

Preoperative Therapy in Esophageal Cancer

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Abstract: Progress has been made in the treatment of locally advanced esophageal cancer. Preoperative and postoperative chemotherapy also appears to improve survival in gastroesophageal junction adenocarcinoma compared to surgery alone. Adding radiotherapy to preoperative chemotherapy enhances rates of curative resection, achieves measurable rates of pathologic complete response, and recent trials indicate a survival benefit for preoperative chemoradiotherapy compared to surgery alone in esophageal cancer. Given the achievement of pathologic complete responses with combined chemoradiotherapy in esophageal cancer, recent trials have evaluated the contribution of surgery after chemoradiotherapy. With currently available systemic therapy for squamous cancers of the esophagus that respond to combined chemoradiotherapy, there is no clear survival benefit for the addition of surgery after chemoradiotherapy despite improvements in local tumor control with the addition of surgery. Surgery may salvage nonresponding patients with biopsy-positive residual disease. For adenocarcinoma of the esophagus, a histology with consistently lower rates of pathologic complete response than squamous cell cancer, surgery appears to play a greater role. Trials are now evaluating the use of newer chemotherapy agents combined with radiotherapy, including taxanes, irinotecan, and oxaliplatin. Response on positron emission tomography early on during induction chemotherapy may be a strong prognostic measure of outcome. Targeted agents, including monoclonal antibodies that target the epidermal and vascular endothelial growth factor receptors, are in active development in phase II and III trials.

For locally advanced esophageal cancer, surgery remains the mainstay of treatment. Various reviews have reported 5-year overall survival (OS) rates from 10% up to 30–40% with surgical resection alone.^{1,2} Primary radiation therapy was previously used for local tumor control, though less successfully. In one large series, the 3-year survival after radiotherapy alone was only 6%.³ For metastatic disease, chemotherapy alone results in response rates of only 20–40% and median survivals of 8–10 months.⁴

Given the activity of all three modalities, numerous studies have combined them in distinct neoadjuvant (preoperative) strategies for locally advanced disease. Multimodality approaches have included chemotherapy, radiotherapy, or concurrent chemoradiotherapy followed by surgery, in an effort to improve the dismal

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prognosis of this aggressive cancer. Relatively few studies have focused on an adjuvant (postoperative) approach.

The results of these studies have been mixed, and their combined outcomes have failed to elevate any preoperative strategies to a clear standard for resectable esophageal cancer. However, recent trials involving preoperative chemoradiotherapy and preoperative and perioperative chemotherapy have demonstrated improved survival over surgery alone. Based on these data, many clinicians now treat locoregional disease with preoperative multimodality therapy.

Neoadjuvant Chemotherapy

Despite the short-lived responses using chemotherapy alone in advanced disease, neoadjuvant chemotherapy is associated with many theoretical benefits.⁵ This approach has the potential to assess tumor response to chemotherapy and direct the possible use of chemotherapy postoperatively or in the metastatic setting. Chemotherapy may also improve baseline dysphagia, downstage the primary tumor and increase resection rates, and treat micrometastatic disease that is undetectable at diagnosis.

Kok and colleagues reported a small, randomized phase III trial in which 148 patients with squamous cell carcinoma were randomized to surgery alone or preoperative cisplatin/etoposide followed by surgery.⁶ Preoperative chemotherapy was associated with a significant improvement in median OS (18.5 vs 11 months). No final report of this study has been published.

However, the large North American Intergroup 113 trial failed to show a survival benefit for perioperative cisplatin/5-fluorouracil (5-FU) plus surgery compared with surgery alone in 440 patients.⁷ Patients in the combined-modality arm received three cycles of cisplatin/5-FU preoperatively and two cycles postoperatively. Pathologic complete responses (pCRs) were seen in only 2.5% of patients receiving preoperative chemotherapy, and there was no improvement in the curative resection rate. The median OS was not significantly different in the two groups, and the 3-year OS with or without chemotherapy was 20%. The addition of chemotherapy did not change the rate of recurrence either locally or at distant sites. Outcome also did not differ by histology, with no benefit seen for preoperative chemotherapy for either adenocarcinoma or squamous cell carcinoma.

