

Clinical Aspects of Multimodality Therapy for Resectable Locoregional Esophageal Cancer

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Radical resection has been considered the only possible way to save the lives of patients with esophageal cancer. Therefore, tremendous efforts have been made in order to improve the surgical results for resectable locoregional esophageal cancer. Various surgical approaches have been developed. Combination therapies such as neoadjuvant, adjuvant chemotherapy, and neoadjuvant chemoradiation have been extensively investigated in numerous randomized clinical trials. Due to insufficient surgical results and high postoperative mortality rates, definitive chemoradiation has been studied as alternative treatment in selected patients, based on the concept that combined-modality therapy allows simultaneous treatment of locoregional disease and systemic micrometastases. Chemoradiation has shown survival rates equivalent to surgery in some non-randomized comparative studies. Presently, concerns appear to be shifting to the question of whether definitive chemoradiation could be an alternative to surgery in the primary treatment of resectable locoregional esophageal cancer. Recently, 2 randomized trials, comparing definitive chemoradiation with chemoradiation and surgery were published. These trials seem to show at first glance that definitive chemoradiation can achieve results comparable to surgery with neoadjuvant chemoradiation. More sophisticated trials should be conducted as treatment modalities used in these trials are far from routine. (*Ann Thorac Cardiovasc Surg* 2006; 12: 234–41)

Key words: esophageal cancer, neoadjuvant therapy, definitive chemoradiation, salvage esophagectomy

Introduction

Esophageal cancer is an increasingly common malignancy. This neoplasm is devastating because of its aggressive clinical course and high mortality rate. The long-term survival rates of under 10% are disappointing in part, due to the high incidence of advanced and/or metastatic disease at the time of diagnosis. Over 2 decades, several treatment modalities have been developed to improve the survival of patients with esophageal cancer. Among these, surgical resection remains the preferred choice. It cur-

rently provides the best palliation for dysphagia and local control and the best chance for cure when compared with other therapeutic options. However, as definitive chemoradiation has been gradually improving, the boundaries of treatment strategies have become blurred in the patients with resectable locoregional esophageal cancer.

This overview will examine the available data on current treatment modalities and discuss the future direction clinical research and treatment.

Preoperative Chemotherapy

Since surgery alone cannot achieve a good survival rate, trials evaluating the efficacy of preoperative chemotherapy followed by surgery for resectable esophageal cancer have been conducted since the 1980s. The rationale of preoperative chemotherapy includes down-staging of the tu-

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Table 1. Phase III trials to investigate the impact of neoadjuvant chemotherapy in patients with resectable esophageal carcinoma

Author/ ref. no.	Year	Protocol	Histology	No. of patients	R0 (%)	Mortality (%)	Median survival (mos)	2-year survival (%)	<i>P</i>
Kelsen et al. ¹⁾	1998	Surgery	SCC/AC	227	59	6	16.1	35	ns
		CDDP/5-FU		213	62	7	14.9	37	
MRCOCWP ²⁾	2002	Surgery	SCC/AC	400	54	10	13.3	34	0.004
		CDDP/5-FU		402	60	10	16.8	43	

R0, microscopically complete resection; mos, months; CDDP, cisplatin; 5-FU, 5-fluorouracil; SCC, squamous cell carcinoma; AC, adenocarcinoma; MRCOCWP, Medical Research Council Oesophageal Cancer Working Party; ns, not significant.

mor and elimination of micrometastatic disease.

Two recent randomized trials evaluating the utility of preoperative chemotherapy for esophageal cancer are summarized in Table 1. They are reported from the U.S. Intergroup trial 0113¹⁾ and the Medical Research Council Oesophageal Cancer Working Party (MRCOCWP).²⁾

