

## Clinical Significance of Salvage Esophagectomy for Patients with Esophageal Cancer and Factors of Influencing Long-term Survival

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**Abstract.** *Background/Aim:* Definitive chemoradiotherapy (CRT) without planned surgery has been recently widely used as a therapeutic option for locally advanced esophageal cancer. Salvage esophagectomy can offer the chance of prolonged survival for patients who have locoregional failure after definitive CRT, but many clinicians oppose the use of surgery due to the associated excessive morbidity and mortality. The aim of this study was to identify patients who are good candidates for salvage surgery by investigating factors influencing long-term survival. *Patients and Methods:* A total of 40 patients underwent concurrent CRT or RT followed by esophagectomy for residual tumor or locoregional recurrence of esophageal squamous cell carcinoma without distant organ metastasis at the Department of General Surgical Science, Gunma University, Gunma, Japan, and were included in this study. As short-term outcomes after salvage esophagectomy, pulmonary and cardiovascular complications, anastomotic leakage, and chylothorax, and the length of postoperative stay were evaluated. Survival rates were calculated using the Kaplan–Meier method, and the Cox proportional hazards model was used for univariate and multivariate analyses of disease-specific survival. *Results:* Postoperative complications were noted in 20 patients (50%), and pulmonary complications were the most common (25%), followed by anastomotic leakage (20%). There was also one case of in-hospital death, caused by multiple organ failure due to chylothorax.

*Univariate analysis revealed that sex, clinical residual tumor, CRT response, pathological tumor depth, and pathological residual tumor were significant factors affecting disease-specific survival ( $p=0.034$ ,  $p=0.009$ ,  $p=0.014$ ,  $p=0.020$ , and  $p=0.026$ , respectively). Moreover, multivariate analysis demonstrated that clinical residual tumor was the only independent factor influencing disease-specific survival ( $p=0.036$ ). Thirteen patients (32.5%) died from other illnesses after salvage surgery, 53.8% patients from pneumonia. Conclusion: Based on long-term survival, recurrence rather than residual tumor after definitive CRT was a favorable indicator for salvage esophagectomy. Not only management of postoperative morbidity and curative operation but, also long-term rigorous outpatient management, including respiratory rehabilitation to reduce pneumonia, is necessary.*

Esophageal cancer is the sixth leading cause of cancer-related mortality worldwide because of its high malignant potential and poor prognosis (1). Each patient should be individually assessed based on the type of cancer, local or regional involvement, and their functional status in order to determine an appropriate treatment regimen. Recent surgical results for patients with advanced esophageal cancer have been improved by extended lymphadenectomy and improved perioperative management; however, the outcome after surgery alone is not necessarily satisfactory (2, 3). Chemoradiotherapy (CRT) is the standard therapy for unresectable esophageal cancer and is also considered an option for resectable cancer. The JCOG 9906 trial, reported by Kato *et al.* (4), showed that CRT is effective for stage II–III esophageal squamous cell carcinoma (ESCC) with manageable acute toxicities and can provide a nonsurgical treatment option. In their report, they showed that the median survival time was 29 months, with 3- and 5-year survival rates of 44.7% and 36.8%, respectively. Increased opportunities for definitive CRT resulted in several

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problems. One problem is long-term toxicities, such as radiation pneumonitis, pleuritis and pericarditis (5). Another is the need to treat residual lesions or recurrent tumors after definitive CRT; locoregional disease persists or recurs in 40-60% of patients (6). For such patients, salvage esophagectomy is the only treatment strategy that offers any chance of long-term survival (6, 7). However, the dose of radiation used in definitive CRT can cause radiation-induced tissue fibrosis or deterioration of the patient's general condition; therefore, salvage esophagectomy after definitive CRT can result in high postoperative morbidity and mortality (7, 8). Moreover, systematic review and pooled analysis showed that salvage esophagectomy has poorer short-term outcomes when compared with planned esophagectomy following neoadjuvant CRT (9). In that review article, salvage esophagectomy was associated with a significantly increased incidence of postoperative mortality, anastomotic leak, and pulmonary complications, as well as longer hospital stays. Recently, Yoo *et al.* reported no in-hospital deaths (0%) after esophagectomy (10), while Chao *et al.* reported a hospital mortality rate after esophagectomy of 2.0% (11). These recent statistics are lower than those of a previous study (12), suggesting that advances in surgical techniques and perioperative intensive care are improving postoperative outcomes after salvage esophagectomy, although the backgrounds of these reports are not identical.

In this study, we retrospectively analyzed the long-term outcomes of patients who underwent salvage esophagectomy at our Institute.

The aim of this study was to identify those patients who were good candidates for salvage surgery by investigating factors influencing long-term survival.