Renewed interest in preoperative chemotherapy was generated by a trial performed by the Medical Research Council Oesophageal Cancer Working Group.⁸ This study randomized 802 patients (nearly double the number of patients in the Intergroup trial) to surgery alone versus two cycles of preoperative cisplatin/5-FU. At a relatively short median follow-up of only 2 years, the chemotherapy-treated group demonstrated improved

median OS (16.8 vs 13.3 months) and 2-year survival (43% vs 34%). The curative resection rate was improved marginally from 55% to 60%, and the pCR rate was 4% in the preoperative therapy group. It may be that the larger sample size compared to the Intergroup 113 trial facilitated the detection of a small improvement with chemotherapy. In addition, a larger proportion of patients on this trial had adenocarcinoma histology compared to the Intergroup 113 trial (66% vs 54%). Two recent meta-analyses suggest a potentially greater survival benefit from preoperative chemotherapy for patients with adenocarcinoma versus squamous cell cancer.^{9,10}

Additional evidence to support the use of perioperative chemotherapy comes from the recent Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial performed in the United Kingdom.¹¹ This trial randomized 503 patients with gastric or gastroesophageal (GE) junction adenocarcinoma to three cycles each of preoperative and postoperative ECF (epirubicin/cisplatin/infusional 5-FU) chemotherapy and surgery or surgery alone. Perioperative chemotherapy resulted in significant improvement in 5-year OS (36% vs 23%). However, there was no improvement in the curative resection rate and there were no cases of pCR. As 26% of patients on this trial had tumors in the GE junction and lower esophagus, the results may apply to esophageal adenocarcinoma as well.

Finally, data from a French trial of 224 patients with gastric or lower esophageal adenocarcinoma were recently presented.¹² Patients were randomized to two or three cycles of preoperative cisplatin/5-FU followed by surgery versus surgery alone. Those patients who appeared to benefit clinically or radiographically from preoperative therapy or who had persistent T3 or node-positive disease at surgery also received an additional three or four cycles of chemotherapy. Preoperative chemotherapy was associated with a significant improvement in R0 resection rate (74% vs 87%), 5-year disease-free survival (34% vs 21%), and 5-year OS (38% vs 24%).

Although comparisons between different clinical trials must be made cautiously, the survival benefit seen with preoperative cisplatin/5-FU on this trial appears to be very similar to that seen with perioperative ECF in the MAGIC trial. Because of the smaller sample size on this trial, however, outcome differences in as few as 10–15 patients would have changed the trial outcome. Also, the trial did not consistently stage patients with endoscopic ultrasound or stratify them by pretherapy stage; and in a small-scale trial, even a slight imbalance in pretherapy stage might affect the trial outcome. Trial data are summarized in Table 1.

Overall, recent trials suggest a survival benefit for perioperative chemotherapy, although preoperative chemotherapy alone is associated with a low pCR rate and

Table 1. Results of Phase III Preoperative Chemotherapy Trials in Esophageal Cancer

Treatment	Histology	Number of Patients	R0 Resection Rate, %	Pathologic CR rate, %	Survival		Local Failure, %	Reference
					Median, months	Overall, %		
Surgery	SCC	41	37	N/A	NS	3-yr 9	NS	Nygaard et al. ¹⁵
Cis/bleo + surgery		50	44	NS		3-yr 3		
RT + surgery		48	55			3-yr 21		
Cis/bleo/RT + surgery		47	44			3-yr 17		
Cis/etop+ surgery	SCC	74	NS		NS	18.5	NS	NS
Surgery		74		N/A	11			
Periop cis/5-FU + surgery	SCC (46%) + adeno (54%)	213	62	2.5	14.9	3-yr 23	32	Kelsen et al. ⁷
Surgery		227	59	N/A	16.1	3-yr 26	31	
Preop cis/5-FU + surgery	SCC (31%) + adeno (66%)	400	60	NS	16.8	2-yr 43	13	Medical Research Council ⁸
Surgery		402	54	N/A	13.3	2-yr 34	11	
Periop ECF + surgery	Adeno	250	69	0	24	5-yr 36	14	Cunningham et al. ¹¹
Surgery		253	66	N/A	20	5-yr 23	21	
Periop cis/5-FU + surgery	Adeno	113	87	3	NS	5-yr 38	NS	Boige et al. ¹²
Surgery		111	74	N/A	NS	5-yr 24	NS	

