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The Effectiveness of Planned Esophagectomy after Neoadjuvant Chemoradiotherapy for Advanced Esophageal Carcinomas

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Abstract. *Background: The best treatment option for patients with locally advanced esophageal carcinoma has not yet been determined, especially because the benefits of esophagectomy after neoadjuvant chemoradiotherapy are still controversial. We report the results of a retrospective cohort comparison of definitive chemoradiotherapy without surgery (CRT) versus neoadjuvant chemoradiotherapy followed by planned surgery (CRTS) in patients with advanced esophageal squamous cell carcinoma (SCC). Materials and Methods: Between January 1991 and December 2002, 67 patients were enrolled in this study. Fifty of the 67 patients were considered to have inoperable tumors due to distant organ metastasis, distant lymph node metastasis, severe organ dysfunction or rejection of surgery by the patient and received CRT, while the remaining 17 patients were treated with CRTS. The clinical responses of the primary tumors were evaluated. Results: In the 50 CRT patients, the one- and 2-year survival rates were 33.8% and 20.2%, respectively, and the median survival time (MST) was 13.5 months. In the 17 CRTS patients, the response rate (CR + PR) was 76.5%, and the pathological complete response (pCR) rate was 29.4%. Their one- and 2-year survival rates were 61.6% and 35.9%, respectively, and the MST was 24.4 months. The survival rates of the CRT patients were lower than those of the CRTS patients (p=0.1288). When the 12 patients with distant organ metastases were removed from the CRT group, the one- and 2-year survival rates of the remaining 38 patients were 36.5% and 24.1%, respectively, and the MST was 14.7 months. The survival rates of these 38 CRT patients without distant organ metastases were similar to those of the 12 CRTS patients in the pathological partial response (pPR) group (p=0.6279). Conclusion: This retrospective cohort comparison of CRT versus CRTS demonstrated that there may not be any survival benefit from the addition of surgery in the pPR group for advanced esophageal carcinomas. For patients with a poor response to neoadjuvant chemoradiotherapy, we suggest that the addition of chemoradiotherapy, instead of planned esophagectomy, may show a similar survival rate to definitive CRT. Thus, a large series of a randomized control study will be required to confirm the benefit of surgery after chemoradiotherapy.*

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Most esophageal carcinomas are still only detected at an advanced stage (1, 2). Since the majority of patients with advanced esophageal carcinomas have a poor outcome when treated by surgery alone, chemotherapy and radiotherapy are currently being investigated as adjuvants to surgery (3). Advances in surgical techniques and adjuvant therapy have improved the 5-year survival rate to about 40% (4).

A combination of 5-fluorouracil and cisplatin has become the standard regimen, not only due to satisfactory clinical outcomes, but also because of the synergism between these two agents and their radiosensitizing effects (5-7). Studies on chemoradiotherapy as a definitive and a preoperative treatment have indicated various advantages in the treatment of carcinomas of the esophagus (6-10). Preoperative chemoradiotherapy has been introduced with the primary objective of increasing the rate of complete resection by reducing the size of the primary tumor, consequently also improving local tumor control and preventing distant metastases (11-13). Recent studies have suggested that chemoradiotherapy followed by surgery for locally advanced carcinoma improves survival rates (9-11, 14-17). On the other hand, Urba *et al.* (13) reported a randomized trial analyzing the survival of patients treated with preoperative chemoradiotherapy followed by surgery

versus surgery alone, and found that patients with potentially resectable esophageal carcinoma did not demonstrate a statistically significant difference in survival.

Regarding comparisons of definitive chemoradiotherapy (without surgery) *versus* surgery alone, Chan *et al.* (18) reported there were no significant differences in disease control and survival between the two treatments, and that combined chemotherapy and radiation was as effective as esophagectomy for localized esophageal cancer. Chan *et al.* (19) found no differences in overall survival in patients with localized carcinoma of the esophagus treated by chemoradiotherapy or chemoradiotherapy followed by surgery. From these studies, it can be seen that the best treatment option remains to be defined for patients with locally advanced esophageal carcinoma and that the benefit of surgery after chemoradiotherapy has still not been proven.

