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REVIEW

Multimodality approach for locally advanced esophageal cancer

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Abstract

Carcinoma of the esophagus is an aggressive and lethal malignancy with an increasing incidence worldwide. Incidence rates vary internationally, with the highest rates found in Southern and Eastern Africa and Eastern Asia, and the lowest in Western and Middle Africa and Central America. Patients with locally advanced disease face a poor prognosis, with 5-year survival rates ranging from 15%-34%. Recent clinical trials have evaluated different strategies for management of locoregional cancer; however, because of stage migration and changes in disease epidemiology, applying these trials to clinical practice has become a daunting task. We searched Medline and conference abstracts for randomized studies published in the last 3 decades. We restricted our search to articles published in English. Neoadjuvant chemoradiotherapy followed by surgical resection is an accepted standard of care in the United States. Esophagectomy remains an essential component of treatment and can lead to improved overall survival, especially when performed at high volume institutions. The role of adjuvant chemotherapy following curative resection is still unclear. External beam radiation therapy alone is considered palliative and is typically reserved for patients with a poor performance status.

INTRODUCTION

Carcinoma of the esophagus is an aggressive disease associated with a poor overall survival (OS). In 2011, 16 980 patients will be diagnosed in the United States, and 14 710 will die from their disease[1]. The incidence of adenocarcinoma of the esophagus is rising dramatically worldwide, while the incidence of squamous cell carcinoma (SCC) is decreasing[2]. While survival rates in metastatic esophageal cancer remain low, outcomes among patients with resectable locoregional disease have improved with the incorporation of multimodality treatment including chemotherapy, radiation and surgical resection. Multiple clinical trials have addressed the preferred treatment sequence in managing locally advanced esophageal cancer (LAEC); however, no standard therapy has been established.

Esophagectomy remains the cornerstone treatment for early-stage esophageal carcinoma; however surgery alone is rarely curative for tumors invading beyond the muscularis propria or involving locoregional lymph nodes. As a result, many clinical trials have addressed the role of chemotherapy and radiation in the neoadjuvant or adjuvant setting, with conflicting results.

The majority of the studies published in the last three decades included mostly patients with SCCs, and a distinction between the two subtypes was not always made. However, it remains unclear as to whether histology should dictate treatment approach. Extrapolation from old literature is acceptable until further data in adenocarcinoma is available. Enrollment in clinical trials should be encouraged.

In this article we will review the literature on the treatment of locally advanced mid-distal esophageal cancer. Treatment recommendations for cervical esophageal cancer will not be included in this review.

TREATMENT WITH SURGERY ALONE *VS* RADIOTHERAPY ALONE

Surgical resection remains the standard treatment for early-stage disease. Endoscopic mucosal resection (EMR) is recommended for T1a tumors if negative margins can be achieved. Esophagectomy upfront is recommended in patients with positive margins following EMR, or in patients with T1b disease.

Surgery alone as a treatment option for esophageal cancer was found to be superior when compared to radiation therapy. In a randomized trial of patients with LAEC, 39 patients were randomized to surgery and 35 patients to 45 Gy to 53 Gy radiation over four to five weeks[3]. The median survival for surgery was 21.6 mo compared with 8.2 mo for the radiation only group. In another trial comparing 47 surgical patients to 52 patients undergoing radiation[4], OS was improved with surgery [odds ratio (OR) 2.74].

Despite innovations in surgical techniques and declines in perioperative mortality, 5-year survival rates rarely exceed 50% among patients with stage Ⅱ or higher disease[5-7]. Median overall and disease-free survival does not appear to differ significantly based on the surgical approach (transthoracic *vs* transhiatal resection)[5]. In recent years, mortality rates after esophagectomy have decreased significantly. High-volume institutions have superior operative mortality rates (more than 12% absolute reduction in mortality when compared to low volume centers)[8].

PREOPERATIVE RADIOTHERAPY *VS* SURGERY ALONE

Radiotherapy as a single modality has been evaluated as a treatment option for esophageal cancer. In a small trial of 17 patients with clinical stage I esophageal SCC treated with radiation alone, the five-year survival rate was 59%[9]. In another single-institution series of 101 patients with LAEC treated with radiotherapy alone, the five-year survival rate was 21%. Survival was superior for adenocarcinoma compared to SCC, however the difference was not statistically significant[10].

