Preoperative Versus Postoperative Chemoradiotherapy in the Trimodality Management of Esophageal Cancer

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Abstract: Chemoradiotherapy (CRT) is commonly employed in the management of esophageal carcinoma—either definitively or as part of a trimodality strategy with includes surgical resection. For patients treated with trimodality therapy, the most optimal sequence of chemoradiation (CRT) in relation to surgical resection is unclear. We reviewed the efficacy, advantages, and disadvantages of preoperative CRT versus postoperative CRT in esophageal cancer patients treated with trimodality therapy. Preoperative chemoradiation enables early treatment of distant metastases while simultaneously treating the primary disease, facilitates definition of radiotherapy target volumes, and may allow resection of advanced disease. It does, however, have considerable toxicity and may reduce the ability of some patients to tolerate resection. Postoperative CRT allows for early debulking, rapidly addresses dysphagia, and allows for CRT based on accurate pathologic staging, but delays systemic treatment. Randomized studies that compare preoperative with postoperative CRT in treating esophageal cancer are needed to identify conclusively the best standard of care. Based on the study information currently available, we conclude that treatment options should be tailored to the individual patient.

Introduction

Esophageal cancer is an aggressive neoplasm with high mortality. The esophagus is surrounded by mediastinal structures with a rich vascular and lymphatic supply; thus invasion and metastases occur early. Approximately 16,470 Americans were diagnosed with esophageal cancer in 2008, and 14,280 were estimated to die of their disease.[1] Squamous cell carcinoma predominates in underdeveloped countries, while the incidence of adenocarcinoma of the distal esophagus and gastroesophageal junction is increasing in developed countries to the point that adenocarcinoma dominates statistically.[2] Multimodality therapy has led to significant improvement in outcomes of patients with localized disease. However, overall survival for esophageal cancer has not improved significantly in the past 25 years.[1] For the rare patients with node-negative, organ-confined disease, surgical resection can achieve cure rates of 60–80%. However, patients with

locally advanced disease have a 5-year survival of 20–30% with resection alone or definitive chemoradiotherapy (CRT).[3] There is some evidence that patients treated with trimodality therapy may have superior outcomes compared to surgery or CRT alone and trimodality therapy has become a commonly employed strategy for managing esophageal cancer.[3,4] For patients treated with trimodality therapy, the best sequence of CRT in relation to surgery is unclear. We review here the efficacy, advantages, and disadvantages of neoadjuvant versus postoperative CRT.

Esophagectomy

Historically, surgical resection has been the primary therapy for localized esophageal cancer. Esophagectomy alone has a low cure rate regardless of surgical method or histology.[5-7] Only 30–50% of the patients presenting with esophageal carcinoma are candidates for resection. Of those who could be resectable, only 60% will actually undergo a potentially curative resection.[8] Even with a complete R0 resection, locoregional recurrences and metastases are common. Esophagectomy has a significant operative morbidity of 48% and mortality of approximately 5–10%.[9] Despite these discouraging data, surgical resection remains the primary treatment for localized esophageal cancer.

Patients who present without regional nodal involvement can be successfully treated with surgery alone. However, patients with nodal disease at the time of resection rarely do well with surgery alone. Unfortunately, a significant percentage of patients with esophageal cancer present with locally advanced, node-positive tumors.[3]

Chemoradiation

Concurrent chemotherapy and radiation therapy is more effective than radiation therapy alone and has improved outcomes.[10] Chemotherapy can address systemic micrometastases while fractionated radiation therapy treats locoregional disease leading to improved survival. However, chemotherapy can also radiosensitize tumors leading to improved locoregional control. Chemotherapeutic agents such as cisplatin, 5-fluorouracil (5-FU), mitomycin C, gemcitabine, and taxol have a greater than additive effect when used in combination with radiation therapy.[11-14]