In the U.S. Intergroup trial, 440 patients with operable esophageal cancer, histologically squamous cell carcinoma (SCC) or adenocarcinoma (AC), stage I to III, were eligible and follow-up data was adequate. A total of 213 patients were assigned to receive chemotherapy consisting of 3 cycles of 5-fluorouracil (5-FU: 1,000 mg/m²/24 hours for 5 days) and cisplatin (CDDP: 100 mg/m²/bolus day 1) followed by surgery. Two additional cycles of the same chemotherapy were administered to these patients after curative resection. The remaining 227 patients were assigned to undergo immediate surgery. There were no significant differences between the 2 groups in the median survival of 14.9 months for the patients who received preoperative chemotherapy and 16.1 months for those who underwent immediate surgery (*p*=0.53). Among the patients whose resection was curative, median survival in each group was over 2 years. At 2 years, the survival rate was 35% and 37% respectively and at 3 years, the survival rate was 23% and 26% respectively. Furthermore, no statistically significant differences were observed between the 2 groups in terms of curative resection rate (59% vs. 62%) and treatment mortality rate (6% vs. 7%). The pattern of failure was almost identical for the 2 groups. The histology of the tumor did not have an effect on response to treatment. Complete responses as assessed by pathological examination were achieved in 2.5% of patients who had received at least 1 cycle of chemotherapy. Preoperative chemotherapy with a combination of 5-FU and CDDP did not demonstrate a survival benefit in the patients with SCC and AC of the esophagus. This trial concluded that surgery alone remains the standard treat-

ment for patients with localized esophageal cancer.

In contrast, in the MRCOCWP trial, 802 previously untreated patients with resectable esophageal cancer were accrued regardless of histologic cell type, 31% with SCC and 69% with AC or undifferentiated carcinoma. Eligible patients were randomly allocated to receive chemotherapy consisting of 2 cycles of 5-FU (1,000 mg/m²/24 hours for 4 days) and CDDP (80 mg/m²/bolus day 1) with an interval of 3 weeks between the first day of each cycle followed by surgery 3 weeks apart or to undergo immediate surgery. In this trial, the curative resection rate was 59% in the preoperative chemotherapy group versus 62% in the resection alone group. The treatment effect was similar for the patients with SCC and those with AC. There were no differences in the postoperative mortality rate of 10% in both groups. The median survival of 16.8 months in the preoperative chemotherapy group was better than 13.3 months in the resection group, and the survival rate at 3 years was 43% and 34% respectively. The MRCOCWP trial suggested that the preoperative chemotherapy regimen used in the study should be considered for patients with resectable cancer of the oesophagus.

It is difficult to explain the difference in survival benefits between these 2 trials. This conflicting difference might be dependent upon the resectability rate of only 80% in the Intergroup and 92% in the MRCOCWP. Although the MRCOCWP trial is not included in this analysis, recently published meta-analysis of 11 randomized controlled trials that compared neoadjuvant chemotherapy and surgery with surgery alone for esophageal cancer did not demonstrate a survival benefit for the treated patients.³⁾ In the papers on randomized trials including esophagectomy, the type of procedures performed and their distribution into groups should be clearly mentioned. The efficacy of neoadjuvant chemotherapy remains controversial but, in any case, seems to be limited.

Table 2. Phase III trials to investigate the impact of adjuvant chemotherapy in patients with resectable esophageal carcinoma

Author/ ref. no.	Year	Protocol	Histology	No. of patients	5-year survival (%)	<i>P</i>
Ando et al. ⁴⁾	1997	Surgery	SCC	100	45.1	ns
		CDDP/VDS		105	48.3	
Ando et al. ⁵⁾	2003	Surgery	SCC	122	52	ns
		CDDP/5-FU		120	61	

CDDP, cisplatin; VDS, vindesine; 5-FU, 5-fluorouracil; SCC, squamous cell carcinoma; ns, not significant.

Postoperative Chemotherapy

The use of chemotherapy in the adjuvant setting could prevent undesired delays in definitive surgery. However, due to the high postoperative mortality and morbidity that accompany complicated surgical procedures, there has been little impetus to promote clinical trials with adjuvant chemotherapy in esophageal cancer, postoperative chemotherapy has not been widely studied in randomized trials.

Postoperative chemotherapy has not been widely studied in randomized trials. However, 2 Japanese randomized trials, involving patients with SCC compared it with surgery alone without preoperative therapy^{4,5)}(Table 2). In the first trial, chemotherapy consisted of 2 cycles of vindesine (VDS: 3 mg/m²/bolus day 1) and CDDP (70 mg/m²/2 hours day 1). In the second trial, chemotherapy consisted of 5-FU (800 mg/m²/24 hours for 5 days) and CDDP (80 mg/m²/2 hours day 1) with an interval of 3 weeks between the first day of each cycle. Chemotherapy was well tolerated in the postoperative setting. Though the first trial did not demonstrate the benefit of adjuvant chemotherapy, the second trial showed a trend toward improved 5-year disease-free survival.