Adeno=adenocarcinoma; bleo=bleomycin; cis=cisplatin; CR=complete response; ECF=epirubicin, cisplatin, 5-fluorouracil; etop=etoposide; 5-FU=5-fluorouracil; N/A=not applicable; NS=not stated; periop=perioperative; preop=preoperative; RT=radiotherapy; SCC=squamous cell carcinoma.

inconsistent improvement in the resection rate. Such a survival benefit was also demonstrated in a recent large, individual patient data meta-analysis of 12 randomized trials involving preoperative chemotherapy.¹⁰ This meta-analysis revealed a 5-year survival benefit of only 4% with preoperative chemotherapy, with a suggestion of a lesser benefit for squamous (4%) compared to adenocarcinoma (7%) histology.

Neoadjuvant Radiation Therapy

Trials that have evaluated the use of preoperative radiation have largely reported no benefit. Kelsen and associates performed a randomized trial comparing preoperative radiation to preoperative chemotherapy in 96 patients with esophageal cancer.¹³ Although there was no increase in operative morbidity or mortality for patients treated with preoperative therapy compared with historical controls treated with surgery alone, there was also no additional treatment benefit. Another randomized trial

involving 176 patients also failed to identify a benefit for preoperative radiation.¹⁴

A prospective, multicenter Scandinavian trial reported by Nygaard and coworkers randomized 186 patients with esophageal squamous cell carcinoma to one of four treatment groups: surgery alone, preoperative chemotherapy (cisplatin/bleomycin) and surgery, preoperative radiation and surgery, or preoperative chemotherapy and radiation followed by surgery.¹⁵ The 3-year OS was significantly higher in the pooled groups receiving radiation compared with the nonradiation groups. The results indicated an intermediate-term survival benefit for preoperative radiation but found that the chemotherapy regimen did not influence survival.

However, a subsequent meta-analysis was unable to establish a significant benefit for preoperative radiation.¹⁶ With a median follow-up of 9 years, an analysis of more than 1,100 patients from five randomized trials suggested a survival benefit of 3% at 2 years and 4% at 5 years that was not statistically significant ($P=.062$).

Adjuvant Therapy

Combined-modality therapy in esophageal carcinoma has long focused on preoperative strategies. The role of adjuvant therapy has not been studied extensively, and the data that are available suggest equivocal results.

Postoperative chemotherapy without preoperative therapy was studied in two Japanese randomized trials, where patients with squamous cell histology were randomized to receive two cycles of chemotherapy with cisplatin/vindesine¹⁷ or cisplatin/5-FU,¹⁸ respectively. Although the trial with cisplatin/vindesine showed no survival benefit, the trial with cisplatin/5-FU did reveal a survival benefit, but only for patients with lymph-node involvement (52% vs 38%, respectively, 5-year disease-free survival).

These results are consistent with those of a randomized French trial, which also found no survival benefit for 6–8 months of adjuvant chemotherapy with cisplatin/5-FU.¹⁹ In fact, the findings showed significantly more complications in the chemotherapy group.

In contrast, a recent pilot Eastern Cooperative Oncology Group (ECOG) trial evaluated four cycles of postoperative paclitaxel/cisplatin in patients with esophageal or GE junction adenocarcinoma.²⁰ Two-year OS was 60%, which is statistically superior compared to the historical control (38%, derived from the Intergroup 113 trial).