The exact mechanism of the interactions between radiation and chemotherapeutic agents is unclear. Therefore, the recommendation is to use both modalities at the dose levels that are optimal when used alone, instead of relying on a synergistic or additive effect. In an important study by Herskovic and colleagues that randomized 121 patients to 5,000 cGy with concurrent chemotherapy with 5-FU and cisplatin versus 6,400 cGy radiation alone,[15-17] 27% of patients from the combined modality group were alive at 5 years versus none in the latter group. The median survival time in the combined modality arm was 14.1 months versus 9.3 months in the radiation only group.[16] A recent Cochrane review examined 19 trials of radiation therapy versus CRT and their meta-analysis demonstrated a 9% absolute overall survival benefit and 12% absolute locoregional control benefit for combined modality treatment.[10] As reviewed by Brenner and coauthors, higher 5-year median survival, higher local control, lower local failure, and lower mortality are observed with CRT compared to radiation alone.[18]

Trimodality Therapy

A commonly employed treatment approach for esophageal cancer is CRT in addition to surgical resection. Many studies have demonstrated the effectiveness of trimodality therapy.[19,20] However, some investigators question the necessity of surgical resection, as other studies have suggested definitive CRT as a viable alternative.[4,21] The optimal management strategy remains a matter of debate and whether a patient receives definitive CRT or trimodality therapy depends on patient preferences, physician preferences, institutional practices, patient performance status, tumor stage and characteristics, and many other factors.

The purpose of this paper is to examine the efficacy of preoperative versus postoperative CRT in patients receiving trimodality therapy. There has never been a randomized trial that directly compares preoperative CRT with postoperative CRT. The vast majority of trials have focused on the efficacy of preoperative CRT, and the literature is much less robust for postoperative CRT. A review of available data can, however, provide some general principles with regard to these 2 treatment strategies.

Trials of Preoperative Chemoradiation

Six published randomized prospective studies have evaluated concurrent preoperative CRT plus resection versus resection alone (Table 1).[19-20,22-25] Although other studies exist, many of these use suboptimal treatment strategies such as sequential CRT[26] or low radiation therapy (XRT) doses.[27]

In 1996, a trial by Walsh and coworkers randomized 123 patients with adenocarcinoma to preoperative CRT versus surgery alone.[20] Patients in the trimodality arm received 40 Gy of radiation therapy delivered in 15 fractions with concomitant chemotherapy consisting of 75 mg/m^2 of cisplatin on day 1 and 15 mg/kg/d of 5- FU for 5 days. A second chemotherapy cycle followed the radiation (week 6) prior to surgical resection. A pathologic complete response was attained in 25% of the patients in the trimodality group. Median survival was

Table 1. Clinical Trials of Neoadjuvant Concurrent Chemoradiotherapy for Resectable Esophageal Cancer

Author	Treatment	RT (Gy)	N	Histology (%)	Median Survival (mo)	3-year survival	*P* value
Walsh[20]	• Cisplatin 100 mg/m^2 D1 Q3W x2 • 5-FU 500 mg/m^2/D D1–5 Q3W x2	40	58	ADC 100	16.0	32	.01
	Surgery alone		55		11.0	6	
Apinop[22]	• Cisplatin 100 mg/m^2 D1 Q4W x2 • 5-FU 1000 mg/m^2 CI D1–4 Q4W x2	40	35	SCC 100	9.7	24*	NR
	Surgery alone		34		7.4	10*	
Urba[19]	• Cisplatin 20 mg/m^2 CI D1–5, 17–21 • 5-FU 300 mg/m^2/D CI D1–21 • Vincristine 1 mg/m^2/D IV D1–4, 17–20	45	50	SCC 26, ADC 74	16.9	30	.15
	Surgery alone	50	100	SCC 24, ADC 76	17.6	16	
Bosset[23]	Cisplatin 80 mg/m^2 D1 Q3W x2	37	143	SCC 100	18.6	38	.78
	Surgery alone		139		18.6	37	
Burmeister[24]	• Cisplatin 80 mg/m^2/D1 • 5-FU 800 mg/m^2/D D1–4	35	128	SCC 35, ADC 63	22.2	36	.57
	Surgery alone		128	SCC 39, ADC 61	19.3	33	
Krasna[25]	• Cisplatin 100 mg/m^2 D1–35 • 5-FU 1,000 mg/m^2/D D1–4, 35–38	50.4	30	SCC 14	54.0	39*	<.008
	Surgery alone		26	ADC 42	21.6	16*	

ADC=adenocarcinoma; CI=continuous infusion; D=day; IM=intramuscular; IV=intravenous; NR=not reported; NS=not significant; RT=radiation therapy; SCC=squamous cell carcinoma

*Five-year survival.

higher in the trimodality arm (16 months) than in the resection alone arm (11 months). The overall survival at 3 years was also better in patients receiving preoperative therapy (32%) versus surgery alone (6%). Despite these promising results, data should be interpreted with caution given the low survival rate in the surgery cohort.