In the second trial with 5-FU and cisplatin, both groups showed no remarkable difference in overall survival. The 5-year survival rate of the surgery alone group was 52% while that for the postoperative chemotherapy group was 61% (*p*=0.13). In contrast, the 5-year disease-free survival rate of 55% in patients in the surgery plus chemotherapy group was significantly better than the 45% achieved by patients in the surgery alone group (*p*=0.037). Furthermore in subgroup analyses, the subgroup with lymph node metastasis showed risk reduction of 52% in the adjuvant group versus 38% in the surgery alone group which was also statistically significant.

The efficacy of postoperative chemotherapy is currently

unclear because of the small number of trials. However, a potential benefit might exist for certain patient subgroups. As long as postoperative mortality and morbidity rates are not decreased, postoperative chemotherapy cannot be easily adapted to the context of clinical trials.

Preoperative Chemoradiation

Another common treatment strategy is preoperative chemoradiation. Neoadjuvant chemoradiation followed by surgery has been extensively studied over the past decade as a result of the pattern of both local and distant failure associated with surgery alone. The rationale of preoperative chemoradiation includes down-staging of the tumor and eradication of micrometastases. Moreover, most chemotherapeutic agents that have an effect on esophageal cancer simultaneously act as radiosensitizers. Although 8 randomized controlled trials have been reported that evaluate the benefit of preoperative chemoradiotherapy in patients with esophageal cancer,⁶⁻¹³⁾ a sufficient number of patients to allow statistically meaningful results have been accrued in only 2 of these trials^{10,13)}(Table 3). Bosset et al.¹⁰⁾ reported the results of a randomized trial of preoperative combined modality therapy from the European Organization for Research and Treatment of Cancer (EORTC). A total of 282 patients with clinically resectable esophageal cancer, histologically SCC and stage I to II, were randomized to receive either preoperative combined modality therapy or surgery alone. The preoperative radiotherapy was unconventional in design and consisted of 5 daily fractions of 3.7 Gy each followed by a 2-week rest and another 3.7 Gy for 5 days. Also unusual was the chemotherapy which consisted of a single use of CDDP given at a dose of 80 mg/m² on day 0-2 before starting radiotherapy. Though the 3-year disease-free survival rate of 40% in patients who received preoperative combined modality therapy was a signifi-

Table 3. Phase III trials to investigate the impact of neoadjuvant chemoradiation in patients with resectable esophageal carcinoma

Author/ ref. no.	Year	Protocol	Histology	No. of patients	R0 (%)	Mortality (%)	Median survival (mos)	3-year survival (%)	<i>P</i>
Nygaard et al. ⁶⁾	1992	Surgery	SCC	41	37	13	7.5	9	ns
		CDDP/BLM+35 Gy		47	55	24	7.5	17	
Le Prise et al. ⁷⁾	1994	Surgery	SCC	45	84	7	10	14	ns
		CDDP/5-FU+20 Gy		41	85	8.5	10	19	
Apinop et al. ⁸⁾	1994	Surgery	SCC	34	na	15	7.4	20	ns
		CDDP/5-FU+40 Gy		35		14	9.7	26	
Walsh et al. ⁹⁾	1996	Surgery	AC	55	na	8	11	6*	0.01
		CDDP/5-FU+40 Gy		58		4	16	32	
Bosset et al. ¹⁰⁾	1997	Surgery	SCC	139	na	3.6	18.6	37	ns
		CDDP+37 Gy		143		12.3	18.6	39	
Law et al. ¹¹⁾	1998	Surgery	SCC	30	42	na	27	na	ns
		CDDP/5-FU+40 Gy		30	80		26		
Urba et al. ¹²⁾	2001	Surgery	SCC/AC	50	na	2	17.6	16	ns
		CDDP/VBL/5-FU+45 Gy		50		16.9	30	30	
Burmeister et al. ¹³⁾	2002	Surgery	SCC/AC	128	na	4.6*	18.5	na	ns
		CDDP/5-FU+35 Gy		128			21.7		

