

Review Article

Radiation therapy in the postoperative management of esophageal cancer

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ABSTRACT

The optimal management of esophageal cancer is complicated since institutional preferences vary, patient characteristics often guide management, and there are data to support multiple approaches for locally advanced esophageal cancer. Although surgery is an important component of therapy, alone it results in unacceptably high rates of local relapse and poor long-term survival rates. Well-studied adjuvant approaches include upfront chemoradiation therapy with or without surgery, perioperative chemotherapy, adjuvant radiation or adjuvant chemoradiation. This review article seeks to examine thoroughly the role of postoperative therapeutic options for the management of esophageal cancer, and in so doing, also overviews prospective trials in the neoadjuvant, definitive and perioperative settings. Studies evaluating radiation field design are also discussed.

KEY WORDS

esophageal cancer; radiation therapy; postoperative; chemoradiation therapy

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Introduction

Esophageal cancer is a rare disease with a poor prognosis, accounting for approximately 1% of all malignancies, with an estimated 16,640 cases in 2010 and 14,500 deaths (1). In the United States, the incidence of adenocarcinoma has risen, while squamous cell carcinoma has declined. It is now recognized in the AJCC staging system that these two histologies can carry different clinical outcomes (2). Institutional preferences and patient characteristics will often guide the management, as there are data to support multiple approaches for locally advanced esophageal cancer including upfront chemoradiation therapy (CRT) with or without surgery, perioperative chemotherapy, adjuvant radiation or chemoradiation. Surgery generally remains a mainstay in management of localized esophageal cancer, but as a single

modality results in unacceptably high rates of local relapse and poor long-term survival rates, leading to the integration of radiation therapy and chemotherapy as neoadjuvant or adjuvant modalities. The results of many studies have led to mixed results; therefore, there is no consensus about the optimal management of these patients.

There is a growing recognition that even in well clinically stage ultrasound T2 N0 esophageal cancer, between 20-25% may be upstaged to have pathologic T3 and/or node positive disease. Hence, these patients would often be referred for postoperative therapy. This review, while addressing the different sequencing of multimodality therapy, aims to focus mostly on how best to manage patients in the postoperative setting.

Definitive chemoradiotherapy

Along the lines of definitive management of esophageal cancer, it is important to discuss the RTOG 8501 trial which was instrumental in defining the superiority of chemoradiation over radiation therapy (3). The trial randomized patients to 64 Gy alone (n=60) to 50 Gy with concurrent cisplatin and 5-FU (n=61) for a total of 4 courses of chemotherapy. Overall survival at 2 years increased from 10% with radiation alone to 38% in the combined therapy group (p=0.001). Distant and local recurrences were also reduced in the chemoradiation group. An update of this

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Table 1 Pros and Cons of preoperative versus postoperative therapy for esophageal cancer (5)

Preoperative therapy	Pros	Cons
	Smaller RT volumes and doses; Sterilization of tumor bed in preparation for surgery	Treatment based on clinical stage, may over treat patients
	Avoidance of surgery in those who may progress with systemic disease	Perception of increased surgical complications with preoperative CRT
	Tumor downstaging	Preoperative dysphagia and issues of nutritional support due to tumor
Postoperative therapy	Pros	Cons
	Treatment decision based on true pathologic stage, avoids CRT in patients who may not otherwise require it	Larger RT volumes and difficulty of RT planning
	More accurate assessment of disease extent to allow for delineation of disease involvement	Usually higher radiation doses due to decreased oxygenation to the tumor bed
	Less concern about increase in perioperative morbidity and mortality after preoperative induction	Inability to assess radiation or chemotherapy tumor response
	Dysphagia has been relieved and postoperative alimentation can be supported by a surgically placed feeding tube, allowing for better tolerance of postoperative therapy	Patient recovery after resection may be difficult precluding the use of postoperative CRT; Reduced functional status after surgery

study showed that the 5-year survival rate with CRT was 27% compared to 0% with radiation alone (4). Approximately 85% of these patients had squamous histology. Of note, the 2010 NCCN guidelines recommend that T1 node positive or T2-T4 Nx esophageal cancer cases be treated with definitive chemoradiation or preoperative chemoradiation (50-50.4 Gy) followed by either esophagectomy (preferred) or observation for those achieving a complete clinical response, or for those with persistent local disease, either esophagectomy (preferred) or palliative treatment. It is recommended adenocarcinoma of the distal esophagus or GEJ be treated with preoperative chemotherapy followed by esophagectomy.

