

# Current strategies in chemoradiation for esophageal cancer

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**Abstract:** Chemoradiotherapy (CRT) has an important role in the treatment of esophageal cancer in both the inoperable and the pre-operative settings. Pre-operative chemoradiation therapy is generally given to 41.4-50.4 Gy with platinum or paclitaxel based chemotherapy. The most common definitive dose in the U.S. is 50-50.4 Gy. New advances in CRT for esophageal cancer have come from looking for ways to minimize toxicity and maximize efficacy. Recent investigations for minimizing toxicity have focused advanced radiation techniques such as IMRT and proton therapy, have sought to further define normal tissue tolerances, and have examined the use of tighter fields with less elective clinical target volume coverage. Efforts to maximize efficacy have included the use of early positron emission tomography (PET) response directed therapy, molecularly targeted therapies, and the use of tumor markers that predict response.

**Keywords:** Esophageal cancer; radiotherapy; positron emission tomography (PET)

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## Esophageal cancer overview

### *Incidence and epidemiology*

Approximately 17,990 new cases of esophageal cancer are estimated to be diagnosed in the U.S. in 2013, with 15,210 deaths (1). Adenocarcinoma has increased in incidence among Caucasians in the United States over the last 25 years (2) and is now the most common histological subtype. Risk factors for esophageal adenocarcinoma include columnar metaplasia (Barrett's esophagus) (3), obesity (4), and smoking (5). Globally, squamous cell carcinoma (SCC) is the more common histology and the incidence of esophageal cancer is ten times higher than the U.S. in certain geographic areas including northern China, Iran, Russia, South Africa, Hong Kong, and Brazil. Part of this discrepancy may be due to ingestion of alcoholic beverages and nitrate-rich foods including pickled vegetables, cured meats, and fish. Esophageal cancer is about three times more common in men than in women. While 95% of esophageal tumors are histologically defined as SCC or adenocarcinoma, other types are occasionally seen including adenoid cystic carcinoma, mucoepidermoid tumors, small cell carcinoma, lymphoma, and melanoma.

### *Presentation and work-up*

Dysphagia is the most common presenting symptom (90% of cases) followed by weight loss (40-70%), and odynophagia (50%), as well as pain, bleeding, hoarseness, and cough (6). Complete diagnostic investigation includes a thorough history and physical examination with special attention to cervical and supraclavicular lymph nodes and head and neck mucosal surfaces as second tumors of the head and neck are common. Laboratory investigations such as a basic metabolic panel, complete blood counts, and liver function tests should be obtained. While barium swallow is common for initial work-up of symptoms, endoscopy is essential to define the location and extent of the primary lesion. Imaging studies should include a computed tomography (CT) scan with IV and oral contrast of the chest and abdomen to identify sites of metastasis. Endoscopic ultrasonography has become a very common study to assess periesophageal and celiac lymph node involvement and the extension of disease through the esophageal wall. Positron emission tomography (PET) is also commonly used to detect nodal and distant metastases.

## Management

Surgery remains a mainstay of treatment for operable patients. Transthoracic esophagectomy (Ivor-Lewis procedure) appears to provide a trend toward improved long-term survival compared to transhiatal approach for mid-to-distal or gastroesophageal junction adenocarcinomas (7). This approach allows for better visualization of the operative field and lymph node dissection. However, higher rates of perioperative morbidity were seen in patients receiving transthoracic esophagectomy in a randomized comparison (7).

Radiation therapy alone is not recommended as a curative strategy. Patients achieved a 0% cure rate at 5 years in the control arm of RTOG 8501 (8). Two trials have examined the omission of surgery [chemoradiotherapy (CRT) alone] compared to tri-modality therapy. The French FFCD 9102 trial randomized patients with operable T3N0-1 thoracic esophageal squamous (90%) or adenocarcinoma (10%) with a response after 46 Gy CRT with cisplatin/5-FU to further CRT to 66 Gy *vs.* surgery (9). Tri-modality therapy resulted in higher local control (65% *vs.* 57%,  $P < 0.05$ ), and fewer stents required (5% *vs.* 32%,  $P < 0.001$ ). There was no difference in overall survival. The German trial reported by Stahl and colleagues employed induction chemotherapy (5-FU, leucovorin, etoposide, cisplatin) followed by CRT to 40 Gy with cisplatin and etoposide followed by surgery versus CRT to 50 Gy in 2 Gy fractions followed by 1.5 Gy BID to 65 Gy for T4 or obstructive T3 tumors or 60 Gy followed by high dose rate (HDR) brachytherapy for non-obstructed T3 tumors (10). Again, no difference was seen in survival, but patients who received surgery had a higher rate of 2-year freedom from local progression (64% *vs.* 41%,  $P = 0.003$ ). In both trials, differences in the rates of surgical complications were non-significant across the treatment arms.

