolong the metastasis-free interval in patients with esophageal cancer. RTOG trial 0113 examined the response rates of induction chemotherapy in a phase II randomized trial of induction and concurrent 5-FU/paclitaxel or paclitaxel/cisplatin combined with 50.4 Gy external-beam radiotherapy.[48] The results were compared to the control cohort from RTOG 9405. Although 1-year survival was 75.7%, this did not meet a predetermined benchmark that would justify incorporation of induction chemotherapy into a phase III trial. In addition, the regimens were associated with substantial morbidity and 3% to 6% mortality. Besides being potentially fatal, the significant morbidity of induction chemotherapy can potentially limit the timely delivery of definitive therapy to patients. Induction therapy may place patients at risk for complications during their definitive treatment as well, with at least one institution reporting an increased rate of radiation pneumonitis in patients receiving induction chemotherapy.[49] In conclusion, the theoretical benefits of induction chemotherapy before definitive chemoradiotherapy have yet to be realized with current regimens.

EXAMINING THE ROLE OF SURGERY WITH CHEMORADIOTHERAPY

Despite dose escalation and altered fractionation, patients receiving definitive chemoradiotherapy suffer from high rates of disease persistence and local recurrence. The combination of chemoradiotherapy and esophagectomy, known as trimodality therapy, was initially used to improve locoregional control of surgical

Table 2. Trials of preoperative combined chemoradiotherapy plus surgery (trimodality) vs. surgery alone

Trial	No. Patients	Chemotherapy	Radiation dose (Gy)	pCR	3-yr survival
Le Prise et al.[90]					
Trimodality	45	Cisplatin, 5-FU	S, 20	9.8%	19.2
Surgery	41				13.8 NS
Walsh et al.[51]					
Trimodality	58	Cisplatin, 5-FU	40 Gy	25%	32
Surgery	55				6 ($P < .01$)
Bosset et al.[91]					
Trimodality	143	Cisplatin	SC, 37 Gy	21%	18.6 mos*
Surgery	139				18.6 mos* NS
Urba et al.[92]					
Trimodality	50	Cisplatin, 5-FU, vinblastine	Hfx 45 Gy	28%	30
Surgery	50				16 NS
Lee et al.[93]					
Trimodality	51	Cisplatin, 5-FU	Hfx 45.6 Gy	43%	28.2*
Surgery	50				57* NS
Burmeister et al.[94]					
Trimodality	128	Cisplatin, 5-FU	35 Gy	16%	22.2 mos*
Surgery	128				27.3 mos* NS
Tepper et al.[52]					
Trimodality	30	Cisplatin, 5-FU	50.4 Gy	40%	39†
Surgery	26				16† ($P = .002$)

All chemotherapy was given concurrently with radiotherapy unless specified.
* Median survival
† 5-year survival
Abbreviations: S = sequential; SC = split course; Hfx = twice daily hyperfractionated; 5-FU = 5-fluorouracil; NS = not statistically significant

resection.[50] Walsh and colleagues randomized patients with esophageal adenocarcinoma to surgery alone or neoadjuvant therapy with 5-FU, cisplatin, and 40 Gy of radiation followed by surgical resection.[51] Despite a high 90-day post-op mortality rate, median and 3-year survival were significantly improved with trimodality therapy (16 months and 32% compared with 11 months and 6%). Chemoradiotherapy was associated with a 25% complete pathologic response and the rate of nodal disease at surgery was nearly half that of the surgery alone arm. However, this trial is often criticized because of the low survival in the surgery alone arm. This can be clearly seen when comparing trimodality trials listed in Table 2.