## Patients and Methods

This was a single-center retrospective study. Between September 1998 and November 2015, a total of 40 patients underwent concurrent CRT or RT followed by esophagectomy for residual tumor or locoregional recurrence of ESCC without distant organ metastasis at the Department of General Surgical Science, Gunma University, Gunma, Japan, and were included in this study. Patients were evaluated by esophagoscopy, computed tomography (CT), endoscopic ultrasonography (EUS), and positron-emission tomography (PET). These were performed initially and preoperatively, or whenever disease recurrence was suspected. Clinical staging and pathological examination for resected specimens were performed according to the Guidelines for Clinical and Pathological Studies on Carcinoma of the Esophagus of the Japanese Society for Esophageal Diseases (13). Postoperative outcomes were obtained from hospital records. Data on patient characteristics, perioperative factors, postoperative complications, 30-day mortality, and 90-day mortality were also collected. Long-term outcomes were evaluated by overall and disease-specific survival.

CRT responses were evaluated by four categories, in accordance with the Guidelines for Clinical and Pathological Studies on

Carcinoma of the Esophagus of the Japanese Society for Esophageal Diseases and Response Evaluation Criteria in Solid Tumor (13) complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Based on clinical findings, primary tumors were classified into two groups: with clinical CR or without. The objective of surgical resection after definitive CRT was potential cure. Resection was indicated for residual tumors or local recurrences of ESCC.

*Radiotherapy and chemoradiotherapy.* Radiation doses ranged from 50.4-70 Gy, and the mean was 62.2 Gy. Several chemotherapeutic regimens were performed during dCRT by historical transition. 5-Fluorouracil (5-FU) plus cisplatin or nedaplatin was administered to 16 patients, docetaxel alone to six patients, and triplet regimen (docetaxel plus cisplatin plus 5-FU) to five patients. Treatment selection was decided based on patient expectations and physicians' judgments, including pretreatment personal evaluation of each patient.

*Statistical analysis.* All quantitative data are expressed as the mean±standard deviation. Statistical analyses were performed using the JMP 5 software program (SAS Institute, Cary, NC, USA). Survival rates were calculated using the Kaplan–Meier method, and statistical significance was determined using the log-rank test.

## Results

*Patient characteristics.* Table I shows patient characteristics in this study. A total of 37 males and 3 females (mean age 68.2 years) underwent salvage esophagectomies. Pretreatment evaluation revealed that 27 patients (67.5%) had resectable tumors, and the remaining patients had unresectable tumors. Fourteen patients were treated with RT alone, and 26 underwent concurrent CRT. The clinical response to initial treatment was CR in 24 patients (60%) and incomplete in 16 patients.

*Perioperative factors and pathological findings.* Perioperative factors and pathological findings of patients are shown in Table II. Eighteen patients (45%) had preoperative comorbidities, including hypertension, diabetes mellitus, chronic obstructive pulmonary disease, history of cerebral infarction, and myocardial infarction. Depending on the location of the tumor and each patient's general condition, the McKeown procedure was performed in 28 patients, Ivor-Lewis procedure in two, transhiatal esophagectomy in eight and partial resection of esophageal cancer in eight. The average (±SD) duration of salvage esophagectomy was 493.6±109.1 minutes, and the average volume of blood transfused was 403.2±334.9 ml. Histology performed after surgery revealed R0 resection in 30 patients (75%), while 10 patients had histologically residual disease. A pathological evaluation revealed that 65% of patients had early-stage disease (stages I/II), while the others had advanced-stage disease (stages III/IV). Postoperative complications were noted in 20 patients (50%), and are listed in Table II.

Table I. Patient characteristics.

Variable	Value
Age at primary treatment (years)	
Mean±SD	68.2±7.9 (55-82)
Gender, n	
Male	37
Female	3
Tumor location, n	
Cervical	7
Thoracic upper	4
Middle	13
Lower	11
Abdomen	2
cT, n	
T1	7
T2	4
T3	15
T4	14
cN, n	
Negative	17
Positive	23
cM, n	
M0	40
M1	0
cStage, n	
I	5
II	11
III	12
IV	12
Resectability, n	
Resectable	27
Unresectable	13
Radiation dose (Gy)	
Mean±SD	62.2±6.37
Concurrent chemotherapy, n	
Present	27
Absent	13
Clinical response, n	
Complete	24
Incomplete	16

Table II. Perioperative factors.