Preoperative versus postoperative therapy

From a radiotherapeutic standpoint, preoperative irradiation is advantageous compared to postoperative irradiation, because of an intact vascular supply allowing for improved oxygenation, generally smaller radiation portals and lesser radiation doses, sterilization of the operative bed, avoidance of surgery in patients with aggressive disease, and tumor downstaging. The advantage of postoperative therapy is the knowledge of the pathological stage to appropriately select patients for therapy. The pros and cons of preoperative versus postoperative therapy are further discussed in Table 1.

With preoperative therapy, optimal tumor downstaging

can result in complete pathological response of the tumor, portending improved survival outcomes for esophageal carcinoma. Pathological complete response (pCR) has often been used as a surrogate for efficacy of therapy and a measure by which various neoadjuvant therapies in esophageal cancer can be compared. Rohatgi et al retrospectively analyzed 235 patients who underwent preoperative CRT for adenocarcinoma (82%) or squamous cell (18%) carcinoma of the esophagus and found that patients who experienced pCR had longer overall and disease free survival rates, fewer distant metastases, and less disease recurrences (6). At 37-month follow-up, patients with pCR had a 74% overall survival, compared to 65% for those with $\leq 50\%$ residual disease after CRT, and 40% for those with $> 50\%$ residual disease after CRT. In addition, pCR may be more predictive of survival for patients with adenocarcinoma than squamous cell carcinoma in those receiving preoperative CRT (7).

Preoperative chemotherapy

Investigators have evaluated multiple neoadjuvant regimens consisting of preoperative chemotherapy or perioperative chemotherapy. Despite the available studies, biases may still remain about the benefit of perioperative chemotherapy versus CRT. RTOG 8911 compared surgery alone with chemotherapy followed by surgery, revealing no overall

survival difference between the two arms. Patients who underwent less than an R0 resection had an ominous prognosis (5-year overall survival for R0 resection 32%, and R1 resection 5%) (8). Cunningham et al evaluated surgery alone compared to a regimen consisting of 3 cycles of both preoperative and postoperative epirubicin, cisplatin, and 5-fluorouracil (ECF) for resectable gastroesophageal cancer and showed significant downstaging, but pathological complete response rates were zero. With the addition of chemotherapy, 5-year survival was improved from 23% to 36% with chemotherapy and progression free survival was also significantly improved (9). The Medical Research Council also demonstrated a significant 2-year overall survival benefit from 34% to 43% with the addition of 2 cycles of preoperative cisplatin and 5-FU ($p=0.004$) (10). A meta-analysis by Urschel et al evaluated 11 randomized clinical trials including nearly 2,000 patients treated with neoadjuvant chemotherapy compared to surgery alone (11). Although higher rates of complete resection (R0) were seen with preoperative chemotherapy, no survival benefit was seen for combined chemotherapy and surgery. Preoperative chemotherapy is considered a standard option for resectable adenocarcinoma of the GEJ but remains controversial for the preoperative management of intrathoracic esophageal cancer.

Preoperative chemoradiotherapy versus surgery alone

Surgery is considered important in the management of esophageal cancers. The CALGB 9781 study randomized esophageal cancer patients (77% adenocarcinoma, 24% squamous cell carcinoma) to preoperative chemoradiation (cisplatin, 5-FU, and RT to 50.4 Gy) followed by surgery versus surgery alone (12). Despite poor accrual (56 out of a planned 475 patients), a significant survival advantage was seen in the trimodality group with 5-year survival of 39% versus 16% with surgery alone and median survival of 4.5 years compared to 1.8 years with surgery alone ($p=0.002$). The addition of chemoradiation in this setting afforded a convincing survival benefit and provided justification for the existing *de-facto* standard of care in patients with clinical stage II-III disease.

In an EORTC study reported by Bosset, 282 patients with squamous cell carcinoma were randomized to preoperative cisplatin with radiation therapy (split course 37 Gy using 3.7 Gy per fraction) followed by surgery versus surgery alone (13). Results showed significant improvements in favor of preoperative therapy for disease-free survival, local control, cancer-related deaths, and curative resection rates; however, there was no difference in overall survival (18.6 months for both groups). Significantly more postoperative deaths

were seen in the group treated with preoperative CRT (12% versus 4% with surgery alone), mainly because of the higher number of patients with respiratory insufficiency, mediastinal infection or sepsis. The authors discussed that the increased number of postoperative deaths in the CRT could have been due to the “deleterious effects of high dose of radiation per fraction or of CRT on lung tissue.” They recommended future studies incorporate 2-Gy range fraction sizes, continuous radiation to overcome repopulation seen with split course therapy, and 5-FU chemotherapy. This trial therefore showed that preoperative CRT could prolong disease-free survival and local control but not overall survival although was likely limited by the radiation scheme.