Trials involving adjuvant radiotherapy have generally reported negative results. A French study randomized 221 patients to surgery alone versus surgery followed by radiation and found no survival benefit from radiation.²¹

Another randomized study of 130 patients from Hong Kong actually demonstrated increased mortality with postoperative radiation (8.7 vs 15.2 months, in favor of the no-adjuvant-therapy group), with the difference attributed to radiation-related deaths and early metastatic disease.²²

Finally, a large prospective Chinese study also failed to detect an OS benefit among 495 patients randomized to adjuvant radiation or no further therapy.²³ However, a subgroup analysis of stage III patients did show a 5-year survival benefit, up from 13.1% in the surgery-only group to 35.1% in the group that received adjuvant radiation.

Though trials of adjuvant radiotherapy alone have not suggested significant benefit, there may be benefit from adjuvant concurrent chemoradiotherapy, as suggested by the results of the Intergroup 116 trial in gastric adenocarcinoma.²⁴ This trial revealed a significant improvement in overall and disease-free survival for the delivery of postoperative therapy with 5-FU/leucovorin and radiation compared to surgery alone. As 20% of the patients treated had proximal gastric cancers (with involvement of the GE junction) and primary GE junction cancers, these

data may justify the use of postoperative therapy in such patients who have not received preoperative therapy.

Combined Neoadjuvant Chemoradiotherapy

Although recent preoperative and perioperative chemotherapy trials have indicated a survival benefit, the low rate of pCR and the inconsistent improvement in operability have led researchers to investigate neoadjuvant chemoradiotherapy.

Chemoradiotherapy typically involves regimens of cisplatin or mitomycin and continuous-infusion 5-FU, with radiotherapy dosages from 30 to 40 Gy and up to 60 Gy in more recent trials. It results in pCR rates of 20–40%, with long-term survival of no more than 25–35%.^{25,26} Superior survival is consistently achieved, though, in patients achieving a pCR to chemoradiotherapy (up to 50–60% at 5 years).²⁷⁻³¹

These results are at the expense of significant toxicities—primarily hematologic and gastrointestinal—which have been greatest in trials employing a higher dose of, or twice-daily, radiation, or in trials in which radiotherapy overlapped all cycles of preoperative chemotherapy.³² The gastrointestinal toxicity associated with cisplatin/5-FU and radiation includes nausea, mucositis, and esophagitis, leading some investigators to mandate placement of enteral feeding tubes prior to treatment initiation.

The seminal phase III US Radiation Therapy Oncology Group (RTOG) trial 85-01 demonstrated the superiority of chemoradiotherapy over radiation alone.³³ This nonoperative study compared standard-fractionation radiation (64 Gy) to radiation (50 Gy) plus concurrent cisplatin/5-FU. The trial was stopped when data from 121 patients showed an improved median OS in favor of chemoradiotherapy (12.5 vs 8.9 months). Two-year survival was also improved in the chemoradiotherapy group (38% vs 10%), as was 5-year survival (21% vs 0%).³⁴ Although the majority of patients treated on this trial had squamous cell carcinoma, long-term survival was also seen in the small number of adenocarcinoma patients on the trial, with 13% of patients alive at 5 years.

In addition to a survival benefit, disease recurrence was significantly reduced by the addition of chemotherapy to radiation. At 1 year, recurrent disease was observed in 62% of the group that received radiation versus 44% in the chemoradiotherapy arm. Distant recurrence rates were 38% and 22%, respectively. Based on this study, chemoradiotherapy was established as the standard of care in the nonsurgical management of locally advanced squamous cell esophageal cancer.