Several randomized trials comparing neoadjuvant radiotherapy and surgery *vs* surgery alone in patients with LAEC have been reported[3,11-15]. Investigators used different radiation doses and techniques. There was no statistically significant difference in OS with preoperative radiotherapy compared with surgery alone.

In a trial by Launois *et al*[11], 124 patients with SCC of the esophagus were randomized to receive preoperative radiation for eight days *vs* surgery alone. No significant differences in outcome were noted between the two groups. Of the 62 irradiated patients, 14 died during operation, compared with 11 of the 47 non-irradiated patients, which was not statistically significant. 5-year survival rates were similarly poor (9.5% *vs* 11.5%).

In 1987, Gignoux *et al*[12] from the European Organization for Research on Treatment of Cancer (EORTC) compared surgery alone to 33 Gy of preoperative radiation therapy followed by surgery. Although local disease control was improved, there was no difference in survival or resectability of tumors.

Another prospective randomized clinical trial (RCT) randomized patients to preoperative radiation followed by surgery (104 patients) *vs* surgery along (102 patients)[13]. No significant differences were reported between the two groups in resection rates, operative mortality, anastomotic leaks, positive margins or lymph nodes metastases. The 5-year survival rates in the combined modality treatment group and the surgery alone group were 35% and 30% respectively.

In a four-arm Scandinavian study of patients with non-metastatic squamous cell esophageal carcinoma[14], patients were randomized to surgery alone, preoperative radiation, preoperative chemotherapy, or preoperative chemoradiation. Although the three-year survival was significantly higher in the pooled groups receiving radiotherapy as compared with the pooled groups not receiving radiotherapy, patients who received preoperative radiation alone *vs* surgery alone had a median survival of 10 mo *vs* 7 mo respectively which was not statistically significant.

In a different study, 176 patients with potentially operable SCC or adenocarcinoma of the esophagus were randomly assigned to preoperative radiotherapy or surgery alone[15]. Preoperative radiotherapy was not associated with any significant operative complications. The median OS for the entire cohort was 8 mo, and the 5-year survival was 13%. There was no significant difference in survival between the two groups. Trials of preoperative radiation are summarized in Table 1.

A meta-analysis of 1147 cases, predominantly SCC, from five RCTs examining preoperative radiotherapy and surgery compared to surgery alone[16] failed to demonstrate a conclusive survival benefit in LAEC. The hazard ratio (HR) associated with neoadjuvant radiotherapy was 0.89 (95% CI: 0.78-1.01; $P = 0.06$).

POSTOPERATIVE RADIOTHERAPY *VS* SURGERY ALONE

In order to reduce the risk of local recurrence, several randomized trials have compared surgery alone to sur-

Table 1 Randomized trials of preoperative radiotherapy *vs* surgery alone

Ref.	Number of patients	Median survival (mo)		5-yr survival[1] (%)	
		+RT	-RT	+RT	-RT
Launois *et al*[11]	124	4.5	8.2	10	12
Gignoux *et al*[12]	229	12.3	12	10	9
Wang *et al*[13]	206	-	-	35	30
Nygaard *et al*[14]	108	10	7	-	-
Arnott *et al*[15]	196	8	8	9	17
Fok *et al*[3]	79	11	22	10	16

[1]Not statistically significant. RT: Radiotherapy.

gery followed by adjuvant radiation therapy. Studies enrolled a heterogonous population including patients with positive celiac nodes[17,18] and R1 resections[19]. Investigators used varying doses of radiation with different fractionations. Radiation was delivered from 6-12 wk following surgery.

These trials had conflicting results: three failed to demonstrate any survival benefits with adjuvant radiation[17,18,20], while one trial showed inferior survival among patients who received adjuvant radiation therapy[19]. One trial showed improvement in quality of life in the surgery-only arm[18] compared to the adjuvant radiation arm. A pooled analysis of the five adjuvant radiation trials[21] showed no significant difference in survival following adjuvant radiotherapy when compared to surgery alone. A reduction in local recurrence was reported in some of these trials at the expense of toxicity. Preoperative radiotherapy was compared to postoperative radiotherapy in a small randomized trial; no difference in survival was detected between the two arms but patients receiving preoperative radiotherapy experienced higher morbidity[3].