An Australian study by Burmeister et al evaluated 257 patients with both adenocarcinoma (63%) and squamous cell carcinoma (27%) of the esophagus (14). Patients were randomized to preoperative cisplatin and 5-FU with concurrent radiation therapy (35 Gy in 15 fractions) or immediate surgical resection. The CRT and surgery groups had significantly more complete resections with clear margins and fewer positive lymph nodes than the surgery alone group did. However, neither progression-free survival (16 months with CRT and surgery versus 12 months with surgery alone, HR=0.82, $p=0.32$) nor overall survival (22 months with CRT and surgery versus 19 months with surgery alone, HR= 0.89, $p=0.57$) differed between the groups. On subset analysis, patient with squamous cell tumors had a better progression-free survival with CRT (HR 0.47, $p=0.014$) than those with non-squamous tumors (HR=1.02, $p=0.92$). Weaknesses of this trial included administration of only one cycle of chemotherapy and relatively low radiation doses.

Multiple trials have evaluated preoperative chemoradiation therapy with some improvement in survival outcomes and notable pathological complete response rates as detailed in Table 2.

Preoperative chemoradiotherapy versus definitive chemoradiotherapy

Some authorities believe that the role of surgery for squamous cell carcinomas remains controversial based on two studies, one from France and another from Germany. The Federation Francophone de Cancerologie Digestive Study 9102 enrolled 444 patients with resectable squamous cell carcinoma (89%) or adenocarcinoma (11%), to receive one of two radiation schemes with 2 courses of concurrent cisplatin and 5-FU: 1) protracted radiotherapy (46 Gy over 4.5 weeks) (64% of participants) or 2) split course radiotherapy with two 1-week courses of 15 Gy with a 2 week break (36%) (17). 259 patients who responded to therapy were randomly assigned to surgery or additional chemoradiation. For the

Table 2 Trials of preoperative chemoradiotherapy

Author	ACA/SCC (%) (n)	Regimens	pCR (%)	Survival	Other
Walsh (15)	100/0 (113)	Surgery vs (5-FU+ CDDP for 2 cycles) + RT (40 Gy/15 fx) →surgery	25%	3YS: 6% vs 32% (sig)	Small patient numbers, non- standard RT fractions, poor outcome of surgery alone
Bosset (13)	0/100 (282)	Surgery vs CDDP for 2 cycles +RT (37 Gy/10 fx) →surgery	26%	3YS: 34% vs 36% (NS)	Split course RT, non- standard RT fractions, no 5-FU/single agent CDDP
Urba (16)	76/24 (43)	Surgery vs (CDDP +5-FU+ vinblastine) +RT 45 Gy in 1.5 Gy BID	28%	3YS: 15% vs 30% (NS)	Underpowered
Burmeister (14)	62/37 (256)	Surgery vs 5-FU+ CDDP + RT (35 Gy/15 fx) → surgery	16%	3YS (ACA) 28% vs 26% (NS); SCC: 35% vs 50% (NS)	pCR more common in SCC, fewer R0 resections in surgery alone group, PFS was sig improved for CRT for SCC

CDDP: cisplatin; fx: fractions; sig: significant; NS: non-significant; SCC: squamous cell carcinoma; PFS : progression-free survival; ACA: adenocarcinoma

non-responders, they continued on a course of CRT with an additional 20 Gy for the protracted course and 15 Gy for the split course CRT. No significant differences were seen in median survival and (17.7 months in those who underwent surgery compared to 19.3 months in the definitive CRT arm) 2-year survival (34% in surgery cohort vs 40% in the CRT arm, $p=0.44$). Nevertheless, the 2-year local control rate was higher with surgery (66%) compared to CRT (57%). The 3-month mortality rate was 9% in the surgery group and 1% in the CRT group. The results of this trial imply that for patients who respond to CRT, surgery may improve local control but not survival.

In a similar study design by Stahl et al, 172 patients with locally advanced squamous cell carcinoma of the esophagus were randomized to either induction chemotherapy (5-FU, leucovorin, etoposide, and cisplatin for 3 cycles) followed by CRT (40 Gy with cisplatin and etoposide) followed by surgery or the same induction chemotherapy followed by CRT (total dose of 60-65 Gy with or without brachytherapy) without surgery (18). Overall survival at 2-years (40% with surgery vs 35% with CRT) and median survivals (16 months vs 15 months) were equivalent. Freedom from local progression was improved with surgery (64% vs 41%, $p=0.003$). Surgery improved outcomes for non-responders to CRT who had 3-year survival rates of 18% with surgery compared to 9% with CRT alone. Treatment related mortality

was also higher in the surgery arm (13% vs 3.5%, $p=0.03$). The addition of surgery to CRT improved tumor control but not survival for squamous cell carcinomas.