A study conducted by Urba and associates at the University of Michigan investigated an aggressive neoadjuvant regimen of cisplatin, 5-FU, and vincristine with 45 Gy of radiation (1.5 Gy/fraction twice daily over 3 weeks) in patients with both squamous cell and adenocarcinoma of the esophagus.[19] The trimodality group and resection only group had similar median survival. The 3-year survival was higher (30%) in the trimodality arm compared with surgery alone (16%), although this failed to reach statistical significance (*P*=.15). The fact that 94% of patients treated with neoadjuvant CRT were able to complete surgery suggests that intensive preoperative therapy does not necessarily compromise resection. Despite these promising results, this twice daily fractionation strategy is rarely used in clinical practice.

The European Organization for Research and Treatment of Cancer (EORTC) randomized 282 patients with squamous cell carcinoma of the esophagus to esophagectomy or to 37 Gy of radiation given over 2 weeks concurrent with 2 courses of cisplatin given each week of the radiation therapy.[23] The trimodality therapy and surgery resulted in similar median and overall survival. A lower cancer-specific death rate in the trimodality arm was offset by a higher postoperative mortality rate (17 deaths vs 5 deaths in the surgery alone arm). The authors postulated that daily XRT fractions of 3.7 Gy were too toxic.

Burmeister and colleagues recently completed a trial of 256 patients randomized to cisplatin and 5-FU plus 35 Gy of radiation given over 3 weeks before surgical resection compared to surgery alone.[24] The study enrolled

patients with both squamous cell and adenocarcinoma histologies. The median survival and the overall 3-year survival rate in the trimodality versus surgery alone groups was 22 versus 19 months and 36% versus 33% (*P*=.57).

Finally, the Cancer and Leukemia Group B started a large intergroup trial in 1997 aiming to enroll 500 patients with stage I–III esophageal cancer.[25] The patients were randomized to receive either surgery alone or 2 cycles of cisplatin and 5-FU plus 50.4 Gy of radiation therapy (1.8 Gy/fraction over 5.5 weeks) followed by resection. Due to extremely slow accrual with only 56 patients enrolled, the study was closed in March of 2000. An analysis of this trial has been published and reveals a significant survival advantage for the trimodality arm. The results favored the trimodality treatment, with a median survival of 4.5 years compared with 1.8 years for patients who received surgery alone (*P*=.02). The 5-year survival rate was 39% for the trimodality group versus 16% for the surgery alone group. A pathologic complete response to neoadjuvant CRT was seen in 40% of patients.

These data suggest that trimodality therapy may improve survival and locoregional control but is associated with higher toxicity. In appropriately selected patients, this is a viable strategy. As therapies improve, it is likely that the toxicity may decrease and neoadjuvant CRT may provide clearer benefit in esophageal cancer.

Postoperative Chemoradiation

Unfortunately, compared to the wealth of data available on preoperative chemoradiation, there are relatively few studies that investigate the effectiveness of postoperative CRT. Although a number of trials compare adjuvant chemotherapy or radiotherapy with surgery alone, there are almost no randomized trials comparing adjuvant CRT with surgery alone. The only exception is a trial by MacDonald and coauthors that compared surgery alone with surgery and adjuvant CRT for 556 patients with resectable cancers of the stomach and gastroesophageal junction.[28] Twenty percent of enrolled patients had lesions in the gastroesophogeal junction. Chemotherapy consisted of 425 mg/m^2 of 5-FU and 20 mg/m^2 leucovorin, while radiation therapy totaled 45 Gy. The median survival in the trimodality group was 36 months versus 27 months in the surgery-only group (*P*=.005). These results suggest that resection followed by concurrent CRT should be considered for patients with adenocarcinoma of the stomach and the gastroesophageal junction.