Building on these results, alternative treatment strategies have also been investigated. In the nonoperative RTOG 90-12 chemoradiotherapy study, induction

Table 2. Results of Phase III Preoperative Chemoradiotherapy Trials in Esophageal Cancer

Treatment	Histology	No. of Patients	R0 Resection Rate, %	Pathologic CR Rate, %	Survival		Local Failure, %	Reference
					Median	Overall, %		
Preop CRT	SCC (24%) + adeno (76%)	50	45	28 (SCC, 38; adeno, 24)	16.9 months	3-yr 30	19%	Urba et al. ³⁸
Surgery		50	45	N/A	17.6 months	3-yr 16	42%	
Preop CRT	Adeno	58	NS	25	16 months	3-yr 32	NS	Walsh et al. ³⁹
Surgery		55		N/A	11 months	3-yr 6		
Preop CRT	SCC	143	81	26	18.6 months	5-yr 26	NS	Bosset et al. ⁴¹
Surgery		139	69	N/A	18.6 months	5-yr 26		
Preop CRT	SCC (35%) + adeno (63%) + other (2%)	128	80	16 (SCC, 27; adeno, 9)	22.2 months	NS	15%	Burmeister et al. ⁴²
Surgery		128	59	N/A	19.3 months	NS	26%	
Preop CRT	SCC (25%) + adeno (75%)	30	NS	40	4.5 years	5-yr 39	NS	Tepper et al. ⁴³
Surgery		26		N/A	1.8 years	5-yr 16	NS	

Adeno=adenocarcinoma; CR=complete response; NS=not stated; Preop CRT=preoperative chemoradiotherapy; SCC=squamous cell carcinoma.

chemotherapy with cisplatin/5-FU followed by chemoradiotherapy with the same regimen did not appear to afford any additional benefit.³⁵ The RTOG 94-05 study compared a total radiation dose of 64.8 Gy versus 50.4 Gy during concurrent cisplatin/5-FU and also failed to demonstrate superior results with the more intense regimen.³⁶ This study confirmed 50.4 Gy as the standard radiation dose when given in combined therapy with cisplatin/5-FU. Finally, the phase I/II RTOG 92-07 trial, which attempted to “boost” radiation with brachytherapy following external-beam radiation, revealed significant toxicity, including a 12% incidence of treatment-related fistulas.³⁷

Phase III Trials of Chemotherapy

Five contemporary randomized trials have compared preoperative chemoradiotherapy followed by surgery versus surgery alone. Four of these have been published, and the last was reported in abstract form. The results are summarized in Table 2.

Urba and colleagues from the University of Michigan randomized 100 patients to preoperative cisplatin/5-FU/vinblastine and radiation or to surgery alone.³⁸ Despite a statistically significant decrease in the rate of local recurrence favoring preoperative therapy

(19% vs 42%), 3-year OS trended toward improvement but was not statistically significant (30% vs 16%; $P=.15$). Rates of curative resection were equivalent in both groups (90%). The majority of patients treated on this trial had adenocarcinoma.

Walsh and associates from Ireland randomized 113 patients with esophageal adenocarcinoma to preoperative cisplatin/5-FU/radiation or surgery alone.³⁹ Rates of negative margin resection were not reported, although it was noted that the preoperative therapy group had a significantly lower incidence of positive lymph nodes or metastatic disease at surgery (42% vs 82%). A significant improvement in 3-year OS was noted (32% vs 6%). Interpretation of this study is confounded by the very poor survival of the surgical control arm—6% at 3 years—which is inconsistent with the approximate 20% 5-year survival rates reported for modern surgical series.⁴⁰ Other shortcomings of this trial included inadequate pretherapy staging that could have led to an imbalance in prognostic factors between both groups, the variable surgical procedures used, premature termination based on an unplanned interim analysis, and the relatively short follow-up period for surviving patients (18 months).

Bosset and coworkers, on behalf of the European Organisation for Research and Treatment of Cancer,

randomized 282 patients with esophageal squamous cell carcinoma to preoperative cisplatin and concurrent split-dose radiation or surgery.⁴¹ Compared to the surgery-only group, the chemoradiotherapy group had a significantly higher rate of curative resection (81% vs 69%), as well as an improvement in disease-free survival and a decreased risk of local recurrence. However, OS (the primary trial endpoint) was not significantly different. It might be that the significantly higher postoperative mortality in the chemoradiotherapy arm (12% vs 4%) outweighed any potential survival benefit for the chemoradiotherapy group.