R0, microscopically complete resection; mos, months; CDDP, cisplatin; BLM, bleomycin; 5-FU, 5-fluorouracil; VBL, vinblastine; SCC, squamous cell carcinoma; AC, adenocarcinoma; na, not available; ns, not significant; *, overall treatment related mortality.

cantly better than the 28% achieved by patients treated with surgery alone, there was no significant difference in the 3-year overall survival rate (37% and 39% respectively) and median survival of 18.6 months in both groups.

A recent randomized trial of 256 patients who received either neoadjuvant chemoradiation consisting of 1 cycle of 5-FU and CDDP given with radiotherapy at a dose of 35 Gy in 15 fractions or surgery alone was reported in abstract form by Burmeister et al.¹³⁾ The results did not show a survival benefit that could be attributed to the added chemoradiation. In a subgroup analysis, patients with SCC had an increased disease-free survival, but not overall survival. The administration of single agent chemotherapy is not effective enough to eradicate micro-metastatic disease.

Given the above data and, despite the widespread use of preoperative chemoradiation, randomized trials have raised significant methodological concerns and have yielded conflicting outcomes. There are several unanswered questions, i.e., optimal radiation dose, adequate radiation field, chemotherapeutic agents and administration schedule, histological distribution, etc. Moreover, preoperative chemoradiation tends to increase postoperative mortality; this may be most important factor swaying the results of trials.^{6,10,12)}

Chemoradiation without Surgery

Treatment with chemotherapy and radiotherapy, has been shown to be superior to radiation alone.

In 1985, the Radiation Therapy Oncology Group (RTOG) started RTOG 85-01, a prospective randomized controlled trial. They evaluated the hypothesis that concurrent chemoradiation could achieve a higher overall survival rate in patients who had localized carcinoma of the thoracic esophagus than was possible with radiation alone.¹⁴⁾ In this study 121 patients were randomly assigned to receive either combined-modality therapy or radiation therapy alone. The chemoradiation therapy consisted of protracted infusion of 5-FU (1,000 mg/m²/24 hours for 4 days) and CDDP (75 mg/m²/bolus day 1) on weeks 1, 5, 8 and 11 with 50 Gy of radiation therapy, while the radiation alone comprised 64 Gy. In this study, patients who received chemoradiation showed a significant improvement in median survival of 12.5 months compared with 8.9 months for patients who received radiation alone. With a 2-year survival rate of 38% and 10% respectively. Histologic type did not have a significant affect on the outcomes. The protocol was closed early because of positive results at the interim analysis. An additional 69 patients treated with the same combined-modality therapy after the closure of the randomization confirmed the results of

Table 4. Phase III trials to investigate the impact of neoadjuvant chemoradiation vs definitive chemoradiation in patients with resectable esophageal carcinoma

Author/ ref. no.	Year	Protocol	Histology	No. of patients	Mortality (%)	Median survival (mos)	2-year survival (%)	<i>P</i>
Bedenne et al. ¹⁸⁾	2002	I-CRT	Surgery	259	9*	17.7	34	0.56
		I-CRT	CRTx			1*	19.3	40
Stahl et al. ¹⁹⁾	2005	I-CT+CRT	Surgery	86	12.8	16.4	39.9	ns
		I-CT+CRT	CRTx	86	3.5	14.9	35.4	

mos, months; I-CRT, induction chemoradiotherapy; I-CT+CRT, induction chemotherapy + chemoradiotherapy; SCC, squamous cell carcinoma; AC, adenocarcinoma; ns, not significant; *, the death rate within 3 months after starting induction treatment.

chemoradiation with a median survival of 17.2 months and 3-year survival rate of 30%.^{15,16)} Based on this positive result, concurrent chemoradiotherapy has become the standard therapy for patients with localized carcinoma of the thoracic esophagus selected for nonsurgical treatment. Although chemoradiation was associated with a higher incidence of toxicity, this problem has led to studies aimed at improving the efficacy of radiotherapy, especially in determining the appropriate radiation dosage a part of combined modality therapy.