The strategy of reserving surgical resection for those patients who experience a less than complete response after CRT has also been examined in the phase II trial, RTOG 0246 (11). Definitive chemoradiation included induction chemotherapy with 5-FU, cisplatin, and paclitaxel for two cycles, followed by concurrent CRT to 50.4 Gy with 5-FU and cisplatin. A total of 51% of patients (21/41) ultimately underwent surgery following CRT because of residual (17 patients, 41%) or recurrent (3 patients, 7%) disease, and 1 patient (2%) underwent surgery by choice. The study was not encouraging however, because the 1-year survival rate of 71% did not meet the study goal of 77.5%. Surgery is also withheld in favor of definitive CRT in the case of SCC of the cervical esophagus because adequate surgical

resection often leads to significant morbidity and loss of the entire larynx, thyroid gland, portions of the pharynx, and the proximal esophagus.

The standard strategy for the treatment of thoracic locally advanced esophageal cancer is now neoadjuvant chemoradiation followed by surgery ("tri-modality therapy"). This strategy has resulted in better outcomes than surgery alone in several randomized trials (12-15) including higher overall survival in a meta-analysis (16). Many U.S. centers now favor tri-modality therapy for all patients except non-surgical candidates for whom definitive chemoradiation is still a viable option (8). The remainder of this review will focus on promising avenues for the optimization these strategies including consideration of radiation dose and technique, chemotherapy, and patient selection. Ongoing and future research will be necessary to fully realize the benefits of therapy.

## Minimizing toxicity

### RT dose

A dose of 50.4 Gy in 28 fractions has generally been regarded as standard in the United States in tri-modality therapy (12) and is being employed in ongoing randomized trials (17,18). In contrast, the CROSS trial (14) utilized a dose of only 41.4 Gy in 23 fractions. The CROSS regimen yielded a pathological complete response rate of 29%, with an excellent locoregional recurrence (LRR) rate of only 14% and a median survival of 49.4 months. This is similar to results that have been seen in preoperative regimens utilizing 50.4 Gy or more (12), raising the possibility that clearly resectable patients could be spared the toxicity of an additional week of radiation therapy. Additional studies have also shown efficacy for preoperative doses of 45 Gy or less (13,19,20), although others have failed to do so (21). Caution must be used in interpreting these results due to the heterogeneity of patient populations, RT fields, chemotherapy, surgical approaches, and pathology techniques involved.

In the setting of definitive chemoradiation, dose-escalation has been a subject of investigation, spurred by the fact that local failure is common after therapy (22). The Intergroup 0123 trial was a randomized investigation of 236 patients with T1-4, N0-1, M0 disease receiving monthly cisplatin (75 mg/m<sup>2</sup>) and 5-fluorouracil (1,000 mg/m<sup>2</sup>) concurrent with radiation of 50.4 Gy plus or minus a 14.4 Gy boost to the tumor only with a 2 cm margin. There was no significant difference in the overall survival, or

locoregional failure between the two arms but there were an unexpected high number of deaths in the boost arm with 7/11 of them occurring before 50.4 Gy for unclear reasons. Brachytherapy boost has also been attempted in a phase II trial (23). In this investigation, 49 eligible patients received 50 Gy EBRT in 2 Gy fractions followed two weeks later by brachytherapy [either three weekly fractions of 5 Gy by HDR or low dose rate of 20 Gy]. All patients received concurrent monthly cisplatin ( $75 \text{ mg/m}^2$ ) and continuous infusion 5-fluorouracil ( $1,000 \text{ mg/m}^2$ ) for four cycles. Because life-threatening toxicity occurred in 24%, including six tracheo-esophageal fistulas, and 10% died, the authors urged caution in employing this technique. Although many European and Asian groups still favor higher doses, the standard of care in the United States remains external beam radiation to 50-50.4 Gy in 1.8-2 Gy fractions.

