Salvage esophagectomy after high-dose chemoradiotherapy for esophageal squamous cell carcinoma

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Objective: Chemoradiotherapy is a popular definitive therapy for esophageal carcinoma among many patients and oncologists. Although the complete response rates are high and short-term survival is favorable after chemoradiotherapy, persistent or recurrent locoregional disease is frequent. Salvage surgery is the sole curative intent treatment option for this course of the disease. The present study evaluates the safety and value of salvage esophagectomy for locoregional failure after high-dose definitive chemoradiotherapy for esophageal squamous cell carcinoma.

Methods: We reviewed 59 consecutive patients with thoracic esophageal squamous cell carcinoma who underwent salvage esophagectomy after definitive chemoradiotherapy. All patients received more than 60 Gy of radiation plus concurrent chemotherapy for curative intent. The data were compared with those of patients who received esophagectomy without preoperative therapy.

Results: Postoperative morbidity and mortality rates were increased among patients who underwent salvage esophagectomy compared with those who underwent esophagectomy without preoperative therapy (mean hospital stay, 38 vs 33 days; anastomotic leak rates, 31% vs 25%; respiratory complication rates, 31% vs 20%; reintubation within 1 week, 2% vs 2%; hospital mortality rates, 8% vs 2%). Tracheobronchial necrosis and gastric conduit necrosis were highly lethal complications after salvage esophagectomy; 3-year postoperative survivals were 38% and 58%, respectively.

Conclusion: Patients who underwent salvage esophagectomy after definitive high-dose chemoradiotherapy had increased morbidity and mortality. Nevertheless, this is acceptable in view of the potential long-term survival after salvage esophagectomy. Such treatment should be considered for carefully selected patients at specialized centers.

Surgical resection has been the standard treatment for localized esophageal squamous cell and adenocarcinoma for several decades. Despite many efforts to improve surgical resection, the associated mortality and morbidity rates remain high and the postoperative quality of life is unsatisfactory. Management algorithms for patients with esophageal carcinoma have changed during the last 2 decades. Multidisciplinary approaches have included surgery, radiotherapy, and chemotherapy, alone or in combination. The Radiation Therapy Oncology Group trial (RTOG 85-01), which added chemotherapy to radiotherapy for resectable esophageal carcinoma, has established chemoradiotherapy (CRT) without surgery as one standard for definitive treatment.^{1,2} Many patients and oncologists have accepted the nonsurgical approach with CRT as definitive therapy for esophageal carcinoma. Evaluations of consecutive patients with esoph-

ageal cancer accessed using the National Cancer Database of the American College of Surgeons have shown that radiation combined with chemotherapy is the most frequent treatment strategy for all stages of squamous cell carcinoma in the United States.³

Although complete response (CR) rates are high and short-term survival is favorable after definitive CRT, locoregional disease persists or recurs in 40% to 60% of patients.⁴ The only curative intent treatment option for locoregional relapse is salvage surgery.⁵ Such patients are at increased risk for esophagectomy because they have been treated with higher doses of radiation and the treatment is usually completed months beforehand.⁶

The present study evaluates the safety and efficacy of salvage esophagectomy for locoregional failure after high-dose definitive CRT for esophageal squamous cell carcinoma. We retrospectively reviewed all patients who underwent esophageal resection between 2000 and 2006 at the National Cancer Center Hospital and selected all patients undergoing salvage esophagectomy after failed definitive CRT (n = 59). We compared the data with those of patients treated by esophagectomy without preoperative therapy during the same period (n = 553).

MATERIALS AND METHODS

We reviewed 59 consecutive patients with thoracic esophageal squamous cell carcinoma who underwent salvage esophagectomy after high-dose

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Abbreviations and Acronyms

CR = complete response

CRT = chemoradiotherapy

RTOG = Radiation Therapy Oncology Group

definitive CRT between 2000 and 2006 at the National Cancer Center Hospital, Tokyo. All selected patients had received more than 60 Gy of external beam radiation as high-dose definitive CRT without planned surgery. The chemotherapeutic regimens for these patients predominantly comprised 5-fluorouracil and cisplatin concurrently with radiation therapy. These patients included 22 who were initially treated at other hospitals with definitive CRT and who were admitted to the National Cancer Center Hospital after the primary tumor relapsed. We reviewed the other hospital records of these patients to confirm treatment details. Assessments of these patients indicated that 23 had achieved CR after CRT, but disease relapsed later. The remaining 36 patients had not achieved CR and underwent salvage surgery for residual tumors.