We report the results of a retrospective cohort comparison of definitive chemoradiotherapy without surgery (CRT) *versus* neoadjuvant chemoradiotherapy followed by planned surgery (CRTS) in patients with advanced esophageal squamous cell carcinoma (SCC).

Materials and Methods

Eligibility criteria and patients. Patients with histologically confirmed primary esophageal SCCs were eligible for this study. The inclusion criteria were a performance status less than 2, white blood cells > 3,000/μl, platelets > 100,000/μl, serum total bilirubin < 2.0 mg/dl, serum transaminase < 3 times the upper normal limit, serum creatinine < 1.5 mg/dl, creatinine clearance > 60 ml/min and no prior chemotherapy or radiotherapy. The exclusion criteria included concomitant malignancies, heart disease and patients with esophago-bronchial fistula. The protocol was approved by our hospital's institutional review board and all the patients gave signed informed consent prior to enrolment into the study.

Between January 1991 and December 2002, 248 patients with thoracic esophageal SCCs were identified at the Department of General Surgical Science, Gunma University, Graduate School of Medicine, Japan. Sixty-seven patients, who met the requirements of the protocol, were enrolled in this study. The tumor stage was determined conventionally by computed tomography (CT) of the neck, chest and abdomen, a bone scan, endoscopic ultrasound (EUS), endoscopy and esophagography. The tumor stages and disease grades were classified according to the TNM classification (fifth edition) of the International Union against Cancer (UICC). Fifty of the 67 patients were considered to have inoperable tumors due to distant organ metastasis, distant lymph node metastasis, severe organ dysfunction or rejection of surgery by the patient. The remaining 17 patients received chemoradiotherapy followed by surgery. Resectability was determined by conventional staging, which included CT of the neck, chest and abdomen, a bone scan, EUS, endoscopy and esophagography.

Chemoradiotherapy and surgery. After the diagnostic procedures, the 50 patients who were not going to undergo surgery received concurrent radiotherapy and chemotherapy. External radiotherapy was delivered by a 2-field technique using a 10- to 15-MV photon beam at 2 Gy per fraction per day, 5 fractions per week, to a total of 60-66 Gy. The concurrent chemotherapy consisted of 80 mg/m^2 nedaplatin (or cisplatin) administered intravenously over 1 h on days 1 and 29, and 350 mg/m^2 5-FU administered as a continuous intravenous infusion on days 1 through 5 and 29 through 33. The tumor response was assessed two weeks after completion of the treatment.

The remaining 17 patients underwent neoadjuvant treatment consisting of concurrent radiotherapy and chemotherapy for four weeks. External radiotherapy was delivered at 2 Gy per fraction per day, 5 fractions per week, to a total of 40 Gy. The concurrent chemotherapy consisted of nedaplatin (or cisplatin) administered intravenously on day 1, and 5-FU administered on days 1 through 5, as described above. The tumor response was assessed by CT, endoscopy and esophagography two weeks after completion of the neoadjuvant treatment. These patients then underwent esophagectomy and regional lymph node dissection 3 weeks after the neoadjuvant treatment.

Surgery was performed using the McKeown method (right thoracotomy followed by laparotomy and neck incision with a cervical anastomosis) and 3-field (thoracoabdominal and cervical) lymph node dissection was performed if indicated. All patients underwent a complete thoracic esophagectomy, including the esophagogastric junction.

Sections (5-mm-thick) of each whole resected esophagus and stomach were prepared, and then fixed, embedded and stained with hematoxylin and eosin. All the prepared specimens were examined under a light microscope by two pathologists.

Response evaluation. Two weeks after the completion of treatment, the clinical response of each primary tumor was evaluated according to the guidelines of the Japanese Society for Esophageal Diseases (JSED) (19). The assessment involved repeat endoscopy, esophagography and CT. Endoscopy and esophagography were conducted by two investigators, who measured the maximal major and minor axes of each tumor before and after treatment. All patients underwent a CT scan of the neck, chest and abdomen. Ten-millimeter continuous scans were obtained from the neck to the bottom of the liver after intravenous injection of a contrast medium. The endoscopic, esophagographic and CT results were discussed by the investigators, and the responses of the primary tumors were classified as follows: complete response (CR), complete disappearance of all clinical evidence of existing lesions for a minimum of 4 weeks; partial response (PR), a decrease in tumor size of more than 50% for a minimum of 4 weeks; or no change (NC), a decrease in tumor size of less than 50%.