Discouragingly, this standard of care is often unable to control local disease as patterns of failure studies show high rates of failure in the treated areas. After CRT alone to 50.4 Gy, 75% of patients in one institutional experience failed in the GTV and 85% failed in the PTV (24). Only three patients failed outside the treatment field as determined by fusion with the planning CT scan. This suggests that current doses are inadequate to sterilize local disease, and dose escalation could hold promise if increased surrounding tissue toxicity could be mitigated.

### *Normal tissue tolerances*

Careful attention must be paid to normal tissue tolerances in esophageal chemoradiation therapy. Depending on the location of the primary tumor the spinal cord, lungs, larynx, brachial plexus, heart, pericardium, normal esophagus, normal stomach, liver, and/or kidneys may be at risk and should be dose constrained. Generally, the spinal cord should be limited to a max-dose of 45 Gy. Rates of lung toxicity after tri-modality therapy were predicted best by the volume of the lung receiving 5 Gy in recent analysis (25). Alternately, mean lung dose less than 20 Gy generally helps keep rates of radiation pneumonitis to acceptable levels. Minimizing dose to the lungs can be accomplished with AP/PA beam weighting but the spinal cord and heart present a competing risk. Keeping the volume of heart receiving 25 Gy less than 10% can limit long-term cardiac mortality (26). Even more common is the shorter-term complication of pericarditis. Pericarditis is found in 20-40% of patients after definitive esophageal chemoradiation therapy with a median time to onset of about 5 months.

Investigators at M.D. Anderson Cancer Center found that the rate of pericarditis is associated with the volume of pericardium receiving 30 Gy (V30) (27). They reported that when the relative V30 of the pericardium was less than 45%, the rate of PCE at 18 months after radiation was 13%, whereas it was 73% when this limit was surpassed.

### *IMRT*

Several dosimetric analyses suggest that IMRT may have potential benefit for esophageal cancer. The theoretical advantages of IMRT include increased target homogeneity, the ability to shape dose to avoid organs at risk, and the possibility of dose escalation with tighter conformality. A dosimetric analysis of ten patients treated with 3D conformal therapy then replanned using four, seven, and nine beam IMRT plans showed a 10% decrease in the lung V10, a 5% decrease in the lung V20, and a 2.5 Gy decrease in the mean lung dose, with no clinically meaningful differences in the irradiated volumes of heart, liver, or spinal cord, or the total body integral dose (28). Another dosimetric analysis from Memorial Sloan-Kettering Cancer Center reviewing 19 patients treated with 5-field IMRT plans compared to theoretical 4-field 3D conformal plans, found a significant reduction in average mean heart dose (22.9 vs. 28.2 Gy) and heart V30 (24.8% vs. 61.0%) with significant sparing of the right coronary artery (average mean dose, 23.8 vs. 35.5 Gy), but no significant improvement in the left coronary artery (mean dose, 11.2 vs. 9.2 Gy) with IMRT (29). It is unclear to what extent this would impact the development of coronary artery disease. This analysis showed no significant difference in lung, liver, kidney, stomach or spinal cord parameters. Nutting and colleagues performed a dosimetric analysis on five patients and noted no advantages to a 9-field IMRT plan, but a reduced mean lung dose when a 4-field IMRT plan was used compared to 3D conformal therapy (30).

Volumetric modulated arc therapy (VMAT), which allows for treatment during gantry rotation with conformal and/or modulated fields, has also been shown to have the potential to reduce the heart V30 (31% vs. 55%,  $P=0.02$ ) compared to 3D conformal therapy (31).

While there is a lack of strong comparative data, retrospective single arm experiences are forthcoming such as an institutional review of 30 patients (18 definitive, 12 preoperative) treated with IMRT at Stanford with chemotherapy for non-cervical esophageal cancer (32). The encouraging results of this study suggest IMRT was at least

safe and effective compared to the published experience with 3D conformal therapy.