The data were compared with those of 553 patients who underwent planned esophagectomy without preoperative therapy during the same period. Long-term outcomes, encompassing overall survival, were obtained from hospital records and the tumor registry. Overall survival was calculated from the day of surgery until death or was censored at the time last known to be alive.

Data were statistically analyzed using the Pearson chi-square test or the Fisher exact test as appropriate. Kaplan–Meier survival curves were estimated with differences based on patient characteristics assessed by the log-rank test to compare the distribution of survival. Survival of the 54 patients who underwent salvage esophagectomy after CRT, excluding perioperative deaths, was examined using univariate and multivariable analyses.

RESULTS

Table 1 compares the clinical characteristics of patients who underwent salvage esophagectomy after CRT (salvage group) with who did not receive preoperative therapy. The salvage group contained more male patients and less advanced pathologic stages, but age and tumor location did not significantly differ. Of 7 patients with no pathologically residual tumors (pT0) in the resected esophagus, analysis of preoperative endoscopic biopsy revealed that 2 had tumor cells. Another 5 patients had stenosis and ulcers with a thickened wall according to computed tomography examinations suggesting recurrence. All patients with M1 had lymph node metastasis in the neck or celiac area. These patients were indicated for 3-field dissections at the National Cancer Center Hospital.⁷ Patients with distant organ metastasis were not candidates for esophagectomy.

Table 2 compares the surgical procedures and results between the 2 groups. Surgical procedures significantly differed, such as in the extent of lymphadenectomy and reconstruction route. The salvage group tended to have fewer cervical anastomoses (75% vs 96%), reflecting a lower proportion of 3-field lymph node dissections (41% vs 91%). Anastomotic techniques in both groups were similar: Neck anastomosis was performed with the single-layer interrupted hand suture technique, and thoracic

TABLE 1. Clinical characteristics and pathologic factors

	Salvage after CRT n = 59	No preoperative therapy n = 553	P value
Gender (No.)			
Male	57 (97%)	483 (87%)	.0330
Female	2 (3%)	70 (13%)	
Age (y)			
Median	63	62	.0821
Range	34–75	41–83	
Location			
Upper	13 (22%)	88 (16%)	.4839
Middle	26 (44%)	261 (47%)	
Lower	20 (34%)	204 (37%)	
pT			
pT0	7 (12%)		
pT1	11 (19%)	176 (32%)	<.0001
pT2	5 (8%)	62 (11%)	
pT3	30 (51%)	277 (50%)	
pT4	6 (10%)	38 (7%)	
pN			
pN0	38 (64%)	161 (29%)	<.0001
pN1	21 (36%)	392 (71%)	
pM			
pM0	52 (88%)	440 (80%)	.1238
pM1 lym	7 (12%)	113 (20%)	
pStage			
pStage 0	6 (10%)		.0006
pStage I	5 (9%)	93 (17%)	
pStage IIA	20 (34%)	58 (11%)	
pStage IIB	5 (9%)	100 (18%)	
pStage III	16 (27%)	189 (34%)	
pStage IVA	2 (3%)	19 (5%)	
pStage IVB	5 (9%)	84 (15%)	

CRT, Chemoradiotherapy.

M1 lym had lymph node metastasis in the neck or in the celiac area.

anastomosis was performed with the stapling technique. The rate of noncurative surgery (R1, R2) tended to be more frequent in the salvage group (15% vs 9%), but the difference did not reach statistical significance.