The histopathological evaluation was conducted by two experienced pathologists who were unaware of the clinical responses. The histopathological response to treatment was classified as grade 0, 1, 2 or 3 in accordance with the guidelines of the JSED (20). Briefly, the degree of viability of the residual tumor cells was assessed as follows: grade 3, histological fibrosis with or without inflammation extending through the different layers of the esophageal wall, but no viable residual tumor cells; grade 2, less than one third of the residual tumor cells were viable; grade 1, more than one third of the residual tumor cells were viable; grade 0, no change.

Statistical analysis. The relationship between each group and other parameters was determined by the analysis of variance method.

Table I. *Patients' characteristics.*

Parameters	CRT group n=50	CRTS group n=17	*p*-value
Age at surgery (years)			
≤60	17	6	0.9227
>60	33	11	
Gender			
Male	47	15	0.4346
Female	3	2	
Location			
Upper	9	4	0.4794
Mid	29	7	
Lower	12	6	
Histology			
G1	6	5	0.1377
G2	25	9	
G3	19	3	
Tumor status			
T2	4	1	0.6278
T3	17	8	
T4	29	8	
Lymph node status			
N0	12	4	0.9686
N1	38	13	
Metastatic status			
M0	29	14	0.0704
M1	21	3	
Pathologic stage			
Stage II	6	2	0.1679
Stage III	23	12	
Stage IV	21	3	
Distant organ metastasis			
Absent	38	17	0.0617
Present	12	0	

G1: well-differentiated carcinoma
G2: moderately-differentiated carcinoma
G3: poorly-differentiated carcinoma

The survival time was defined as the period between the first day of treatment and the date of death or final follow-up. Survival rates were calculated by the Kaplan-Meier method for analysis of censored data. The significance of the difference in survival was determined by means of the log-rank test applied to univariate analysis.

Results

Sixty-seven patients (62 men and 5 women; age, 36-79 years; median age, 64.7 years) with thoracic esophageal SCC were investigated. The mean follow-up period for all the patients was 13.8 ± 11.9 months (range, 2.9 to 68.2 months). The clinical features of the patients are summarized in Table I. Of the 50 patients who underwent chemoradiotherapy without surgery (CRT), 12 had distant organ metastases: 6 in the liver, 3 in a lung and 3 in bone. Seven of the 50 achieved a CR, 28 had a PR and 15 showed NC. The response rate (CR + PR) of these patients was 70%. Their one- and 2-year survival rates were 33.8% and 20.2%, respectively, with a median survival time (MST) of 13.5 months (Figure 1).

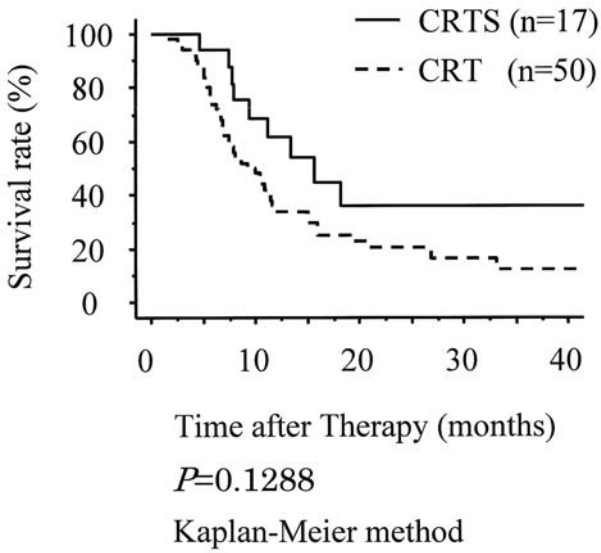

Figure 1. *Survival curves of 17 patients who received neoadjuvant chemoradiotherapy followed by planned surgery (CRTS) and 50 patients who received chemoradiotherapy without surgery (CRT). The CRTS patients have one- and 2-year survival rates of 61.6% and 35.9%, respectively, with a median survival time (MST) of 24.4 months. The CRT patients have one- and 2-year survival rates of 33.8% and 20.2%, respectively, with a MST of 13.5 months. The survival rates of the CRT patients are lower than those of the CRTS patients (log-rank p=0.1288).*