### *Proton therapy*

Proton therapy has theoretical advantages in the mediastinum where a sharp dose drop off may be able to limit dose to structures such as the heart and lungs, and may enable dose escalation in the target volume without a corresponding dose increase in surrounding tissues. In a dosimetric study, investigators at MD Anderson Cancer Center examined theoretical distal esophageal intensity modulated proton therapy (IMPT) plans using AP/PA, LPO/RPO, or AP/LPO/RPO beam arrangements compared actual IMRT plans with beam angles optimized for each patient (33). All three of the IMPT plan types were advantageous over IMRT. The AP/PA plans achieved optimal lung sparing, and LPO/RPO plans optimized sparing of cardiac tissue. IMPT plans with three beam angles (AP/LPO/RPO) were associated with lowered mean lung (4.3 *vs.* 8.3 Gy,  $P=0.0002$ ), heart (17 *vs.* 21 Gy,  $P=0.003$ ), and liver (14.9 *vs.* 5.4 Gy,  $P<0.0001$ ) doses compared to IMRT. In these plans, the prescribed dose was 65.8 Gy to the GTV and 50.4 Gy to the PTV in 28 fractions using concomitant boost, suggesting the possibility for high dose delivery with this method. Proton therapy to thoracic targets must take into account respiratory motion however, especially when using a pencil beam scanning technique. Concurrent carboplatin/paclitaxel with proton beam therapy followed by surgery is being investigated in current phase II (34) and phase III trials (50.4 Gy *vs.* IMRT to same dose) (35).

### *Field size*

Lymphatic drainage of the esophagus follows an extensive longitudinal network, and lymph can travel for a considerable length of the esophagus before draining into lymph nodes (36). The lymphatic system of the esophagus drains into nodes that generally follow arteries, including the gastric artery/celiac axis, which represents a dominant area of lymph node metastasis for all but cervical esophageal cancer (37). Patterns of lymphatic spread are influenced by the location of the primary tumor. Historically, large elective nodal fields were used to cover the area at risk. Modern treatment techniques generally omit elective lymph node irradiation. However, celiac and SCV nodes that are not easily dissected can be included electively depending

on the location of the primary tumor. Conversely, when the celiac station is dissected as in the CROSS trials, lower esophageal and gastroesophageal junction lesions can be treated without elective celiac nodal irradiation with a celiac recurrence rate of 3.8% in patients receiving tri-modality therapy (17). Local recurrences are more common after definitive CRT without surgery and most relapses after definitive CRT are in the region of the primary tumor. An analysis by Button and colleagues from Cardiff, UK analyzed the recurrence patterns of patients treated with chemotherapy followed by definitive CRT to 50 Gy in 25 fractions using an EUS defined GTV plus a 3 cm superior/inferior expansion and 1 cm radial CTV expansion from GTV plus 0.5 cm radial PTV expansion from the superior/inferior expanded volume (38). At a median follow-up of 18 months, 88 of 145 (61%) patients had evidence of relapse. A total of 49% failed locally as a part of their first site of relapse. While the field expansions used were minimal compared to the widely used 5 cm superior/inferior margins as required by Int-0123 (22), 96% of locoregional relapses occurred within the radiation field and thus would not have been prevented by larger fields, nor would the three locoregional relapses occurring outside the field been prevented by clinically acceptable larger fields. The percentage of infield relapse was not significantly associated with AJCC stage, disease length, and lymph node involvement.

An analysis of patterns of failure of patients on the CROSS trials showed that, in 213 evaluable patients treated with CRT followed by surgery, 14% experienced LRR (17), 5% experienced LRR in the radiation target volume, 2% at the margins, 6% outside of the target volume, and 1% experienced LRR with unclear relation to the radiation target volume. In these trials a total of 41.4 Gy was delivered in 23 fractions with a superior/inferior margin of 4 cm (3 cm distal margin if extending into gastric cardia) and a radial margin of 1.5 cm.

While some trials have used even more conformal fields, there is still not enough evidence to stray from the standard 3-5 cm superior/inferior expansion. Current RTOG protocol calls for a 4 cm superior/inferior CTV expansion and 1.0-1.5 cm radial CTV expansion plus a uniform 0.5-1.0 cm PTV expansion to 45 Gy followed by a uniform 0.5-1.0 cm uniform expansion around the GTV for the last three fractions to 50.4 Gy (39). In practice, the field expansions depend partially on the confidence of the radiation oncologist in the staging workup, motion management, and set-up accuracy of the treatment.