Postoperative morbidity and mortality rates were increased in the salvage group compared with those who did not receive preoperative therapy (Table 3). The salvage group had more respiratory complications (32% vs 20%), including more empyema, mediastinitis, and tracheobronchial necrosis. Tracheobronchial necrosis developed in 4 patients in the salvage group. Tracheobronchial necrosis without anastomotic leak in the neck developed in 2 patients; 1 patient died and 1 patient survived after an omental patch was grafted onto the tracheobronchial fistula. All patients in both groups were extubated in the operating room immediately after surgery. The ratio of those requiring reintubation and ventilation within 1 week after surgery was not increased in the salvage group (2% vs 2%), whereas rates of anastomotic leakage (31% vs 25%) and wound infection

TABLE 2. Surgical factors

	Salvage after CRT n = 59	No preoperative therapy n = 553	P value
Resection approach			
Right thoracotomy	56 (95%)	539 (97%)	.2740
Left thoracotomy		3 (1%)	
Transhiatal	3 (5%)	11 (2%)	
Lymph node dissection			
3-field	24 (41%)	504 (91%)	<.0001
Others	35 (59%)	49 (9%)	
Reconstruction conduit			
Stomach	56 (95%)	506 (92%)	.6931
Colon	3 (5%)	42 (8%)	
Jejunum		2 (.4%)	
Reconstruction route			
Anterior	26 (44%)	404 (73%)	<.0001
Posterior	31 (53%)	132 (24%)	
Subcutaneous	2 (3%)	17 (3%)	
Anastomosis			
Cervical	44 (75%)	530 (96%)	<.0001
Thoracic	13 (22%)	17 (3%)	
Subcutaneous	2 (3%)	6 (1%)	
Curability			
R0	50 (85%)	505 (91%)	.1018
R1, R2	9 (15%)	48 (9%)	

CRT, Chemoradiotherapy.

(27% vs 15%) were significantly increased in the salvage group.

Mean hospital stay (38 vs 33 days) tended to be increased in the salvage group in parallel with increased postoperative morbidity. The hospital mortality rate (8% vs 2%) was significantly increased in the salvage group. Table 4 lists the causes of postoperative hospital mortality. A reconstruction via the anterior mediastinum with cervical anastomosis is our standard procedure. One patient died of tracheobron-

TABLE 3. Postoperative morbidity and mortality

	Salvage after CRT n = 59	No preoperative therapy n = 553	P value
Respiratory complication	19 (32%)	113 (20%)	.0452
Pneumonia	6 (10%)	46 (8%)	
Empyema and mediastinitis	7 (12%)	27 (5%)	
Tracheobronchial necrosis	4 (7%)	1 (.2%)	
Recurrent nerve paralysis	11 (19%)	127 (23%)	.3396
Ventilation within 1 wk	1 (2%)	10 (2%)	>.9999
Tracheotomy	2 (3%)	6 (1%)	
Anastomotic leak	18 (31%)	138 (25%)	.0034
Conduit necrosis	2 (3%)	1 (.2%)	
Wound infection	16 (27%)	83 (15%)	.0163
Hospital stay (d)	38.3 ± 35.1	31.2 ± 33.8	.1279
Hospital mortality	5 (8%)	10 (2%)	.0099
Operative mortality		1 (.2%)	

CRT, Chemoradiotherapy.

TABLE 4. Causes of postoperative hospital mortality

	Salvage after CRT n = 59	No preoperative therapy n = 553
Tracheobronchial necrosis	1 (2%)	
Conduit necrosis and tracheobronchial necrosis	2 (3%)	1 (0.2%)
Leakage and arterial bleeding	1 (2%)	1 (0.2%)
Radiation pneumonitis and cardiac failure	1 (2%)	
Pneumonia		3 (0.5%)
Leakage and mediastinitis		5 (0.9%)

CRT, Chemoradiotherapy.

chial necrosis without anastomotic leak in the neck. A leak into the posterior mediastinum developed in 1 patient, causing mediastinitis and tracheobronchial necrosis; this patient survived after an omental patch was grafted onto the tracheobronchial fistula. A leak and fatal bleeding from the carotid artery developed in 1 patient. After these events, the reconstruction route was changed to the posterior mediastinum with intrathoracic anastomosis and omental cover onto the tracheobronchus. However, gastric conduit necrosis in the posterior mediastinum caused mediastinitis and tracheobronchial necrosis in 2 patients. After these events, the reconstruction route was returned again to the anterior mediastinum with cervical anastomosis. Neck dissection was canceled in the salvage group, in contrast with the other group who underwent 3-field dissection as a standard procedure. One patient died of interstitial pneumonitis and cardiac failure, which were presumed to have been caused by late toxicity of CRT. Three patients in the salvage group died of respiratory failure and cardiac failure, which were presumed to have been caused by late toxicity of CRT, more than 12 months after salvage surgery.