Recently, a phase III trial of trimodality therapy conducted by the CALGB was reported.[52] Patients were eligible if they had resectable (T1-3) SCC or adenocarcinoma tumors of the thoracic esophagus or GE junction; patients with lymph node metastases to the supraclavicular basin or levels 15–20 were also eligible, as long as the lymph nodes were 1.5 cm or less on CT. Patients were randomized to either surgery alone or preoperative chemoradiotherapy using 50.4 Gy radiation given with cisplatin and 5-FU. Unfortunately, this trial closed early after only 52 eligible patients were enrolled. Only one patient died within 30 days of surgery in the surgery-alone arm and there was no 30-day postoperative mortality in the trimodality arm. Trimodality therapy was associated with a 40% complete response rate and 50% of patients with pre-treatment nodal disease were downstaged to pN0. With a median follow-up of 6 years, five-year overall survival was significantly improved by trimodality therapy, 39% vs. 16%.

A recent meta-analysis by Gebski and colleagues examined 10 randomized studies comparing trimodality therapy, using either sequential or concurrent chemoradiotherapy, to surgery alone.[53] Although only two studies individually showed a benefit in all-cause mortality, pooled results showed a statistically significant relative reduction in mortality for patients receiving trimodality therapy with a hazard ratio of 0.81. When analyzed by histologic subtype, concurrent neoadjuvant paradigms significantly reduced the hazard ratio for death to 0.76 and 0.75 for SCC and adenocarcinoma, respectively.

Two trials have addressed the necessity of surgery in patients with esophageal cancer. Stahl and colleagues randomized patients with esophageal cancer who had all received three cycles of induction chemotherapy to either definitive chemoradiotherapy or trimodality therapy.[54] Patients in the trimodality arm received 40 Gy in 2-Gy fractions along with cisplatin/etoposide. Three to 4 weeks after chemoradiotherapy, esophagectomy was performed. Patients in the chemoradiotherapy arm received cisplatin/etoposide and 50 Gy in 2-Gy fractions to a large field. This was followed by a boost to a smaller field given over 1 week using 1.5 Gy administered twice daily to a total dose of 65 Gy for patients with either T4 or T3 obstructive lesions. In the case of patients with nonobstructing lesions, a smaller field was treated with an additional 10 Gy in 2-Gy fractions followed by two 4-Gy brachytherapy boosts to bring the total dose to 68 Gy. Two-year and median survival were statistically equivalent between the trimodality and chemoradiotherapy arms at 39.9% vs. 35.4% and 16.4 months vs. 14.9 months, respectively. However, local progression-free survival was significantly improved in the group that received surgery; 64.3% vs. 40.7% ($P = .003$). Response to induction chemotherapy was found to be a strong predictor of survival; the 3-year survival in this subset of patients was over 50%.

The FFCD (Federation Francophone de Cancerologie Digestive) hypothesized that chemoradiotherapy and trimodality therapy would yield equivalent outcomes in patients responding to induction chemoradiotherapy.[55] Patients received chemoradiotherapy using either split-course radiation to 30 Gy in 3-Gy fractions or conventionally fractionated radiation to 46 Gy in 2-Gy fractions, all combined with 5-FU and cisplatin. Patients were then evaluated for symptomatic and radiographic response. Partial or complete responders were then randomized to either surgery or completion chemoradiotherapy. Further radiation was given as either one course of 15 Gy in 3-Gy fractions or 20 Gy in 2-Gy fractions to a total dose of 45 Gy or 66 Gy combined with three cycles of chemotherapy. For the 259 randomly assigned patients, median survival was 18.6 months; 17.7 months in the surgery arm, and 19.3 in the chemoradiotherapy arm. Two-year survival was equivalent at 33.6% and 39.8% in the surgery and chemoradiotherapy arms, respectively. However, there were significantly more local-regional relapses after chemoradiotherapy alone, 64.3% vs. 40.7%.

These two trials comprise the only level-I evidence comparing definitive chemoradiotherapy to trimodality therapy. As such, they highlight the difficulty of translating the local control benefit obtained with surgical resection into a meaningful survival benefit in patients with operable/resectable esophageal cancer. Assessing response to neoadjuvant therapy may result in better risk-adapted treatment strategies to employ trimodality therapy more appropriately.