Along with the traditional workup consisting of CT and endoscopy, the incorporation of advanced staging procedures such as PET and EUS helps to better define the tumor and may justify a smaller CTV expansion. PET fusion to the CT simulation scan may help define the extent of disease (40). In practice, when multiple diagnostic modalities (Endoscopy, EUS, CT, PET) are obtained during diagnostic work-up, generally the greatest extent of disease found should determine the size of the GTV.

## Maximizing efficacy

### *PET guided therapy*

Improving upon standard chemoradiation strategies in esophageal cancer treatment involves selecting the patients who are most likely to benefit. One way of individualizing esophageal cancer treatment is to adapt therapy based on early PET response. Weber and colleagues showed that PET response after 14 days of chemotherapy predicted for higher rates of pCR (53% *vs.* 15%,  $P < 0.01$ ), longer time to progression/recurrence ( $P = 0.01$ ), and longer OS ( $P = 0.04$ ) (41). This analysis established a decrease in SUVmax of 35% as the optimal cutoff for differentiation. Because of this study and others (42-44), prospective studies have now shown that tailoring therapy based on early PET response is feasible (45). In the prospective MUNICON study, locally advanced esophageal adenocarcinoma patients with a metabolic response (>35% decrease in SUVmax) after two weeks of neoadjuvant chemotherapy continued chemotherapy for up to 12 weeks followed by surgery (45). Those without a metabolic response discontinued chemotherapy and underwent resection. The 49% of patients achieving a metabolic response had a pCR rate of 58% (0% in non-metabolic responders), and had higher rates of OS ( $P = 0.015$ ) and event-free survival ( $P = 0.002$ ) than non-metabolic responders. Retrospective comparison of non-responders who received abbreviated neoadjuvant chemotherapy and previous patients treated by the MUNICON group suggested no detriment to discontinuation.

Early PET response during combined chemoradiation therapy is muddled by non-specific radiation induced inflammation causing SUV uptake. Using PET response has not been shown to be useful in selecting patients for early termination of CRT (46,47), but has been correlated with tumor response and patient survival (48). PET response after the completion of neoadjuvant or definitive CRT has been shown to be a significant prognostic factor

in some studies (49,50) and not prognostic in others (51). Overall, its value in guiding further treatment decisions is not definitely established (52). The MUNICON II trial examined PET response after induction chemotherapy (cisplatin, fluorouracil, and leucovorin as well as paclitaxel in some patients) followed by CRT in non-responders in an attempt to improve the rate of pathologic CR and thus survival (53). However, none of the initial non-responders achieved a pCR. This has been attributed to study design factors including a low radiation dose (32 Gy in 1.6 Gy BID fractionation) and the continuation of part of the same “failed” chemotherapy (cisplatin) during RT.

Current prospective trials are looking at a strategy of induction chemotherapy followed by PET evaluation and individualization of the chemotherapy to be used concurrent with radiation (18,54). CALGB 80803 is a multicenter phase II trial looking at PET response adapted neoadjuvant therapy for T1N+ or T2-4(N0/N+) esophageal cancer (18). Patients are randomized to modified FOLFOX 6 for three cycles or carboplatin/paclitaxel for two cycles after which they are evaluated by PET. Patients who achieve a greater than 35% decrease in SUVmax continue the same chemotherapy during RT, followed by surgery. If the SUVmax response is less than 35%, they cross over to the chemotherapy of the other arm during RT, followed by surgery. The primary endpoint is to induce a complete pathologic response in patients who cross over. In the IMAGE trial sponsored by the EORTC, early PET responders will continue with induction chemotherapy, whereas those who do not respond will be randomized to immediate surgery versus a change to taxane based chemoradiation therapy followed by surgery.

One final domain in which PET response may be instrumental in guiding treatment is the decision between tri-modality therapy and chemoradiation alone. A retrospective review of 272 patients treated at MDACC showed that OS and DFS were higher among patients receiving tri-modality therapy, yet among patients exhibiting a PET SUVmax  $\leq 4.6$  after CRT, the addition of surgery was not associated with improved OS ( $P = 0.22$ ) or DFS ( $P = 0.37$ ) (55).