There are a number of nonrandomized trials that have studied postoperative CRT in treating esophageal cancers (Table 2).[29-35] In a retrospective review of 31 patients with locoregionally advanced (T3-4, N1, or M1a) adenocarcinoma or squamous cell esophageal carcinoma, Rice and coworkers found that patients treated with postoperative adjuvant CRT had improved survival.[29] In order to minimize confounding factors, patients were matched in propensity scores based on demographic, tumor, and surgical factors. The survival benefit with postoperative CRT was also observed in these propensity-matched patient pairs. The median, 1-year and 4-year survivals were higher, and median time to recurrence was lower in the trimodality group. Median time to recurrence was 25 and 13 months (*P*=.04) and recurrence-free survival was 22 and 10 months (*P*=.02), respectively. Rice and coworkers concluded that when R0 resection is possible, patients with locoregionally advanced esophageal cancer should be considered for esophagectomy followed by postoperative adjuvant chemoradiotherapy. This treatment regimen results in better survival, decreased recurrence, and longer recurrence-free survival.

A retrospective study conducted by Bedard and associates demonstrated a survival advantage for patients with lymph node–positive esophageal carcinoma who were treated with resection and postoperative CRT compared to patients with resection alone.[30] This group had less local recurrences, longer overall survival, and greater rate of survival at 1 year, 3 years, and 5 years. Multivariate analysis showed that postoperative CRT (treatment received) and ECOG score were predictors of survival (95% confidence interval, 0.16–0.76; *P*=.007) and correlated with significantly decreased risk of death in patients with lymph node–positive, resected esophageal carcinoma. They concluded that in patients with lymph node–positive, resected esophageal carcinoma, postoperative CRT prolongs survival.

Kurtzman and colleagues demonstrated improved survival in 165 patients with adenocarcinoma of the esophagus using the combination of postoperative radiation and outpatient-modulated 5-FU and leucovorin with or without γ-interferon.[31] The dose of radiation was 54 Gy in patients without residual tumor and 59.4–63.0 Gy in patients with positive margins or residual tumor. Survival at 1 year, 2 years, and 3 years was 71%, 45%, and 39%, respectively. Three patients treated with modulated 5-FU, leucovorin, and γ-interferon needed intravenous hydration, and 2 patients experienced grade 3 leukopenia. This treatment regimen was determined to be well tolerated and effective.

A study by Kang and coauthors similarly concluded that postoperative administration of cisplatin and 5-FU concurrent with 40–50 Gy of radiation is generally a well-tolerated and effective treatment protocol.[32] Chemotherapy entailed 100 mg/m^2 of cisplatin on day 1, 1,000mg/m^2 of 5-FU on days 1–5, 60 mg/m^2 of cisplatin on day 15, 800 mg/m^2 of 5-FU on days 15–19; 10 patients received an additional 60 mg/m^2 of cisplatin

Table 2. Trials of Postoperative Concurrent Chemoradiation

Author	Treatment	RT(Gy)	N	Histology (%)	Median Survival (mo)	3-year Survival	*P* value
Rice[29]	• Cisplatin 20 mg/m² IV D1–4, 22–25 • 5-FU 1,000 mg/m² IV D1–4, 22–25	50.4–59.4	31	SCC 5, ADC 26	28	44±9.0%†	.05
	Surgery alone		52	SCC 9, ADC 43	14	17±5.6%†	
Rice[29]*	• Cisplatin 20 mg/m² IV D1–4, 22–25 • 5-FU 1,000 mg/m² IV D1–4, 22–25	50.4–59.4	20	SCC 4, ADC 16	28	44±11.3%†	.05
	Surgery alone		20	SCC 4, ADC 16	15	0%†	
Bedard[30‡]	• Cisplatin 60 mg/m² CI D1–21 x4 • 5-FU 200 mg/m² CI D1–21 x4 • Epirubicin 50 mg/m² added for 6 patients	50	38	SCC and ADC	47.5	62%	.001
	Surgery alone		28		14.1	25%	
Kurtzman[31]	• 5-FU • Leucovorin • γ-interferon given to some patients	54–63	165	ADC 165	NR	39%	NR
Kang[32]	• Cisplatin 100 mg/m² D1 • 5-FU 1,000 mg/m² D1-5 • Cisplatin 60 mg/m² D15 • 5-FU 800 mg/m² D15–19 • Cisplatin 60 mg/m² D22 for 10 patients • 5-FU 800 mg/m² D22–26 for 10 patients	40–50	15	NR	NR	NR	NR
Ebie[33]	• Cisplatin 100 mg/m² D1 • 5-FU 1,000 mg/m² CI D1–5 • Cisplatin 60 mg/m² D15, 29, 43 • 5-FU 800 mg/m² CI D15–19, 29–33, 43–47	38–50	25	SCC 10, ADC 15	19	32%§	NR
Taylor[34] (control to Ebie)	• Cisplatin 60 mg/m² D1 x2–6 • 5-FU 800 mg/m² CI D1–5	20–60	17	SCC 14, ADC 3	NR	6%¶	NR
Saito[35]	• Cisplatin 50 mg/m² IV D21,49 • Vindesine 3 mg/m² IV D21,49 • Pepleomycin 5 mg IM D22–26, 50–54	40–50	35	SCC 35	39††	30.9±9.4%** 45.2±13.4%†† **	<.05
	Historical data	50	26		9.5–13	5.1±4.8%**	