According to differences in operative morbidity and mortality, overall survival was significantly better in the group who received no preoperative therapy (Figure 1).

FIGURE 1. Overall survival curves of patients undergoing salvage esophagectomy after definitive CRT (n = 59) or no preoperative therapy (n = 553). CRT, Chemoradiotherapy.

FIGURE 2. Overall survival curves of patients undergoing salvage esophagectomy ($n = 54$) according to CRT response (excluding perioperative deaths, $n = 5$). CR, Complete response.

Three-year postoperative survivals were 37.8% in the salvage group and 60.8% in the group without preoperative therapy.

We evaluated the factors associated with long-term survival after salvage esophagectomy in the 54 patients who survived the perioperative period. Univariate analysis revealed no associations between increased survival and any of gender, age (<60 or ≥ 60 years), tumor location, CRT response (recurrence after CR or non-CR; Figure 2), time from CRT to salvage esophagectomy (≤ 12 or >12 months), or pathologic N and M factors (Table 5). Pathologic T factor (T1-3 or T4) and R0 resection (R0 or R1-2) were associated with increased survival (Figures 3 and 4). Patients with pathologic T4 and those with noncurative resection (R1-2) closely overlapped. Of 6 patients with pathologic T4 tumors, R0 resection was performed in only 1 patient via combined resection of the pericardium. Noncurative resection was also completed in 2 patients with peritoneal dissemination and in

FIGURE 3. Overall survival curves of patients undergoing salvage esophagectomy ($n = 54$) according to pathologic T factor (excluding perioperative deaths, $n = 5$).

1 patient with extended node metastasis. The most significant factor associated with increased survival seemed to be R0 resection.

DISCUSSION

In contrast with Western countries, where the rate of adenocarcinoma is increasing, squamous cell carcinoma persists among most Japanese patients with esophageal cancer.^{8,9} The landmark RTOG 85-01 randomized trials have clearly demonstrated that CRT is a curative approach for squamous cell carcinoma.^{1,2} Medical and radiation oncologists have reported improved survival of patients with esophageal cancer treated by definitive CRT without surgery.¹⁰⁻¹³ Definitive CRT without planned surgery has been offered to patients with potentially resectable esophageal tumors in many Japanese institutions during the past decade.¹⁴ During the period of this analysis, 480 patients received definitive

TABLE 5. Univariate and multivariate analyses of salvage esophagectomy long-term survival

Characteristics	Univariate/Multivariate			
	P value	HR	95% CI	P value
Gender (F/M)	.9288	1.574	0.168–14.710	.6910
Age (≥ 60 y/ <60 y)	.8989	3.471	0.997–12.084	.0505
Location (upper/lower)	.5313	1.114	0.228–5.436	.8942
(middle/lower)	.1773	1.884	0.578–6.140	.2934
CRT response (recurrence after CR/non-CR)	.6371	0.786	0.212–2.918	.7188
Time from CRT to salvage (≤ 12 mo/ >12 mo)	.5534	1.460	0.454–4.698	.5256
pT (T1–3/T4)	$<.0001$	0.047	0.006–0.364	.0034
pN (N0/N1)	.1517	0.522	0.203–1.342	.1772
pM (M0/M1-lym)	.0694	0.128	0.030–0.557	.0061
R (R0/R1-2)	$<.0001$	0.421	0.070–2.522	.3437

HR, Hazard ratio; CI, confidence interval; CRT, chemoradiotherapy; CR, complete response.

FIGURE 4. Overall survival curves of patients undergoing salvage esophagectomy ($n = 54$) according to R classification (excluding perioperative deaths, $n = 5$).

high-dose CRT for stages I to III excluding T4 esophageal squamous cell carcinoma in our institution.