PREOPERATIVE CHEMOTHERAPY *VS* SURGERY ALONE

Multiple randomized trials compared preoperative chemotherapy to surgery alone for the treatment of resectable esophageal cancer. Of the seven trials summarized in Table 2, four showed no survival benefit while three were positive demonstrating improved survival with neoadjuvant chemotherapy. Roth *et al*[22] randomized 39 patients with potentially resectable cancer of the middle or lower esophagus to receive either surgery along, or preoperative and postoperative therapy with cisplatin, vindesine, and bleomycin. The overall resectability rates were similar for the two groups. Patients responding to chemotherapy preoperatively had a significantly prolonged survival (greater than 20 mo) when compared with either nonresponders (median 6.2 mo) or patients in the surgical monotherapy arm (median 8.6 mo).

In a phase Ⅲ study[23], forty six patients with potentially resectable SCC of the esophagus were randomized to undergo either immediate surgery (n = 24) or surgery plus preoperative chemotherapy (n = 22). Chemotherapy consisted of three cycles with cisplatin and 5-fluorouracil (5-FU). The response rate to chemotherapy was 50% (17 of 34 patients). Side effects of therapy were higher than expected based on results of previous phase Ⅱ studies. Two drug-related deaths were observed. The resectability rate for patients in the surgery only group was 79% compared with 70% for patients receiving preoperative chemotherapy. Patients who responded to preoperative chemotherapy had a prolonged median survival (13 mo) compared with nonresponders (5 mo), but the median survival for the chemotherapy group and the surgery only group was identical (10 mo).

In a later study, Law *et al*[24] randomized 147 patients to receive surgery alone or preoperative cisplatin and 5-FU. Of the 60 patients in the preoperative chemotherapy arm, 58% had a significant response. Curative resections were possible in 67% of these patients compared with 35% in the control group. Median survivals were 16.8 and 13 mo, respectively (P = 0.17).

In a randomized phase Ⅲ trial[25], 42 patients were randomized to receive either two cycles of chemotherapy (cisplatin, bleomycin, 5-FU and vinblastine) followed by surgery or surgery alone. Median survival time was 17 mo in both groups. However, early survival appeared to be better in the control group.

Larger, more recent studies have shown improved benefits for patient receiving neoadjuvant therapy. In the medical research council study[26], 802 patients with resectable esophageal cancer were randomly allocated either two cycles of cisplatin and 5-FU followed by surgical resection or resection alone.

Postoperative complications were similar in both groups. OS was prolonged in the chemotherapy group with a median survival of 16.8 mo compared with 13.3 mo in the surgery only group. In the Medical Research Council adjuvant gastric infusional chemotherapy trial[27], 503 patients with resectable adenocarcinoma of the stomach, esophagogastric junction, or lower esophagus were randomly assigned to either perioperative chemotherapy or surgery alone. Chemotherapy consisted of three preoperative and three postoperative cycles of intravenous epirubicin, cisplatin and continuous intravenous infusion of 5-FU. With a median follow-up of four years, OS was significantly improved in the perioperative chemotherapy arm (36% *vs* 23%).

Several pooled and meta-analyses addressed the role of neoadjuvant chemotherapy followed by surgery compared to surgery alone. Malthaner *et al*[21] included five studies in a meta-analysis[14,23-26,28]. No significant difference in outcome was detected (relative risk ratio, 1.00; 95% CI: 0.83-1.19; P = 0.98).