Of the 17 patients who underwent neoadjuvant chemoradiotherapy followed by planned surgery (CRTS), 2 of the 17 achieved a CR, 11 had a PR and 4 showed NC. The response rate (CR + PR) of these patients was 76.5%. The histological response evaluated from the resected specimen was grade 3 in 5 patients, grade 2 in 9 and grade 1 in 3. The pathological complete response (pCR) rate of the 17 patients with resectable esophageal cancers was 29.4%. Their one- and 2-year survival rates were 61.6% and 35.9%, respectively, with an MST of 24.4 months (Figure 1). The survival rates of the CRT patients were lower than those of the CRTS patients (log-rank $p=0.1288$, Figure 1).

When the CRTS patients were divided into a pCR group (grade 3) and a pathological partial response (pPR) group (grades 2 and 1), the one-year survival rates were 75.0% and 56.3% and the 2-year survival rates were 50.0% and 22.5%, respectively (log-rank $p=0.3573$).

When the 12 patients with distant organ metastases were removed from the CRT group, the one- and 2-year survival rates of the remaining 38 patients were 36.5% and 24.1%,

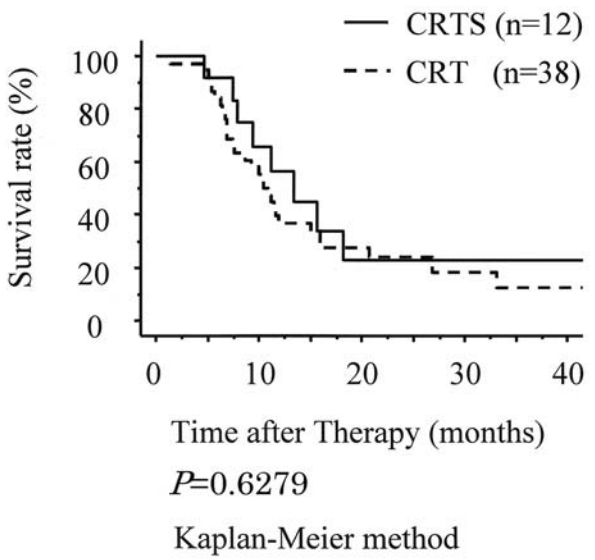

Figure 2. *Survival curves for comparison of the 38 patients without distant organ metastases who received chemoradiotherapy without surgery (CRT) and the 12 patients in the pathological partial response (pPR) group who received neoadjuvant chemoradiotherapy followed by planned surgery (CRTS). The one- and 2-year survival rates of the 38 CRT patients without distant organ metastases are 36.5% and 24.1%, respectively, with a median survival time (MST) of 14.7 months. The one- and 2-year survival rates of the 12 CRTS patients in the pPR group are 56.3% and 22.5%, respectively, with an MST of 19.6 months. The survival rates of the 38 CRT patients without distant organ metastases are similar to those of the 12 CRTS patients in the pPR group (log-rank p=0.6279).*

Table II. *Patients' characteristics.*

Parameters	CRT group[1] n=38	CRTS group[2] n=12	*p*-value
Age at surgery (years)			
≤60	12	4	0.9096
>60	26	8	
Gender			
Male	35	12	0.7590
Female	3	0	
Location			
Upper	8	2	0.0964
Mid	25	5	
Lower	5	5	
Histology			
G1	6	2	0.8320
G2	19	7	
G3	13	3	
Tumor status			
T2	4	1	0.2194
T3	9	6	
T4	25	5	
Lymph node status			
N0	10	2	0.4951
N1	28	10	
Metastatic status			
M0	29	10	0.6089
M1	9	2	
Pathologic stage			
Stage II	6	1	0.6489
Stage III	23	9	
Stage IV	9	2	

G1: well-differentiated carcinoma
G2: moderately-differentiated carcinoma
G3: poorly-differentiated carcinoma

CRT group[1] : 38 patients without distant organ metastases who received CRT.
CRTS group[2] : 12 patients with partial responce to neoadjuvant chemoradiation.

respectively, with a MST of 14.7 months (Figure 2). With regard to the clinicopathological characteristics, there were no significant associations between the 38 CRT patients without distant organ metastases and the 12 CRTS patients in the pPR group (Table II). The survival rates of the 38 CRT patients without distant organ metastases were similar to those of the 12 CRTS patients in the pPR group (log-rank $p=0.6279$, Figure 2).