Because many of the randomized clinical trials investigating surgery versus preoperative therapy have been underpowered, meta-analyses have been performed. GebSKI et al showed a 13% absolute survival benefit at 2 years with the neoadjuvant CRT (hazard ratio 0.81, $p=0.02$) with similar results for squamous cell carcinoma (hazard ratio of 0.84, $p=0.04$) and adenocarcinoma (hazard ratio 0.75, $p=0.02$). Neoadjuvant chemotherapy portended a 2-year absolute survival benefit of 7% with only a significant effect on all-cause mortality for adenocarcinoma of the esophagus and not squamous cell carcinoma (19). Urschel et al also demonstrated improved 3-year survival, higher rates of R0 resection and tumor downstaging, and reduced local-regional recurrence with neoadjuvant CRT compared to surgery alone (20, 21). In sum, there does appear to be a survival benefit with the addition of CRT to surgery.

Adjuvant (postoperative) therapy

The goal of adjuvant radiation therapy for esophageal cancer is to decrease the risk of locoregional recurrence and in so doing, can contribute to a survival benefit. As noted earlier, it is not uncommon for patients with clinically staged

ultrasound T2 N0 diseased to be upstaged to pathologic T3 or node positive status following resection (22). Rationale for postoperative radiotherapy includes advanced tumor stage (T3 or T4), nodal positivity, positive margins, or subtotal resection (23).

Postoperative radiation therapy versus surgery alone

Most of the series which will be discussed in the upcoming sections are based on populations of squamous cell carcinoma of the esophagus. There is a clear benefit in local control with the addition of radiation and possibly a survival advantage. However, many of these studies were conducted prior to the advent of PET staging by which we now can identify 10-15% of patients with occult metastatic disease which may change their management and survival outcomes.

The largest of these series is by Xiao and included 495 patients with squamous cell carcinoma of the esophagus who received postoperative radiation therapy (n=220) or surgery alone (n=275) (24). Radiation portals encompassed the bilateral supraclavicular areas and entire mediastinum to a total of 60 Gy (40 Gy prescribed to midplane and 20 Gy from horizontal portals, treated over 6 weeks). Survival was improved non-significantly with the addition of RT from 32% to 41% (p=0.45). Stage III patients had a distinct, significant overall survival improvement with the addition of RT from 13% to 35% at 5 years (p=0.003). This trial has been criticized for not employing an intention-to-treat analysis, since it excluded 54 patients who did not complete the planned course of treatment. The lack of informed patient consent called into question the ethical standards of this trial (25).

In a separate retrospective analysis by Xiao et al by extent of lymph node status, 549 patients were classified into three groups: Group 1: no lymph node involvement, Group 2: one-two positive lymph nodes, Group 3: three or more positive lymph nodes. The 5-year survival rate of patients with positive lymph nodes (Groups 2 and 3) was 18% with surgery alone compared to 34% with the addition of RT (p=0.038) (26). Also, for similar stage III patients, the number of lymph nodes predicted survival outcomes with 5-year survival at 58% for group 1, 31% for Group 2, and 14% for Group 3. Although there was no survival benefit for lymph node negative patients, those with one to two positive lymph nodes had an improvement in 5-year overall survival with the addition of RT from 24% to 45%. For patients with 3 or more positive lymph nodes, 5-year survival outcomes were 21% with RT versus no survivors with surgery alone. Not only is number of metastatic lymph nodes prognostic, but the addition of RT improved survival in patients with positive lymph nodes.

An analysis of the Surveillance Epidemiology and End Results (SEER) database evaluated the impact of adjuvant

radiation in 1046 patients, who received surgery alone (65%) or postoperative radiation (35%) (27). For Stage III patients there was significant improvement in median (15 to 19 months), 3-year overall survival (18 to 29%) (p< 0.001), and disease specific survival (18 to 24 months) (p< 0.001) which was present for both adenocarcinoma and squamous cell carcinomas. No improvement in survival was seen with Stage II esophageal cancer (AJCC 6th edition) with the addition of postoperative RT. Multivariate analysis also confirmed that the addition of adjuvant RT was associated with an improved survival (HR 0.70, 95% CI 0.59-0.83, p<0.001). This analysis is limited by the lack of information about chemotherapy, radiation fields and doses, and margin status.