In the intergroup INT 0123 (RTOG 94-05),¹⁷⁾ 236 patients with esophageal cancer, histologically SCC or AC, clinical stage T1 to 4, N0/1, M0 were allocated to receive either combined-modality therapy consisting of 4 monthly cycles of 5-FU (1,000 mg/m²/24 hours for 4 days) and CDDP (100 mg/m²/bolus day 1) with concurrent 64.8 Gy radiation or the same chemotherapy dose and schedule but with 50.4 Gy. Since the data revealed that it was highly unlikely there would be any advantages to using the high dose radiation compared with the standard dose, this trial was closed at the time of the planned interim analysis. For the 218 eligible patients, there was actually no significant difference in median survival of 13.0 months for the high dose arm and 18.1 months for the standard dose arm. The survival rate at 2 years for the 2 arms was 31% and 40%, and local persistence or failure, respectively. Although 11 treatment related deaths occurred in the high dose arm compared with 2 in the standard dose arm, 7 of the 11 deaths occurred in patients who had received 50.4 Gy or less. It is unlikely that the increase in treatment related deaths in the high dose arm was related to a higher dose of radiation. Thus the standard radiation dose for patients treated with 5-FU and CDDP chemotherapy is 50.4 Gy.

This randomized trial data suggest the clear superiority of chemoradiation over radiotherapy alone. Defini-

tive chemoradiation is thus widely recognized as the standard of nonsurgical treatment for locoregional operable esophageal cancer.

Necessity for Surgery after Chemoradiation

Chemotherapy and radiotherapy without surgery has not been compared with surgery alone in prospective clinical trials. Recently 2 trials have been reported from the Federation Francaise de Cancerologie Digestive (FFCD) and the German Oesophageal Cancer Study Group (GOCSG)^{18,19)} that indicate the necessity of surgery after radiation (Table 4).

In the FFCD trial (FFCD 9102), 445 patients with operable thoracic esophageal cancer, histologically SCC, stage T3-4N0-1M0 were eligible. Induction therapy consists of 2 cycles of 5-FU and CDDP (days 1-5 and 22-26) plus concurrent protracted (46 Gy in 4.5 weeks) or split-course (15 Gy in days 1-5 and 22-26) radiation. The 259 patients who had at least a partial response were randomly allocated to receive additional chemoradiation or perform surgery. The additional chemoradiation consisted of 3 cycles of the same chemotherapy and concurrent protracted (20 Gy) or split-course (15 Gy) radiation. The 2-year survival rate was 34% in the surgery group versus 40% in the chemoradiation group, which was not significant (*p*=0.56). Furthermore, median survival was 17.7 months versus 19.3 months respectively. Thus, the FFCD 9102 trial concluded that additional chemoradiation is an alternative to surgery in patients with locally advanced resectable esophageal cancer who respond to initial chemoradiation.

The GOCSG compared preoperative chemoradiation followed by surgery with chemoradiation alone. In this trial, 172 patients with locally advanced SCC of the esophagus, stage T3-4N0-1M0 were randomized to ei-

ther induction chemotherapy followed by chemoradiation (40 Gy) followed by surgery, or the same induction chemotherapy followed by definitive chemoradiation (at least 65 Gy) without surgery. Induction chemotherapy consists of 3 cycles of bolus 5-FU, leucovorin, etoposide, and CDDP on days 1–3 every 3 weeks. This was followed by concomitant chemoradiation with CDDP and etoposide. In the surgery arm, transthoracic esophagectomy was performed 3–4 weeks after the end of irradiation. In the definite chemoradiation arm, the same combined chemoradiation was administered with a radiation dose of 40 Gy. Afterwards, the radiation dose was increased to at least 65 Gy with hyperfractionated external-beam radiotherapy or high dose-rate afterloading brachytherapy. Although the local progression-free survival rate at 2 years (64.3% in the surgery group and 40.7% in the chemoradiation group) was significantly different, ($p=0.003$), overall survival in both treatment groups, was roughly equal (39.9% at 2 years and 35.4%, 31.3% and 24.4% at 3 years). Median survival of each group also showed no difference. As a result, the GOCSG concluded that chemoradiation followed by surgery can no longer be recommended as routine treatment in patients with good tumor response to induction therapy. However, surgery is recommended in limited cases to provide survival benefit in patients defined as nonresponders.