FUTURE DIRECTIONS

As trimodality therapy is only applicable to a select subgroup of patients with esophageal cancer, a burgeoning area of research has focused on improving definitive chemoradiotherapy strategies through the incorporation of newer chemotherapeutic agents and targeted biologic agents.

Topoisomerase Inhibitors

Topoisomerase is essential for DNA replication, RNA transcription, and regulation of DNA supercoiling. It is upregulated in tumor cells in comparison to normal tissues, making it a logical target of drug therapy.[56,57] Topoisomerase inhibitors stabilize the TOP1-DNA complex, thereby causing DNA breaks and interference with replication. These effects are preferentially seen in rapidly dividing cells. As TOP1-inhibitors are S-phase specific, they may arrest cells in the radiosensitive G2 phase as well as promulgate radiation-induced DNA damage.[56] The two most studied agents are topotecan and irinotecan.

A large phase III non-inferiority trial comparing cisplatin/5-FU (CF) chemotherapy to irinotecan/5-FU (IF) in patients with metastatic gastric or GE junction adenocarcinomas has recently been reported.[58] This study showed the IF regimen to have equivalent outcomes as compared to CF. Upon intent-to-treat analysis,

the authors found a longer time to failure in the IF arm. A phase II trial combining irinotecan with cisplatin as an induction regimen before definitive chemoradiotherapy found a 58% complete clinical response rate.[59] Unfortunately, a recent phase II trial comparing neoadjuvant irinotecan/cisplatin/radiation to paclitaxel/cisplatin/radiation has found neither a survival benefit nor an increase in pathologic complete response with the former regimen.[60] Given these data, the potential therapeutic gain of the topoisomerase inhibitors has yet to be uncovered.

Targeted Therapies

Judah Folkman first proposed targeting tumor vasculature as a therapeutic pathway over 35 years ago.[61] After many years of preclinical research, bevacizumab, an antiangiogenic monoclonal antibody targeting the vascular endothelial growth factor (VEGF) has demonstrated potential as a radiation sensitizer. By mediating vascular normalization within the tumor, bevacizumab actually enhances the efficacy of both chemotherapy and radiotherapy.[62,63] VEGF receptor expression is present in 30%–60% of esophageal cancers and has been shown to be a poor prognostic factor in patients undergoing esophagectomy or definitive chemoradiotherapy.[64–67] Unfortunately, the use of bevacizumab in patients with esophageal cancer has been limited to those with GE junction tumors, after fatal hemoptysis was reported with its use in lung cancer patients.[68] Even in these patients, its use in combination with chemotherapy has been associated with gastric perforation, thromboembolic events, and myocardial infarction.[69,70] On the other hand, in combination with chemotherapy, it has shown response rates of 65%. Despite these significant response rates, the associated adverse toxicity has caused research with this agent to proceed cautiously in esophageal cancer.

Several epidermal growth factor receptors have also recently become targets of therapy. Human epidermal growth factor receptor 2 (HER2/neu or ErbB-2), is a member of the ErbB receptor family that is a significant factor in the pathogenesis of aggressive breast cancers. However, it has also been found to be overexpressed in some esophageal cancer cell lines and is associated with several aggressive characteristics, including tumor invasiveness, lymph node metastasis, and chemoresistance.[71–73] Trastuzumab is a humanized IgG1 antibody that targets the HER-2 receptor. There appear to be multiple mechanisms through which the antibody exerts its effect, including G_1 cell-cycle arrest, downregulation of the HER2/neu receptor, disruption of downstream signaling cascades, suppression of angiogenesis, and promotion of apoptosis. A phase I/II trial of patients with locally advanced esophageal adenocarcinoma screened for HER2/neu overexpression examined a targeted chemoradiotherapy regimen of trastuzumab, paclitaxel, cisplatin, and radiotherapy. The median survival for the experimental cohort was 18 months, with 42% of patients alive at 2 years. Rates of grade 3 and 4 esophagitis were relatively low, and patients experienced little change in mean left ventricular ejection fraction after treatment.[38] Although the feasibility of this regimen is evident, the efficacy of this agent compared to standard therapy remains to be determined.