### *Predictive tumor markers-ERCC1*

The success of chemoradiation therapy in individual patients can be partially predicted by the expression of certain gene products. The excision repair cross-

complementing (ERCC-1) protein is a component of the ERCC1-XPR endonuclease complex that functions to repair platinum damaged DNA through the nucleotide excision repair pathway. When compared to patients who receive surgery alone, patients with ERCC-1 negative tumors tend to achieve longer event free survival (51 *vs.* 20 months,  $P=0.042$ ) and overall survival (59 *vs.* 25 months,  $P=0.057$ ) when treated with preoperative cisplatin-based chemoradiation therapy (56). However, the addition of pre-operative chemoradiation therapy made no difference in outcomes in patients with ERCC-1 positive tumors in this retrospective study. SWOG S0353 was a prospective phase II trial investigating the effect of mRNA levels of ERCC-1 as well as thymidylate synthase (TS) in the tri-modality treatment of clinically staged II or III esophageal cancer using oxaliplatin and 5-FU (57). Intra-tumor ERCC-1 expression with a cutoff of 1.7 was significantly inversely related to 2-year overall survival (16% *vs.* 62%) and progression free survival (39% *vs.* 72%). TS gene expression was not associated with survival.

### **Targeted agents**

Because disease free survival is poor even in the best studies, further advances are still desperately needed. In the dawning age of cancer genomics, targeted agents including antibodies, tyrosine kinase inhibitors, and immune modulators are coming into the mainstream for many cancer types. In esophageal cancer, HER-2/neu gene amplification has been shown to correlate with shortened patient survival in Barrett's esophagus-associated adenocarcinoma (58). The monoclonal antibody trastuzumab is being investigated in patients with esophageal adenocarcinoma in RTOG 1010 (39). This ongoing trial tests the addition of concurrent and adjuvant trastuzumab to carboplatin, paclitaxel, and radiation (50.4 Gy) in patients with esophageal cancers that overexpress HER-2. Surgery follows 5-8 weeks after the completion of RT in both arms.

Attempts to use cetuximab in the treatment of esophageal cancer have not been encouraging however. RTOG 0436 randomized 344 unselected, inoperable esophageal cancer patients to cisplatin, paclitaxel, and radiation (50.4 Gy) versus the same therapy with concurrent weekly cetuximab (59). Cetuximab failed to improve overall survival (the primary endpoint), or clinical response, as evaluated by endoscopy 6-8 weeks after the completion of treatment. These results were consistent with those from previous studies of EGFR inhibitors in metastatic and locally advanced gastric and

esophageal adenocarcinoma where cetuximab (60) and panitumumab (61) have been shown to be ineffective in phase III trials.

### **Right chemotherapy**

An essential task in maximizing the efficacy of chemoradiation therapy is selecting the best cytotoxic agents. Some earlier positive trials of pre-operative CRT *vs.* surgery alone used cisplatin-based chemotherapy (12,13). Most recently, the CROSS trial showed increased overall survival (49 *vs.* 24 months,  $P=0.003$ ), and R0 resections (92% *vs.* 69%,  $P<0.001$ ) when carboplatin and paclitaxel based CRT were used compared to surgery alone (14). The results of this trial and several promising phase II trials of two- and three-drug paclitaxel based CRT regimens (62,63) may result in their increasing use (64). Retrospective data has not produced a clear winner (65) while prospective head-to-head comparisons are in want.

### **Altered fractionation**

Another way of intensifying Tx is through altered fractionation radiation therapy during pre-operative CRT. Hyperfractionation has been looked at in single armed studies, but has shown high toxicity in one paclitaxel based regimen (66), as well as high operative mortality, albeit with an impressive 56% pathological complete response (67).

### **Conclusions**

Chemoradiation therapy followed by surgery is the standard strategy for the treatment of locally advanced esophageal cancer. However, optimization of radiation dose, technique, chemotherapy, and patient selection is necessary to maximize its benefits. In the future, newer radiation techniques such as IMRT and proton therapy may take hold as a way to reduce toxicity. Also, a better understanding of predictive tumor markers may dictate which patients benefit most from CRT and spare toxicity to those less likely to respond. PET response is also a promising area that can help individualize CRT strategy. This is a fast moving and exciting area of oncology in which much work remains to be done.

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