Teniere et al evaluated patients with squamous cell carcinoma of the middle to lower third of the esophagus and randomized them to observation (n=102) or postoperative RT (n=119) (45-55 Gy in 1.8 Gy per fraction to the bilateral supraclavicular regions, mediastinum, and involved celiac lymph nodes) (28). Patients were stratified by nodal involvement extent. Five-year survival in node negative patients was 38% versus 7% with involved nodes. Postoperative RT did not confer a survival benefit (5-year survival of 19% in both arms). Rates of local regional recurrence were lower in patients receiving postoperative radiation versus surgery alone (85% vs 70%) but not statistically significant. Patients without nodal involvement did have significant improvement in local regional recurrence with the addition of radiation therapy (90% vs 65%).

Fok et al included both squamous cell carcinoma and adenocarcinoma histologies in their study and stratified patients based on palliative (n=70) versus curative (n=60) resection prior to randomization to postoperative RT versus observation (29). Prescribed radiation doses of 49 Gy for curative resection and 52.5 Gy for palliative resection in 3.5 Gy per fraction were used, delivered to a 5 cm margin both proximal and distal to the initial tumor extent as delineated by barium swallow. Although they demonstrated a decline in local recurrence rates for those who underwent palliative resection followed by adjuvant RT (20% postoperative RT, 46% no RT, p=0.04), there was no statistical difference in local recurrence for those who had complete resection (15% with RT versus 31% with surgery alone, p=0.06). The overall median survival was significantly shorter for patients receiving postoperative RT (8.7 months) versus control (15.2 months). In patients with residual tumor in the mediastinum after resection, two died of tracheobronchial obstruction compared to nine in the control group. The authors concluded that the shorter survival of patients who underwent postoperative radiotherapy was the result of irradiation-related death and the early appearance of metastatic disease, although patients were less likely to have a recurrence obstructing

Table 3 Trials postoperative radiotherapy versus surgery alone

Author	ACA/SCC (%) (n)	Radiation fields	Survival	Other
Xiao (24)	0/100 (495)	60 Gy to bilat SCV and mediast	5YS: 13% vs 35% (sig)	No intention-to- treat analysis
Schreiber (27)	66/34 (1046)	Unknown (SEER analysis)	3YS: 18% vs 29% (sig) for Stage III patients	No benefit for Stage II patients
Teniere (28)	0/100 (221)	45-55 Gy to bilat SCV and mediast+ involved celiac LN	5YS: 19% in both arms (NS); node-positive: 38% vs 7% (sig)	Improved local control in node positive patients (85% vs 70%, NS)
Fok (29)	(130)	49 Gy (curative resection)/ 52.5 Gy (palliative resection) to 5 cm proximal and distal to tumor by barium swallow	Median survival: 15.2 mo (surgery) vs 8.7 (postop RT)	Decreased LR for palliative resections with addition of RT 40% vs 20% (sig); Daily fraction size of 3.5 Gy possibly causing worse survival with RT

ACA: adenocarcinoma; SCC: squamous cell carcinoma; postop: postoperative; bilat: bilateral; SCV: supraclavicular regions; sig: significant; NS: non-significant; LR: local recurrence; YS: year survival; mediast: mediastinum; LN: Lymph nodes

the tracheobronchial tree. The major criticism of this trial has been the large fraction sizes and total dose delivered which may have contributed to the increased mortality rates and resulted in substantially higher gastric pull-up complications (37% with RT versus 6% with surgery alone) and six fatal bleeding events in the RT group. Similarly, Zieren et al evaluated 68 squamous cell carcinoma patients who were randomized to either observation or postoperative RT, finding no difference in overall or disease-free survivals, but an increase in fibrotic esophageal strictures in the RT arm (30).

In a meta-analysis of postoperative radiotherapy trials, no significant difference in the risk of mortality with postoperative radiotherapy and surgery at one year compared with surgery alone was detected (RR, 1.23; 95% CI, 0.95 to 1.59; $p = 0.11$) (31). The rate of local recurrence with radiotherapy was lower in the trials of Xiao and Fok (24, 29), but the two trials of Teniere and Zieren (28, 30) noted this benefit was achieved at the expense of increased morbidity.

Given modern day techniques, improved treatment planning with strict dose volume histogram data, postoperative RT is expected to be safer with less toxicity than previous studies. Based on the aforementioned studies, improvements in local control can be expected and is particularly important in the setting of nodal positivity or R1/R2 resection.