ADC=adenocarcinoma; CI=continuous infusion; D=day; IM=intramuscular; IV=intravenous; NR=not reported; RT=radiation therapy; SCC=squamous cell carcinoma.

*Data shown for patients with matching propensity scores.

†Survival at four years.

‡Trimodality group included patients who received concurrent or sequential chemoradiation.

§Survival at 2 years.

¶Survival at 51 months.

**Survival at five years;

††In patients with locoregional disease (stages II-III) only.

on day 22 and 800 mg/m^2 of 5-FU on days 22–26. The study reported a 93% local control rate in 15 patients with resected esophageal carcinoma treated with CRT. At a median follow-up of 20.6 months, 47% of patients were disease-free. For subsequent patients, the radiation dose was reduced to avoid radiation-related complications such as mucositis, ulcerations, and T-E fistulas.

Ebie and coworkers compared the efficacy of a phase I pilot protocol of initial esophagectomy and subsequent CRT[33] with results of a trial of chemoradiotherapy alone published from the same institution.[34] They showed that resection and postoperative CRT is superior to CRT alone with a higher local control rate (84% vs 47–59%) and survival rate (32% 2-year survival vs 6% 5-year survival). However, despite good local control most patients died from disease with distant metastases.

In an attempt to improve the outcomes traditionally obtained with CRT, Saito and associates explored regional lymphadenectomy in addition to trimodality therapy.[35] This study compared 35 patients treated with extensive resection (esophagectomy and lymphadenectomy) and postoperative CRT with 26 historical control patients having been treated with radiation only. There were no significant differences in prognostic variables between the 2 groups. Of the 35 patients who received postoperative CRT, 28 had locoregional diseases (stages II–III), and 7 had disseminated diseases (stage IV). Survival at 5 years was better in patients treated with trimodality therapy compared to all conventionally treated patients (30.9 ± 9.4% vs 5.1 ± 4.8%). Comparing survival based on whether the disease was locoregional or disseminated showed that improved survival occurred only in patients with locoregional disease (stages II–III, $P<.05$) and not with disseminated disease. The 5-year survival rate for patients with locoregional disease (stages II–III) was 45.2 ± 13.4% for the trimodality group. Results of this protocol are significant, but the usefulness of radical resection, such as extended lymphadenectomy for patients with esophageal carcinoma, has not been proven.

Conclusion

Trimodality therapy with CRT for esophageal cancer is a commonly employed strategy for the management of esophageal cancer. Whether CRT should be adjuvant or neoadjuvant is unclear and there are no randomized studies comparing the 2 strategies. The advantages and disadvantages of both pre- and postoperative chemoradiation are presented in Table 3.

Preoperative CRT treats primary disease and enables simultaneous early treatment of distant micrometastases. Administering CRT before resection also allows patients to receive treatment when they can best tolerate toxicities and may increase the likelihood for resectability by downstaging the tumor. The patient's responsiveness to CRT can be a factor used to make informed decisions and influence strategies used to treat patients accordingly. Additionally, radiotherapy target volumes are more precisely defined prior to resection. Preoperative CRT, however, can result in a high therapy-induced mortality rate of 10–18% or can render the patient inoperable. In addition, esophagectomy performed in tissues that were previously radiated may be more difficult due to radiation-induced changes in the tissue.