In a recent Australian trial, Burmeister and colleagues randomized 256 patients to one cycle of preoperative cisplatin/5-FU and radiation or to surgery alone.⁴² Though the trial failed to show a survival advantage for patients who received chemoradiotherapy, it did show a significantly higher curative resection rate compared to the surgery-only patients (80% vs 59%). In this study, the administration of a single chemotherapy cycle may represent suboptimal delivery of chemotherapy. The pCR rate was also unexpectedly low in the adenocarcinoma patients (9%), perhaps also a reflection of the inadequacy of systemic chemotherapy administered on this trial.

Finally, results of the Cancer and Leukemia Group B (CALGB) trial 9781 have been presented in abstract form by Tepper and associates.⁴³ This trial randomized patients to two cycles of preoperative cisplatin/5-FU and radiation or to surgery alone. Fifty-six patients were randomized before the trial was closed for poor accrual. Patients assigned to chemoradiotherapy had substantially improved median survival (4.5 vs 1.8 years) and 5-year OS (39% vs 16%) compared to patients undergoing surgery alone.

Overall, these randomized trials are associated with methodologic concerns, are significantly smaller than randomized preoperative chemotherapy trials, and produce conflicting results. However, they do suggest improved curative resection rates as well as decreased local recurrence. A survival advantage for preoperative chemoradiotherapy over surgery alone is not clearly demonstrated, although several studies suggest such a trend.

These observations are further supported by a recent meta-analysis in which 10 randomized trials of preoperative chemoradiotherapy versus surgery alone and 8 trials of preoperative chemotherapy versus surgery alone were analyzed.⁹ Preoperative chemoradiotherapy was associated with a hazard ratio (HR) of all-cause mortality of 0.81 versus surgery alone (95% confidence interval [CI], 0.70–0.93; $P=.002$), which translated to a 13% absolute difference in mortality at 2 years. This benefit was irrespective of histology. Preoperative chemotherapy was associated with an HR of 0.90

(95% CI, 0.81–1.00; $P=.05$) compared to surgery alone, which related to a 2-year absolute survival benefit of 7%. There did not appear to be any benefit of preoperative chemotherapy for patients with squamous histology (HR=0.88; 95% CI, 0.75–1.03; $P=.12$), although there was a benefit for patients with adenocarcinoma histology (HR=0.78; 95% CI, 0.64–0.95; $P=.014$).

The possible superiority of preoperative chemoradiotherapy over preoperative chemotherapy has also been suggested by a randomized study recently presented in abstract form.⁴⁴ In this study by Stahl and associates for the German Esophageal Cancer Study Group, patients were randomized to preoperative chemotherapy with cisplatin/5-FU/leucovorin followed by surgery versus cisplatin/5-FU/leucovorin followed by chemoradiotherapy with cisplatin/etoposide and then surgery. Before the trial was closed due to poor accrual, 120 eligible patients were randomized. The results revealed a trend toward improved local progression-free survival (PFS; 77% vs 59%), median OS (32.8 vs 21.1 months), and 3-year survival (43% vs 27%) for the chemoradiotherapy over chemotherapy group, but these results were not statistically significant ($P=.14$). Both the pCR rate (16% vs 2%) and node-negative status (64% vs 37%) were significantly higher in the chemoradiotherapy group. Strengths of this trial included the careful pretherapy staging (which included endoscopic ultrasound and laparoscopy), the enrollment of only high-risk patients with at least T3 or node-positive tumors, and the careful balancing of pretherapy staging between the two treatment arms.