Postoperative radiation therapy versus post-

operative chemo-therapy

The Japanese Esophageal Oncology Group evaluated postoperative radiotherapy (50 Gy to supraclavicular regions and upper mediastinum in 2 Gy/day) versus 2 cycles of cisplatin and vindesine (32). Of the 258 patients randomized, 73% had positive lymph nodes and 65-70% of patients had T3 or T4 disease, but histology was not delineated. Overall survival was no different (3-year survival rates were 51% (RT) and 52% (chemotherapy) and local recurrence rates were also equivalent. In contrast, in a retrospective study by Chen et al of 366 patients with squamous cell carcinoma of the mid-thoracic esophagus, local recurrence rates were significantly lower with adjuvant radiation therapy compared to chemotherapy or observation (20%, 32%, 43%, respectively) (33).

Postoperative chemoradiation versus surgery alone

The INT-0116 trial published by MacDonald et al prospectively randomized 556 patients with gastroesophageal junction (GEJ) (approximately 20%) or gastric adenocarcinoma patients, Stage IB-IV (AJCC 3rd Edition) who had undergone curative resection with negative margins to receive no further therapy or to postoperative chemoradiation (one cycle of 5-FU and leucovorin followed by concurrent radiation to 45 Gy with the same agents, followed by two additional cycles of 5-FU and leucovorin) (34). Patients were required to have sufficient caloric intake of

Table 4 Prospective trials of postoperative chemoradiation

Author	ACA/SCC (%) (n)	Regimens	Survival	Other
		Surgery alone versus postoperative		
MacDonald (34)	100 (556)	5-FU+ LV → RT (45 Gy) + 5FU+LV → 5-FU+ LV	3YS: 41% (surg) vs 50% (postop CRT)	LR reduced from 29% to 19% with radiation
Adelstein (5)	86/14 (50)	Surgery → 5-FU + CDDP + RT (50.4-59.4 Gy)	4YS: 51%	Phase II trial, local control: 86%

ACA: adenocarcinoma; SCC: squamous cell carcinoma; postop: postoperative; sig: significant; NS: non-significant; LR: local recurrence; YS: year survival; LV: leucovorin; CDDP: cisplatin

1500 Kcal per day. Because of the complicated nature of RT field design for gastric carcinomas, RT quality assurance was conducted prior to radiation delivery, and both minor and major deviations were detected in 35% of cases and corrected. Three-year overall survival improved with addition of chemoradiation from 41% to 50% as well as median survival from 27 months to 36 months with chemoradiation. (HR 1.35 for death with surgery alone group compared to adjuvant CRT, 95% CI 1.09-1.66, $p=0.005$). Local recurrence rates were also reduced from 29% with surgery alone to 19% with the addition of CRT. This trial provides the rationale for the use of postoperative CRT for GEJ adenocarcinomas. In patients with GEJ adenocarcinomas, CRT is appropriate to improve survival and local control.

Of note, in the 6th Edition of the AJCC manual, GEJ carcinomas could be included in esophageal or gastric stage groupings and could produce different stage groupings depending on either the use of the esophageal or gastric stage groupings. GEJ carcinoma also previously included the locally advanced stages of T4 Nx or Tx N3 (Stage IV as stated above) when grouped with gastric cancer (35). In the AJCC 7th Edition, the GEJ carcinomas are now staged with esophageal, rather than gastric cancers, and include cancer within the first 5 cm of the stomach that extends into the GEJ or distal thoracic esophagus (2, 36). In addition, Stage IV disease currently only refers to M1 staging and does not include any locally advanced disease.

A phase II trial of postoperative CRT for poor prognosis esophagus and GEJ adenocarcinoma (86%) and squamous cell carcinomas (14%) investigated postoperative 5-FU, cisplatin and RT to 50.4-59.4 Gy in 50 patients with node positive or T3/T4 tumors (5). 4-year freedom from recurrence was 50%, distant metastatic control 56%, and locoregional control 86%, with a median survival of 53 months, comparing favorably with a historical median survival of 28 months in prior trials (37).

Bedard et al retrospectively evaluated 28 node positive

patients treated with surgery alone compared to 38 patients treated with surgery and postoperative CRT. There were more local recurrences with surgery alone (35% versus 13% with CRT, $p=0.09$) (38). Overall survival was significantly improved with postoperative CRT, and median survival was 47.5 months with CRT versus 14.1 months with surgery alone. Similarly, Rice et al, on retrospective analysis, demonstrated a 28-month with CRT versus 14-month median survival with surgery alone (37, 39).

In modern day practice, it would reasonable to add chemotherapy to postoperative radiation therapy as per NCCN guidelines, to maximize the benefit of radiosensitization with systemic therapy, especially if the patient could tolerate such a course. The available data do suggest that postoperative RT alone also would be appropriate. For adenocarcinomas of the GEJ, the MacDonald protocol is reasonable.