The phase III randomized controlled trial, INT 0123 (RTOG 9405), found no improvement in survival in dose comparisons of high-dose (64.8 Gy) versus standard-dose (50.4 Gy) radiation and the effect on locoregional control did not improve.¹⁵ Thus, the standard radiation dose for definitive CRT has become 50 to 50.4 Gy in the United States. Definitive CRT has mostly comprised combinations with a conventional radiation dose of more than 60 Gy in Japan.¹⁰⁻¹³ Clinical trials for definitive CRT at a dose of 50.4 Gy are ongoing. All patients analyzed in the present study were dosed with more than 60 Gy of external beam radiation as definitive CRT.

Before and during the period of this analysis, 2 consecutive phase III randomized controlled trials at the National Cancer Center Hospital compared the outcomes of postoperative chemotherapy with surgery alone (JCOG9208)¹⁶ and postoperative chemotherapy with preoperative chemotherapy (JCOG9907) for surgical patients. Less than 10 surgical candidates received the preoperative CRT, and 45 patients received preoperative chemotherapy. Patients who received no preoperative treatment, including surgery alone or surgery with postoperative chemotherapy, comprised the control group for analysis in the present study.

The morbidity and mortality rates of patients who underwent salvage esophagectomy after CRT increased because of the effects of the radiation administered to the mediastinum and the tissues used as conduits.¹⁷ Higher doses of radiation are associated with increased morbidity,^{18,19} and irradiation of the esophagus and stomach might affect the blood supply, which might contribute to leakage. Gastric conduit necrosis in the posterior mediastinum caused mortal mediastinitis in 2 patients, necessitating surgical modifications to reduce the impact of leaks into the thoracic cavity. The reconstruction route was changed to the anterior mediastinum with cervical anastomosis.

Ischemic tracheobronchial lesions are serious complications of esophagectomy with extensive lymph node dissection, particularly in patients undergoing preoperative CRT.²⁰ Four patients in the salvage group developed tracheobronchial necrosis, of which 3 of them died. The remaining patient who received an omental patch graft survived. Protective measures to prevent ischemic tracheobronchial lesions include, in addition to careful dissection around the airway, preservation of the bronchial arteries during resection.²¹ We changed our salvage esophagectomy procedure to preserve the right posterior bronchial artery. Neck dissection was also avoided to preserve the blood supply from the inferior thyroidal artery to the trachea. Although our standard surgery for esophageal cancer is right thoracotomy and 3-field dissection, the extent of lymphadenectomy was reduced in salvage esophagectomy because of high operative risk.

The incidence of acute toxicity of CRT seemed to be substantial. However, long-term or late cardiopulmonary toxicity cannot be ignored in patients who survive after CRT^{22,23} or in those who undergo salvage esophagectomy after CRT. One patient in the salvage group died of interstitial pneumonitis and cardiac failure postoperatively, which were supposedly caused by late toxicity of CRT. In addition, 3 patients died of respiratory failure and cardiac failure more than 12 months after salvage surgery. A strategy to minimize the normal tissue toxicity of CRT should be identified.

We reviewed several factors to identify which subset of patients derived a benefit from salvage esophagectomy. Univariate analysis revealed that T1-3 and R0 were significant factors. The most significant factor associated with long-term survival seemed to be R0 resection.^{24,25} Fibrosis is usually promoted in radiation fields, and some cancer cells are likely to be left behind in the deep layer of the esophageal wall after radiotherapy. Therefore, to accurately evaluate the T factor of irradiated patients might be difficult preoperatively, and irradiated tissues are difficult to distinguish from tumors during surgery.

CONCLUSIONS

Patients who underwent salvage esophagectomy after definitive high-dose CRT had higher morbidity and mortality rates than patients undergoing esophagectomy without preoperative therapy. Nevertheless, this is the only established treatment strategy that offers any chance of long-term survival. This morbidity rate is acceptable in view of the potential for long-term survival after salvage esophagectomy. Patients should be carefully selected for salvage esophagectomy after high-dose CRT at referral centers that specialize in esophageal cancers.

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