Chemoradiotherapy With or Without Surgery

Two recent randomized trials have compared definitive chemoradiotherapy versus chemoradiotherapy followed by surgery. The first study was performed by the German Esophageal Cancer Study Group, which assigned 172 patients with squamous cell carcinoma to preoperative therapy (3 cycles of cisplatin/5-FU/leucovorin/etoposide, then cisplatin/etoposide and concurrent radiation to 40 Gy) followed by surgery, or to preoperative therapy alone with a higher radiation dose (to at least 65 Gy) in lieu of surgery.²⁹ Although local PFS was improved with the addition of surgery (HR for chemoradiotherapy-only group vs surgery group=2.1; 95% CI, 1.3–3.5; $P=.003$), there was only a nonsignificant trend towards improvement in 3-year OS (31.3% vs 24.4%). Treatment-related mortality was also significantly higher in the surgery group compared to the chemoradiotherapy-only group (12.8% vs 3.5%).

In the French FFCD 9102 trial, 444 patients with mostly squamous cell histology underwent initial chemoradiotherapy with cisplatin/5-FU.⁴⁵ Those who

responded to initial therapy were then randomized to either undergo surgery or receive an additional three cycles of cisplatin/5-FU with radiation, as the researchers felt it would be inappropriate to continue chemoradiotherapy in patients not responding to therapy. Of the 444 patients, 259 were randomized. The 2-year survival rate was not significantly different between the two groups (34% in surgery group vs 40% in chemoradiotherapy-only group; $P=.44$). However, locoregional recurrence was higher in the chemoradiotherapy-only group (43% vs 34%) and there was also a higher incidence of stent placement in this group (32% vs 5%). Three-month mortality was significantly higher in the surgery group (9.3% vs 0.8%). Based on these data, the authors concluded that patients with tumors, especially of squamous cell histology, who responded to initial chemoradiotherapy did not derive any survival benefit from subsequent surgery. Patients who underwent surgery did have improved local control of their disease, albeit at the cost of increased treatment-related mortality.

As a related issue, definitive chemoradiotherapy alone versus surgery alone has also recently been compared in a Scandinavian phase III trial of 91 patients with adenocarcinoma and squamous cell carcinoma who were randomized to receive either cisplatin/5-FU and radiation alone or surgery.⁴⁶ At a median follow-up of 51.8 months, there was no survival difference between the groups. Although this study may be underpowered to detect small survival differences, the data collectively support definitive chemoradiotherapy as an acceptable approach for patients who have contraindications to surgery.

Newer Chemotherapeutic Regimens

The poor results obtained with conventional cisplatin/5-FU-based regimens, as well as the toxicity of therapy, have led to the search for more effective and better-tolerated regimens. Paclitaxel-based chemotherapy has undergone extensive evaluation in combined-modality therapy trials with radiation. These phase II trials have combined a conventional schedule of paclitaxel/cisplatin every 3 weeks;^{47,48} weekly paclitaxel with cisplatin every 3 weeks;⁴⁹ or weekly paclitaxel with weekly cisplatin^{50,51} or with weekly carboplatin.⁵² pCR rates of 19–46% were reported, with toxicities generally less in trials with weekly chemotherapeutic regimens. Consistently, pCR rates in recent trials are higher in patients with squamous cancer compared to patients with adenocarcinoma histology.⁴²

Other trials have combined paclitaxel and continuous-infusion 5-FU and cisplatin or carboplatin.^{53–56} These three-drug trials have reported substantial toxicities, including severe myelosuppression and esophagitis, but have not consistently demonstrated superior results.

Retrospective data from Massachusetts General Hospital indicated similar pCR rates and 3-year survival for a three-drug regimen of paclitaxel/cisplatin/5-FU and radiation compared to cisplatin/5-FU and radiation.⁵⁷

The relative efficacy and toxicity of paclitaxel-based chemotherapy will be measured in the recently completed RTOG 01-13 trial. In this trial, a regimen of weekly paclitaxel/cisplatin and radiation was compared to weekly paclitaxel/5-FU and radiation in locally advanced esophageal cancer, as definitive therapy without surgery.

In addition, irinotecan-based regimens have also been investigated. Based on activity observed in the metastatic setting,⁵⁸ a regimen of weekly irinotecan/cisplatin and radiation has been evaluated in phase I and II studies.^{59–61} The regimen was found to be tolerable and is associated with pCR rates of 19–35%.