Postoperative chemoradiation versus postoperative radiation therapy alone

A non-randomized prospective study from Taiwan evaluated postoperative patients with T3-4 and N0-1 esophageal carcinoma who were assigned to either CRT with weekly cisplatin followed by adjuvant chemotherapy consisting of cisplatin and 5-FU for four cycles ($n=30$) or postoperative RT alone ($n=30$) (39). RT was delivered to 55-60 Gy in both arms. A significantly better overall survival was seen with CRT (31 months vs 21 months) and 3-year survival was improved to 70% with CRT versus 34% with RT alone ($p=0.003$).

Radiation therapy field design

Patients undergo a simulation with a contrast-enhanced computed tomographic (CT) scan, in the treatment position along with an immobilization device, usually in a supine position. Many investigators are utilizing four-dimensional CT scans (40). Appreciation of how the post-resection

esophageal conduit moves with respiration, will aid the radiation oncologist in developing portals that cover sites at highest risk for loco-regional recurrence.

In pathological analysis of patients with esophageal and GEJ carcinoma, Gao et al prospectively collected and evaluated 34 squamous cell carcinomas and 32 carcinomas of the GEJ to assess microscopic spread both proximally and distally in the specimens (41). For squamous cell carcinomas, mean microscopic tumor extension beyond the gross tumor was found to be 10.5 ± 13.5 mm proximally (<30 mm in 94%) and 10.6 ± 8.1 mm distally (<30 mm in 97%). In GEJ adenocarcinomas, the spread was 10.3 ± 7.2 mm proximally (<30 mm in all cases) and 18.3 ± 16.3 mm distally (<30 mm in 84%). Lymph node metastases were observed in 35% of patients with middle and lower esophageal squamous cell carcinomas and 47% of patients with GEJ carcinomas. The recommended Clinical Target Volume (CTV) margin was <30 mm in about 94% of esophageal cancers (pleural), except for distal microscopic spread in GEJ adenocarcinomas (pleural), in which 50 mm was needed to cover 94% of cases.

In a comparison of efficacy of regional and extensive

clinical target volumes in postoperative radiotherapy for esophageal squamous cell carcinoma, 102 patients with T3/T4 or N1 disease treated with ≥ 50 Gy were reviewed (42). In extensive portal irradiation (n=43) cohort, the CTV encompassed the bilateral supraclavicular regions, all mediastinal lymph nodes, the anastomotic sites, and the left gastric and pericardial lymphatics. In the regional irradiation group (n=59), the CTV was confined to the tumor bed and the lymph nodes in the immediate region of the primary lesion. The 1-, 3-, and 5-year survival rates between the two groups were nearly identical. It is appropriate to use a regional portal which affords similar survival outcomes to an extended field and less acute and long-term toxicity.

At the University of Erlangen, Meier et al, analyzed patterns of regional spread using pathology reports of 326 patients with adenocarcinoma of the GEJ who had undergone primary resection with ≥ 15 lymph nodes examined (43). Tumors were classified into Type I (distal esophagus), Type II (cardia), and Type III (subcardial) based on pathology and endoscopy reports. Marked esophageal invasion of GEJ Type II and III significantly correlated with paraesophageal

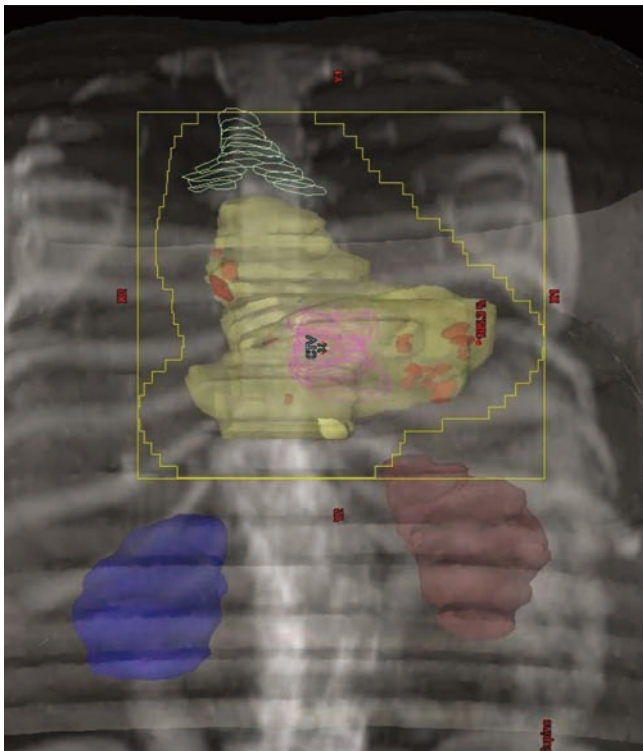


Figure 1 Lower esophageal ACA status post esophagectomy and partial gastrectomy with gastric pull up. Blue: right kidney; Brown: left kidney; Red: clips; Pink: preoperative tumor volume; Yellow: gastric remnant; Green: Carina. An anterior inferior oblique field is used to spare the kidneys.