Another meta-analysis was published in 2002 and included eleven RTCs comparing surgery alone to preoperative chemotherapy[29]. Again, there was no statistically significant difference in 3-year survival rates among patients who received preoperative chemotherapy com-

Table 2 Randomized trials of preoperative chemotherapy *vs* surgery alone

Ref.	Number of patients	Chemotherapy	Median survival (mo)		3-yr survival (%)	
			+CT	-CT	+CT	-CT
Roth JA *et al*[22]	39	CDDP/bleomycin/vindesin	> 20[1]	8.6	-	-
Nygaard *et al*[14]	112	CDDP/bleomycin	7	7	3	9
Schlag[23]	46	CDDP/5-FU	7.5	5	-	-
Maipang *et al*[25]	46	CDDP/bleomycin	17	17	31	36
Law *et al*[24]	147	CDDP/5-FU	16.8	13	38	14
Kelsen *et al*[56]	440	CDDP/5-FU	14.9	16.1	42	45
MRC[26]	802	CDDP/5-FU	16.8	13.3	35	27
Ancona *et al*[28][1]	94	CDDP/5-FU	25	24	44	41
Cunningham *et al*[27][1]	503	ECF	-	-	79	50

[1]The difference in survival was statistically significant. MRC: Medical Research Council Oesophageal Cancer Working Group; CDDP: Cisplatin; 5-FU: 5-flurouracil; ECF: Epirubicin, cisplatin and 5-fluorouracil; CT: Chemotherapy.

pared to those who did not.

Two other meta-analyses showed survival benefits with preoperative chemotherapy; the first was a Cochrane Review which pooled 11 RTCs. A statistically significant difference in survival favouring preoperative chemotherapy was detected at five years[30]. A more updated meta-analysis[31] comparing survival with or without neoadjuvant chemotherapy in 9 RTCs (total of 1981 patients) found that chemotherapy was associated with a significant survival benefit (pooled HR of 0.87; $P = 0.005$) corresponding to an absolute survival difference at 2 years of 5.1%.

POSTOPERATIVE CHEMOTHERAPY *VS* SURGERY ALONE

A small number of randomized trials have evaluated postoperative chemotherapy compared with surgery alone. Pouliquen *et al*[32] found no improvement in survival rates with postoperative chemotherapy consisting of cisplatin and 5-FU in patients with SCC. Duration of dysphagia was similar for both groups as well. Another randomized trial compared surgery alone *vs* surgery followed by adjuvant cisplatin and 5-FU in 242 Japanese patients with SCC[33]. Disease free survival at 5 years favoured the adjuvant therapy arm (55% *vs* 45%), however, improvement in OS did not reach statistical significance (61% *vs* 52%). Despite the short duration of adjuvant chemotherapy, 25% of patients in the chemotherapy arm failed to receive the full course of adjuvant therapy.

PREOPERATIVE *VS* POSTOPERATIVE CHEMOTHERAPY

A small number of randomized trials have evaluated postoperative chemotherapy compared to preoperative chemotherapy. A recent Japanese study[34] randomized 330 patients with SCC of the esophagus to surgery followed or preceded by two courses of cisplatin plus 5-FU. The primary end point was progression-free survival. Progression-free survival did not reach the stopping boundary, but OS in the preoperative group was superior to that of postoperative group. The study was published early and concluded that preoperative chemotherapy with cisplatin plus 5-FU can be regarded as standard treatment. In a prior trial[33], PFS was better in patients who received postoperative *vs* preoperative chemotherapy, but the OS was not different for the two groups. Patients with node-negative cancer did not benefit from postoperative chemotherapy.

Concurrent chemotherapy and radiation

Concurrent chemoradiation has been tested in LAEC as neoadjuvant, adjuvant or definitive therapy in order to optimize local and systemic disease control.

Definitive chemoradiation: Definitive chemoradiation has been studied in primarily in locally advanced, squamous cell unresectable esophageal cancer. RTOG 85-01[35] was a pivotal trial which compared radiation alone *vs* concurrent chemoradiation (cisplatin and 5-FU) in patients with LAEC, ninety percent of whom had SCC. The chemoradiotherapy group received two additional chemotherapy cycles following radiation.

An interim analysis showed a significant benefit with chemoradiation with a five-year survival of 27% compared to 0 %[36]. However, 46% of patients in the chemoradiation arm had locally recurrent or persistent disease in the esophagus which lead to the intergroup 0123[37] trial where patients with LAEC were randomized to two different radiation doses concurrent with chemotherapy (50.4 gray *vs* 64.8 gray). A higher dose was not associated with improved locoregional control.

Preoperative chemoradiation: The poor outcome associated with surgery alone and the high locoregional recurrence with definitive chemoradiation provided the rational for evaluating neoadjuvant chemoradiation followed by surgery in patients with resectable esophageal cancer.