Based on these positive results, the CALGB 80302 trial is currently evaluating weekly irinotecan/cisplatin with concurrent radiation for locally advanced esophageal cancer. The ECOG 1201 trial recently compared weekly irinotecan/cisplatin versus weekly paclitaxel/cisplatin, with concurrent radiation, followed by surgery in patients with esophageal adenocarcinoma.⁶² The results, presented in abstract form, revealed a disappointingly low pCR rate of 15% and 16%, respectively, with a toxicity profile comparable to that historically noted with standard cisplatin/5-FU and radiation. However, these pCR rates are within the range of 9–25% reported as the pCR rates for adenocarcinoma histology in the phase III trials of chemoradiotherapy described earlier. Survival data are pending.

Positron Emission Tomography-directed Therapy

¹⁸F-2-fluoro-deoxy-D-glucose positron emission tomography (PET) scanning is emerging as an important tool to investigate response to therapy. Several studies have demonstrated that the degree of response detected by PET following preoperative chemoradiotherapy^{63,64} or chemotherapy^{65,66} is highly correlated with pathologic response at surgery and with patient survival.

The German MUNICON trial evaluated the strategy of taking patients with locally advanced GE junction tumors with a suboptimal response to 2 weeks of induction chemotherapy with cisplatin/5-FU, as determined by serial PET scans, directly to immediate surgery, instead of continuing with presumably ineffective chemotherapy.⁶⁷ Patients with a metabolic response by PET (defined as $\geq 35\%$ reduction in standard uptake value between baseline and repeat PET scan) continued with an additional 12 weeks of chemotherapy prior to surgery. This trial revealed a significantly improved R0 resection rate

(96% vs 74%), major pathologic response rate (58% vs 0%), median event-free survival (29.7 vs 14.1 months), and median OS (median not reached vs 25.8 months) for PET responders versus PET nonresponders. The outcome for PET nonresponders referred for immediate surgery was similar to the outcome of such patients in an earlier trial who completed 3 months of preoperative chemotherapy,⁶⁵ indicating that nonresponding patients were not compromised by referral to immediate surgery.

Based on the poor outcome of PET nonresponders in the above study who proceeded directly to surgery, another possible strategy would be to use PET assessment after induction chemotherapy to dictate subsequent chemotherapy during concurrent radiation. Responding patients can continue with the same chemotherapy regimen during concurrent radiation whereas nonresponding patients can be switched to alternative, non-cross-resistant chemotherapy during radiation. Long-term disease-free survival has been reported in patients who progressed on induction chemotherapy but were changed to alternative chemotherapy during subsequent combined chemoradiotherapy.⁶¹

Conclusion

The treatment of esophageal squamous cell carcinoma and adenocarcinoma remain a great challenge to medical, surgical, and radiation oncologists. Nevertheless, recent trials indicate that more than surgery alone should be offered to patients. Primary chemoradiotherapy is now the standard of care in the treatment of inoperable, localized disease. The use of preoperative chemoradiotherapy continues to be investigated but appears to lead to improved OS in patients who have had a pCR. Several recent trials have suggested that perioperative chemotherapy is also a valid strategy in adenocarcinoma. The use of preoperative chemotherapy alone in squamous cell cancer is supported less by the literature, given the equivocal phase III data and limited survival benefit seen in meta-analyses. For patients undergoing primary resection of esophageal adenocarcinoma, postoperative chemoradiotherapy also appears to improve survival compared to surgery alone.

Although surgery remains the standard curative treatment for early-stage disease, there are data suggesting that definitive chemoradiotherapy results in similar survival rates as surgery alone. Similarly, patients with squamous cell carcinoma who respond to initial chemoradiotherapy do not appear to derive a survival benefit from subsequent surgery. Surgery, however, does improve local control with a reduction in local tumor recurrence.

Finally, the development and evaluation of new chemotherapeutic regimens, the incorporation of targeted biological agents, and the use of sensitive metabolic imag-

ing to assess response to therapy represent future directions for the improved treatment of esophageal cancer.

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