The epidermal growth factor receptor (EGFR, ErbB-1) is another member of the ErbB family of receptor tyrosine kinases and is involved in multiple cellular signaling cascades. EGFR activation is known to play an important role in angiogenesis, cell-cycle progression, development of metastases, and induction of antiapoptotic pathways. EGFR expression has been shown to be a poor prognostic factor in patients undergoing treatment for squamous cell esophageal cancer as well as esophageal adenocarcinoma.[74–77] The prevalence of EGFR expression in esophageal cancer cell lines ranges from 30%–70% and tends to be higher in squamous cell carcinoma.[77,78]

Tyrosine kinase inhibitors (TKIs) have been developed to target EGFR pathways. These small molecules cross the plasma membrane and interact with the cytoplasmic portion of cellular receptors. Once in the cytoplasm, these molecules often act non-specifically which can both amplify therapeutic effect and increase toxicity.[78] The EGFR TKI erlotinib has been found to have activity in gastric and GE junction adenocarcinomas.[79] Recently, a phase I trial examining the use of erlotinib in patients with esophageal carcinoma was reported.[80] The investigators combined erlotinib in increasing doses with concurrent 5-FU, cisplatin, and radiotherapy to a total dose of 50.4 Gy. The major toxicities were grade 1/2 diarrhea (18%, 18%), rash (54%), grade 3 dehydration (27%), and grade 4 esophagitis (9%). The investigation of erlotinib in combination with chemoradiotherapy for esophageal cancer is ongoing.

Monoclonal antibodies targeting EGFR are being extensively evaluated in many cancer sites including esophageal cancer. Cetuximab, a monoclonal (IgG1) antibody (mAb) directed against the extracellular domain of EGFR, is thought to induce G1 cell-cycle arrest, inhibit cellular proliferation, promote radiation-induced apoptosis, inhibit radiation-induced DNA damage repair, and inhibit tumor angiogenesis. Data from phase III trials have demonstrated an overall survival benefit with the addition of cetuximab to radiation in head and neck cancer patients.[81] In esophageal cancer, two phase II studies incorporating cetuximab with chemoradiotherapy have recently been reported with conflicting results.

One study used a trimodality regimen consisting of 50.4 Gy external-beam radiotherapy combined with concurrent weekly cisplatin, irinotecan, and cetuximab followed by surgery. In this trial of 17 patients, the addition of cetuximab resulted in a lower complete response rate and higher overall toxicity as compared to historical chemoradiotherapy regimens.[82] However, in a larger trial using cetuximab, carboplatin, paclitaxel, and 50.4 Gy of concurrent radiotherapy, patients were able to achieve an endoscopic complete response rate of 67% and, in those that went on to surgery, 43% were found to have a pathologic complete response.[83] A separate toxicity analysis of this regimen showed the rates of grade 3 and 4 esophagitis to be an acceptable 12% and 3%, respectively.[84] There was a 23% grade 3 dermatologic toxicity rate associated with cetuximab. Because of these encouraging results, RTOG 0436 is currently investigating the combination of cetuximab, cisplatin, and paclitaxel in a large phase III trial. In addition, a phase II/III trial in the UK is currently testing a chemoradiotherapy regimen of capecitabine, cisplatin, and radiotherapy with and without the addition of cetuximab.

CONCLUSIONS

Chemoradiotherapy has emerged as a viable definitive treatment option for patients with localized esophageal cancer. The addition of surgery does deliver a local control benefit, albeit at the cost of increased morbidity and mortality. Some patients may derive a survival benefit from trimodality therapy, but identifying these patients remains a clinical challenge. Optimization of chemoradiotherapy regimens using targeted therapies and newer chemotherapeutic agents is a major goal of current research and is the basis of many current randomized trials for esophageal cancer.

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Disclosures of Potential Conflicts of Interest

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