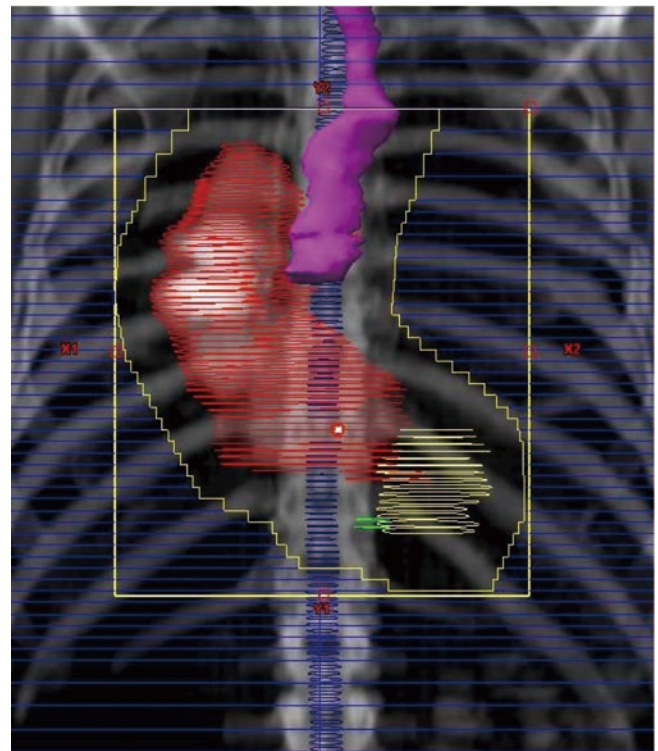


Figure 2 Mid-esophageal adenocarcinoma status post Ivor-Lewis esophagectomy. Red: stomach; Magenta: residual esophagus; Yellow: preoperative tumor volume; Blue: spinal cord. Anterior-posterior field demonstrated.

nodal disease, and T3-T4 Type II/III had a significant rate of splenic hilum/artery nodes. Therefore, middle and lower paraesophageal nodes should be treated in T2-T4 Type I and II with ≥ 15 mm of involvement above the Z line, and T3-T4 Type II. In addition, a study from Japan, in which 102 of cases were examined (85% squamous cell carcinoma), showed that the rates of lymph node metastases for the upper, middle, lower and abdominal esophagus were 37.5%, 32.5%, 46% and 70%, respectively (44).

It is helpful to know which lymph nodal stations are involved with metastatic disease in order to develop rationale field designs (41). Positive nodes may be seen in approximately one-third of resected middle and lower esophageal SCCA cases, with the subcardial, paraesophageal, and left gastric nodal stations being the most common sites (41). Distal adenocarcinoma lesions may harbor node positive disease almost half of the time with the left gastric and para-cardiac nodal stations being the most common (Figure 1 and 2).

In the postoperative setting, it seems reasonable to treat a regional field encompassing the preoperative intrathoracic esophageal tumor volume with a 3 cm cephalad and caudal margin for the clinical target volume (CTV), and 3-5 cm cephalad and caudal margins for GEJ carcinomas. Regional lymph nodes will also be treated as well as anastomotic sites. If daily image guidance techniques, such cone-beam CT scans are utilized, it may be possible to reduce the planning target volume (PTV). Postoperative doses of 45-50.4 Gy for R0 complete surgical resection with negative margins are appropriate to reduce long-term complications such as stricture. Higher doses of 54-60 Gy would be recommended for patients with R1 resections.

Conclusions

Adjuvant chemoradiation is a suitable option for the management of the resected, locally advanced esophageal cancer patient, especially for T3/T4 disease, nodal positivity, and R1 or R2 resection. Doses of 45 to 50.4 Gy can be used for R0 to R1 resections, but for gross residual disease, a boost of 5-9 Gy may be considered. For tumors of the intrathoracic esophagus, concurrent cisplatin and 5-FU can be used, and for GEJ carcinomas, the INT-0116 protocol can be recommended. The available data suggests an improvement in local control and a possible survival improvement with the use of postoperative radiation therapy.

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