Discussion

Neoadjuvant chemotherapy together with radiotherapy is widely used for the management of patients with locally advanced esophageal cancer (13-15). Combined chemotherapy and radiotherapy might produce better local tumor downstaging and increase the pathological complete response rate (14, 15). Combined chemoradiotherapy followed by planned surgery (CRTS) has been examined in several institutions (13-15).

In the present retrospective study, the survival rates of the CRTS patients tended to be higher than those of the CRT patients. This may be because the staging distributions of the CRT patients were more advanced than those of the CRTS patients. Furthermore, when the 12 patients with distant organ metastases were removed from the CRT group, there was no significant difference in survival between the 38 CRT patients without distant organ metastases and the 12 CRTS patients in the pPR group. In short, we consider that there may not be any survival benefit from the addition of surgery in the pPR group. In other words, for patients with a poor response to neoadjuvant chemoradiotherapy for advanced esophageal carcinomas, the addition of chemoradiotherapy, instead of planned esophagectomy, may show a similar survival rate to definitive CRT and, consequently, esophagectomy does not appear to be necessary.

Prospective studies in single institutions have shown promising results for CRTS (21-23). Gill *et al.* (21) used the endoscopic response after initial chemoradiotherapy to

decide whether to use esophagectomy or further chemoradiotherapy. Despite rigorous patient selection for esophagectomy after initial chemoradiotherapy, no difference in survival was found between the CRT and CRTS groups. Kavanagh *et al.* (22) studied 143 patients in a phase I/II protocol and found improvement in local control with the addition of surgery but no improvement in survival, again despite a rigorous selection bias favoring the surgical patients. Burmeister *et al.* (24) reported multi-institutional prospective non-randomized data from Australia on CRT *vs.* CRTS, and no significant difference in survival was found. These trials comparing CRTS to CRT for esophageal cancer did not show any significant survival benefits for CRTS. However, many of the individual trials were small and, thus, underpowered to detect modest differences in outcomes.

Some studies have suggested that a good histological response of the tumor correlates well with longer survival (10, 25). The results of the present study suggest that if the response to neoadjuvant chemoradiotherapy is good, longer-term survival might be gained from surgery after the neoadjuvant chemoradiotherapy. Therefore, correct identification of patients who respond to neoadjuvant chemoradiotherapy before surgery is crucial. A predictor of chemoradiotherapeutic effects *via* oncological measurements could thus play an important role in the future (26). Furthermore, it is very important to accurately differentiate between partial and complete responses of tumors after neoadjuvant therapy (27). Computed tomography, endoscopy with biopsy and endoscopic ultrasound do not reliably differentiate patients with complete responses from those with partial responses. Initial reports on positive emission tomography (PET) are very encouraging, and this could become the investigation method of choice for assessing treatment responses (27, 28).

Finally, Urschel *et al.* (29) reviewed the debate on salvage esophagectomy after CRT, and reported that definitive chemoradiotherapy with consideration of salvage surgery for selected patients, and neoadjuvant chemoradiotherapy followed by planned surgery, are commonly used treatments for locally advanced esophageal cancer. However, planned surgery after chemoradiotherapy does not appear to be necessary and, although experience with salvage surgery is limited, there are genuine concerns about the safety of this operation.

In conclusion, the results of this retrospective cohort comparison of CRT *versus* CRTS demonstrated no apparent survival benefits for the addition of surgery in patients who did not show a pathological complete response. Thus, for patients with a poor response to neoadjuvant chemoradiotherapy for advanced esophageal carcinomas, the addition of chemoradiotherapy, instead of planned esophagectomy, may show a similar survival rate to definitive CRT. Thus, a large series of a randomized control study will be required to confirm the benefit of surgery after chemoradiotherapy.

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