In these 2 trials, definite chemoradiation appears to be an alternative to surgery in the initial treatment of locoregional advanced esophageal cancer. However, several issues should be raised, e.g., 1) since each trials include clinical T4 which could lead to non-curative resection (R1–R2), the patients with this stage of tumor should be excluded because prognoses were extremely poor in patients whose resection was incomplete; 2) treatment schedule in radiotherapy should be integrated into 1 regimen, and there are significant methodological concerns, including radiation field, dose, fraction and split; 3) even now, a combination of 5-FU and cisplatin remains the standard regimen for esophageal cancer. Since the protocol used for chemotherapy in the German study is not the common protocol, the validity of the study's conclusion is not easily acceptable; and 4) of the randomized trials comparing concurrent chemoradiation followed by surgery with surgery alone, only one trial reported by Walsh et al.,⁹⁾ in which only adenocarcinoma patients were eligible, demonstrated a significantly better median survival and 3-year survival rate. This result means histology could have an important influence on outcome. Thus randomized controlled tri-

als of non-surgical approaches ought to be planned for patients with different histologies.

Salvage Esophagectomy after Definitive Chemoradiation Therapy

Isolated persistence or local failure of the disease to respond is not uncommon after definitive chemoradiation. Although salvage esophagectomy is one of the strategies for selected patients, it is a far riskier operation from the standpoint of mortality and morbidity than planned esophagectomy with or without neoadjuvant therapy. In general, anastomotic leakage and pulmonary complications are more common when esophagectomy is performed after definitive chemoradiation. Swisher et al.²⁰⁾ reported anastomotic leak rates of 39% in patients who underwent salvage esophagectomy. This was significantly higher than the 7% leak rate experienced by those who received planned esophagectomy ($p=0.005$) and the average hospital stay (29.4 days) for the former was significantly longer than that for the latter (18.4 days) ($p=0.03$). Postoperative mortality rates for salvage esophagectomy patients trended upward (15% vs. 6%, $p=0.2$). Swisher et al.²⁰⁾ also described how salvage esophagectomy increased the complexity or difficulty of resecting the relapsed tumors. Meunier et al.²¹⁾ also stressed the difficulty of surgery.

Thus surgeons who perform salvage esophagectomy face a difficult challenge in trying to reduce concomitant postoperative mortality and morbidity.

Conclusion

The view that surgery might not be essential and that the apparent advantage of chemoradiation alone arises from the avoidance of perioperative mortality. The treatment modality of resectable locoregional esophageal cancer seems to be evolving from surgery alone to definitive chemoradiation and preoperative chemoradiation. Though the survival rates for definitive chemoradiation and surgery appear similar, surgery-related death rates might be most important factors swaying the results of studies. On the other hand, local failure occurs more frequently in the patients treated with definitive chemoradiation alone. Patients with local recurrence or residual disease after chemoradiation should be referred for surgery by a medical oncologist. Considering the high postoperative mortality and morbidity rates, salvage esophagectomy could be considered a difficult challenge for a surgeon. If de-

definitive chemoradiation is carried out on the assumption that local failure can be salvaged by surgery, it is difficult to regard it as a valid treatment strategy. Moreover, if a method of predicting results before and during treatment can be developed, definitive chemoradiation could become acceptable as a separate treatment option. There are no widely accepted clinical trials contrasting definitive chemoradiation with surgery using standard and appropriate protocols. These issues can only be resolved by carefully designed, randomized, controlled trials. At present, such trials have yet to be carried out. It should be noted that neoadjuvant therapy which is mainly performed in Western countries might increase the postoperative mortality rate. The possibility cannot be denied that surgical treatment might prove to be superior as long as concomitant mortality can be reduced.

The survival advantage over surgery in all neoadjuvant and adjuvant settings remains unclear. A breakthrough seems impossible unless more promising chemotherapeutic agents are developed, as the efficacy of both definitive chemoradiation and surgical results have reached their limit. Thus one must conclude that surgery remains the gold standard for resectable locoregional esophageal cancer with which other treatment options must be compared.

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