On the other hand, delivering chemoradiation postoperatively can offer its own advantages and disadvantages. Adjuvant CRT allows for more accurate staging based on surgical pathology rather than clinical staging. Areas of nodal spread can be more accurately defined since computed tomography scans have both false positives and false negatives. Patients who may not need adjuvant CRT can be identified and avoid unnecessary toxicity. Early surgery can relieve dysphagia and esophageal obstruction. Surgery itself can enable the patient to swallow and maintain nutritional status or a feeding tube can be placed to enable nutritional intake. Postoperative CRT, however, can decrease the efficacy of chemotherapy delivered to the tumor bed by reducing the blood supply to the resected area. Postsurgical complications can be severe enough to preclude adjuvant therapy. Adjuvant CRT also increases the likelihood of treatment-related toxicity to the gastric mucosa. Postoperative CRT is unpopular among radiation oncologists because once the tumor is resected and esophagus mobilized for anastomosis, defining the XRT target becomes much more difficult.

There are a limited number of postoperative CRT studies available. Data comparing pre- and postoperative CRT is even scarcer and randomized studies are needed to determine the best strategy of trimodality therapy for esophageal cancer patients. Until such data becomes available, treatment should be tailored to the individual patient's disease, taking into account institutional practices and patient preferences. A few general guidelines can be gleaned from the data. First, extrapolating from the results of the Minsky trial[21] examining CRT radiotherapy dose escalation, external beam radiation doses should not routinely exceed 50.4 Gy regardless of whether it is administered definitively, adjuvantly, or neoadjuvantly. Patients who present with advanced disease, where an R0 resection is impossible or unlikely, should be offered neoadjuvant CRT to shrink disease. Patients treated with resection alone should be offered adjuvant CRT for positive margins. At Wake Forest University, neoadjuvant CRT is commonly employed for patients with advanced esophageal cancer since this strategy has been more thoroughly evaluated in randomized trials.

Table 3. Advantages and Disadvantages to Pre- and Postoperative Chemoradiation in Treating Esophageal Cancer

Advantages to Preoperative Chemoradiation	Advantages to Postoperative Chemoradiation
• Early treatment of distant micrometastases while simultaneously treating primary disease. • Allows the administration of chemoradiotherapy (CRT) when the patient can best tolerate toxicities. • Can identify patients who respond to CRT and make an informed decision based on that information. • May increase resectability rate by downstaging tumor. • Radiotherapy target easier to define as compared with postoperative radiotherapy.	• Therapy is based on pathologic stage instead of possibly inaccurate clinical stage from computed tomography or transesophageal ultrasound. • Patients who may not need CRT can be identified and avoid unnecessary toxicity. • Resection first avoids delay from induction therapy. • Early debulking relieves dysphagia and enables swallowing and immediate nutritional intake. • Can maintain nutrition with feeding tubes placed at operation. • Post CRT can address residual microscopic tumor.
Disadvantages to Preoperative Chemoradiation	**Disadvantages to Postoperative Chemoradiation**
• Postradiation esophagectomy is more difficult due to the location of the esophagus and its rich vascular supply and lymphatic drainage. • Can result in high therapy-related mortality rate of 10–18% from neoadjuvant CRT. • Risk becoming inoperable due to neoadjuvant therapy complications.	• Long-term toxicity to gastric mucosa. • Reduced blood supply to the resected area—decreased chemotherapy delivered to the tumor bed. • Radiation therapy target is removed with resection, complicating the radiation therapy planning. • Postoperative complications may preclude adjuvant therapy. • Delays systemic therapy.

In patients receiving trimodality therapy, outcomes remain modest and distant failure is still a major problem. As chemotherapeutic agents improve, novel targeted therapies are adopted, and XRT target definition and treatment delivery improve, it is likely that the therapeutic ratio of CRT, both in the pre- and postoperative setting, will increase making the question of timing of CRT in relation to surgery even more critical.

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