More than ten randomized trials compared neoadjuvant chemoradiation followed by surgery to other treatment modalities. These trials are summarized in Table 3.

Table 3 Randomized trials of preoperative chemotherapy and radiation *vs* surgery alone

Ref.	Number of patients	Chemotherapy	Median survival (mo)		3-yr survival (%)	
			+CRT	-CRT	+CRT	-CRT
Nygaard *et al*[14]1	103	CDDP/bleomycin	7	7	17	9
Le Prise *et al*[39]	86	CDDP/5-FU	11	11	19	14
Apinop *et al*[40]	69	CDDP/5-FU	9.7	7.4	26	20
Walsh *et al*[47]1	113	CDDP/5-FU	16	11	32	6
Bosset *et al*[38]	282	CDDP	18.6	18.6	39	37
Urba *et al*[46]	100	CDDP/vinblastine/5-FU	17.6	16.9	30	16
Burmeister *et al*[43]	257	CDDP/5-FU	22	19	-	-
Lee *et al*[48]	101	CDDP/5-FU	28.2	27.3	-	-
Tepper[45]1	56	CDDP/5-FU	53	21	-	-
van Hagen[41]1	386	Carbo/paclitaxel	49	24	58	44

[1]The difference in survival was statistically significant. CDDP: Cisplatin; 5-FU: 5-flurouracil; CRT: Chemotherapy and radiation.

Four trials were conducted with preoperative sequential chemotherapy and radiation and 8 trials were performed with chemoradio-therapy. The sequential trials were restricted to SCC and all but three of the concurrent trials included patients with adenocarcinoma. None of the four trials of sequential therapy showed a survival benefit[14,38-40]. However, the combined radiation arms in the second Scandinavian trial showed a survival benefit compared to the non-radiation arms[14]. Additionally, chemotherapy was not associated with a survival benefit. In the EORTC trial, while preoperative therapy was associated with longer disease-free survival, longer interval of local control, and lower rates of cancer-related deaths, postoperative deaths were higher and were attributed to the hypofractionated radiation regimen used[38]. Of the 8 randomized trials of neoadjuvant chemoradiation[41-49], 4 showed a survival benefit from[41,45,47,49]. In the Irish study, 113 patients were randomized to 40 Gy in 3 wk concurrent with cisplatin and 5-FU followed by surgery *vs* surgery alone[47]. The trial resulted in a significant survival benefit with a median and 3 year survival of 16 mo and 32% for the chemoradiation group *vs* 11 mo and 6% for the surgery only group ($P = 0.01$). This trial was highly criticized for the low survival in the surgery only arm compared to other studies and for short follow up. Tepper *et al*[45] intended to randomize 475 patients to neoadjuvant chemoradiotherapy with 50.4 Gy over 5.5 wk concurrent with cisplatin and 5-FU and surgery *vs* surgery alone in a Cancer and Leukemia Group B study, however the trial was closed due to poor accrual. Only 56 patients were enrolled. Median and 5 year survival was 4.5 years and 39% for chemoradiation patients *vs* 1.8 years and 16% for surgery only patients ($P = 0.02$). The study was criticized for being underpowered. While the Michigan study showed a near doubling of 3-year survival in chemoradiation patients, the study was also underpowered to detect a significant difference. The study was powered to detect an increase in median OS from 1 year to 2.2 years[46]. A recently published phase Ⅲ study (the study "Effect of preoperative concurrent chemoradiotherapy on survival of patients with resectable esophageal or esophagogastric junction cancer")[41] randomized patients with resectable esophageal cancer to receive surgery alone or weekly administration of carboplatin and paclitaxel for 5 wk and concurrent radiotherapy followed by surgery. Seventy-five percent of patients had adenocarcinoma. R0 resection was achieved in 92% of patients in the chemoradiotherapy-surgery group *vs* 69% in the surgery group ($P < 0.001$). A pathological CR was achieved in 29% of patients who underwent resection after chemoradiotherapy. Postoperative complications were similar in both groups as was in-hospital mortality. Median OS was 49.4 mo in the chemoradiotherapy-surgery group *vs* 24.0 mo in the surgery group (HR 0.657; 95% CI: 0.495-0.871; $P = 0.003$).

A three arm study from China, where patients with SCC were randomized to preoperative chemoradiation, postoperative chemoradiation, or surgery alone, showed a survival benefit for both preoperative and postoperative chemoradiation. A recent French trial (FFCD9901) determined the effect of preoperative chemoradiation in stage I and II esophageal cancers (71% SCC)[44]. There was no difference in survival and postoperative 30 d mortality rates were trending higher in chemoradiation patients (7.3% *vs* 1.1%; $P = 0.054$).

The majority of patients included in these studies had SCC. Clinical staging was suboptimal by modern standards. An Irish[47] and Dutch[41] trial each showed statistically significant improvement in OS with combined preoperative chemoradiation but the Irish study was criticized for the lack of appropriate staging, premature closure, and an unusually poor survival rate in the surgery-alone arm.

Several meta-analyses have addressed the benefit of trimodality therapy over surgery alone for esophageal cancer. The first, by Fiorica *et al*[49] pooled six RCTs comparing preoperative chemoradiation and surgery *vs* surgery alone. Chemotherapy and radiation followed by surgery significantly decreased mortality (OR 0.53; 95% CI: 0.31-0.92; $P = 0.03$). However, the risk of postoperative mortality was higher in the multimodality arm.

A second meta-analysis, by Urschel *et al*[50], pooled nine RCTs including 1116 patients. A statistically significant survival difference was found at three years in

favor of preoperative chemoradiation (OR 0.66; 95% CI: 0.47-0.92; $P = 0.016$). Neoadjuvant chemoradiation was associated with a lower rate of resection, but a higher rate of complete (R0) resection. There was a non-significant trend toward increased treatment mortality with neoadjuvant chemoradiation.

A third meta-analysis by Gebski *et al*[51] pooled 10 RTCs comparing neoadjuvant chemoradiotherapy *vs* surgery alone with a total of 1209 patients. A significant survival benefit was evident for preoperative chemoradiotherapy with a HR of 0.81 (0.70-0.93; $P = 0.002$), corresponding to a 13% absolute difference in survival at 2 years. The HR was 0.84 (0.71-0.99; $P = 0.04$) for SCC and 0.75 (0.59-0.95; $P = 0.02$) for adenocarcinoma.

A fourth meta-analysis by Jin *et al*[52] pooled 11 RTCs comparing neoadjuvant chemoradiotherapy *vs* surgery alone with a total of 1308 patients. A significant survival benefit was evident for preoperative chemoradiotherapy at 3 years with an OR of 1.78 (1.20-2.66; $P = 0.004$). In a sub-group analysis, SCC patients did not benefit from neoadjuvant chemoradiotherapy.

The most recent meta-analysis by Sjoquist *et al*[31] included 12 RTCs of neoadjuvant chemoradiotherapy *vs* surgery alone. The HR for all-cause mortality with neoadjuvant chemoradiotherapy was 0.78 (95% CI: 0.70-0.88; $P < 0.0001$); the HR for SCC was 0.80 (95% CI: 0.68-0.93; $P = 0.004$) and for adenocarcinoma was 0.75 (95% CI: 0.59-0.95; $P = 0.02$). This analysis also compared neoadjuvant chemoradiation *vs* chemotherapy and demonstrated a non-statistically-significant survival benefit for neoadjuvant chemoradiation (HR 0.88, 95% CI: 0.76-1.01; $P = 0.07$).

Postoperative chemoradiation: There are no randomized trials demonstrating that chemoradiation benefits patients who did not receive neoadjuvant therapy for LAEC. The role of adjuvant therapy is particularly uncertain in patients who have positive margins or node positive disease. Based on the intergroup 0116 trial[53] of patients with gastric cancer [20% of whom had gastro-esophageal junction (GEJ) adenocarcinoma], patients often receive adjuvant chemoradiation following resection; however toxicities associated with administration of chemoradiation after esophagectomy (e.g., pneumonitis) can be significant.

One randomized trial evaluated postoperative chemoradiation *vs* postoperative radiotherapy following esophagectomy. No difference in survival was detected (38 mo for both groups)[3]. Toxicity was higher in the combined treatment arm.

NEOADJUVANT CHEMOTHERAPY *VS* NEOADJUVANT CHEMO-RADIATION

Two randomized trials compared neoadjuvant chemotherapy to neoadjuvant chemoradiation. Both trials included patients with adenocarcinoma, were closed early, and were underpowered to show a survival advantage.

In an Australian trial[54], 75 patients were randomized to receive preoperative cisplatin and 5-FU or preoperative chemoradiation with the same drugs at lower doses. The pathological response rate was higher in the combination arm (31% *vs* 8%; $P = 0.01$). The median progression-free survival was 26 mo in the combination arm *vs* 14 mo in the chemotherapy arm ($P = 0.37$). The median OS was 29 mo *vs* 32 mo for the combination arm but did not reach statistical significance ($P = 0.83$).

In the German phase Ⅲ Preoperative Chemotherapy or Radiochemotherapy in Esophago-gastric Adenocarcinoma trial[54,55], 126 patients with GEJ adenocarcinoma were randomly assigned to neoadjuvant chemotherapy alone (cisplatin and 5-FU) for 16 wk *vs* 12 wk of the same regimen followed by low-dose radiotherapy concurrent with cisplatin and etoposide. The pathologic complete remission rate was significantly higher in the induction arm (16% *vs* 2%), with a non-significant trend towards superior three-year survival as well (47% *vs* 28%; $P = 0.07$). A meta-analysis of the two trials[31] favored neoadjuvant chemoradiation but this was not statistically significant.

DISCUSSION

Esophageal cancer is not a common disease with less than 20 000 cases diagnosed in the US every year. Several clinical trials have evaluated different modalities for management of locoregional cancer; however, large phase Ⅲ trials comparing chemotherapy, radiation, surgery or any combination are lacking. Clinical trials reviewed in this article included heterogeneous groups of patients with adenocarcinoma and SCC without uniform staging studies. Stage migration and changes in disease epidemiology impede application of these trials to clinical practice. Comparing outcome (survival or progression free survival) across clinical trials is not recommended in oncology in general and especially in esophageal cancer as the changes in outcome might not be related to the different chemotherapy agents or radiation techniques as much as disease pathology, patient selection and changes in surgical outcomes across more than three decades.

Accumulating evidence suggests that patients whose tumors have invaded beyond the submucosa (T2 or above) and who are surgical candidates should undergo some form of neoadjuvant therapy including chemotherapy, radiation or both prior to surgical resection. Although controversial, esophagectomy remains an essential part of treatment and can lead to improved OS, especially when performed in a high-volume institution. Even in patients with SCC, where definitive chemoradiotherapy is a potentially curative, there remains a high rate of local failure after chemoradiotherapy alone. We therefore recommend surgical resection in all patients with mid to distal esophageal cancer who are surgical candidates. Based on the above trials and meta-analyses, we generally administer neoadjuvant chemoradiotherapy rather than neoadjuvant chemotherapy or surgery alone for LAEC. While neoadjuvant chemotherapy provides

a significant survival benefit, local failure rates are still higher than in patients treated with neoadjuvant chemoradiation. Moreover, data on neoadjuvant chemotherapy without radiation are lacking in SCC.

The optimal neoadjuvant regimen has not yet been established. The above mentioned trials used different drugs, doses, and schedules of chemotherapy and radiotherapy. We recommend platinum-based combination chemotherapy rather than a single agent cisplatin.

Following resection, data on adjuvant therapy are lacking. For patients with completely-resected node-positive disease who have not received neoadjuvant therapy, we suggest postoperative adjuvant therapy with chemotherapy and radiation. In patients with residual lymph node positivity following neoadjuvant chemoradiation, long-term recurrence rates are high; however the potential benefits of further adjuvant chemotherapy in this setting are not clear.

Future trials in LAEC should include neoadjuvant chemoradiotherapy as a control arm. While OS should remain a primary endpoint, secondary endpoints should include local disease control and quality of life. Treatment decisions for individual patients should be based on co-morbidities and effects of neoadjuvant therapy on the patient's performance-status and quality of life. Targeted therapies, such as trastuzumab, should be studied in the neoadjuvant and adjuvant settings to improve long-term outcomes.

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