Characteristic	Value
Preoperative comorbidity, n (%)	
Negative	18 (45.0)
Positive	22 (55.0)
Surgical procedure, n (%)	
Mckeown	28 (70.0)
Ivor-Lewis	2 (5.0)
Transhiatal esophagectomy	8 (20.0)
Partial resection of esophageal cancer	2 (5.0)
Operative factors, mean±SD	
Time (minutes)	493.6±109.1
Blood transfusion (ml)	403.2±334.9
Pathological stage, n (%)	
I	17 (42.5)
II	9 (22.5)
III	9 (22.5)
IV	5 (12.5)
Residual tumor, n (%)	
R0	30 (75.0)
R1/R2	10 (25.0)
Surgical complication, n (%)	
Pulmonary complication	10 (25.0)
Cardiovascular complication	1 (2.5)
Anastomotic leakage	8 (20.0)
Chylothorax	1 (2.5)
Reoperation, n (%)	
1	1 (2.5)
Mechanical ventilation (days)	
Mean±SD	2.7±4.7
Postoperative ICU stay (days)	
Mean±SD	3.2±3.6
Mortality, n (%)	
Surgical	1 (2.5)
Hospital	1 (2.5)

Pulmonary complications were most common complication (25%), followed by anastomotic leakage (20%). Conservative management, including fasting and antibiotic treatment for anastomotic leakage, resolved the complications in all cases. One patient exhibited postoperative chylothorax, and reoperation was performed 8 days after the first surgery. There was one case of postoperative death in our study population. This patient died due to pulmonary dysfunction from severe pneumonia. There was also one in-hospital death – a patient who died of multiple organ failure due to chylothorax. The mean duration of mechanical ventilation and postoperative intensive care unit stay were 2.7±4.7 and 3.2±3.6 days, respectively.

*Postoperative disease-specific survival and predictors for survival after salvage esophagectomy.* Disease-specific survival at 2 and 5 years postoperatively was 53.0% and 39.7%, respectively (Figure 1). Univariate analysis (Table III) revealed that being female, reason for operation (clinical residual tumor rather than recurrent tumor, non CR to CRT, pathological tumor depth of ypT4, and residual tumor were significant factors negatively affecting disease-specific survival. The disease-specific survival of the 26 patients with recurrence was significantly better as compared to the 14 patients with residual tumor (Figure 2a:  $p=0.01$ ). Patients with clinical CR ( $n=24$ ) in primary tumors had better disease-specific survival than those with non-CR ( $n=16$ ) (Figure 2b:  $p=0.009$ ). Moreover, the cancer-specific survival of the 30 patients with R0 resection was significantly better as compared to the 10 patients with non-curative resection (R1 or R2 resection) (Figure 2c:  $p=0.012$ ). Patients with pathological tumor depth of yp T1-3

Table III. Univariate and multivariate analysis of salvage esophagectomy prognostic factors in disease-specific survival.

Variable	Referent		Univariate analysis			Multivariate analysis		
			HR	95% CI	p-Value	HR	95% CI	p-Value
Sex	Female	Male	2.94	1.103-6.392	0.034	1.50	0.474-4.280	0.462
Age	>70 Years	≤70 Years	0.60	0.236-1.174	0.147			
Location	Lower	Upper	1.04	0.536-1.849	0.905			
Reason for operation	Residual	Recurrence	2.19	1.215-4.113	0.009	3.76	1.083-20.77	0.036
Clinical stage	cT1-3	cT4	0.84	0.486-1.535	0.555			
	cN0	Positive	0.99	0.327-3.101	0.988			
Response to CRT	Non-CR	CR	2.01	1.154-3.680	0.014	0.48	0.090-1.700	0.272
Pathological stage	ypT4	ypT1-3	1.93	1.112-3.411	0.020	2.02	0.963-4.2.6	0.062
	ypN0	Positive	0.59	0.344-1.059	0.077			
Residual tumor	R1+R2	R0	1.93	1.089-3.360	0.026	1.66	0.754-3.484	0.201

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

Table IV. Summary of deaths from other illnesses.

Age (years)	Comorbidity	Survival duration after surgery (month)	Cause of death
82	Hypertension	2.7	Pneumonia
67	None	10.3	Pneumonia
64	None	10.6	Pneumonia
67	Emphysema, asthma	12.5	Pneumonia
75	Hypertension, diabetes mellitus	14.8	Pneumonia
81	None	26.6	Pneumonia
76	None	41	Pneumonia
82	Hypertension	17.2	Renal failure
77	Old myocardial infarction	4.9	Lung cancer
62	None	41.3	Gastric cancer
68	None	0.3	Treatment-related mortality
71	None	4	Unknown
67	None	12.7	Unknown

(n=35) had significantly better prognoses than those with yp T4 (n=5) (Figure 2d:  $p=0.011$ ).

Multivariate analysis (Table III) demonstrated that the reason for surgery (clinical residual tumor *vs.* recurrence tumor) was the only independent factor significantly influencing disease-specific survival.

*Death from other illnesses after salvage esophagectomy.*

Table IV shows statistics of deaths from other illnesses after salvage surgery. Thirteen patients (32.5%) died from other illnesses after salvage surgery – 53.8% of these patients died from pneumonia, which occurred an average of 12.9 months after salvage esophagectomy. Analysis of disease-specific death showed that residual tumor (R1 or R2) was the only significant factor. Other factors did not influence the occurrence of pneumonia (data not shown).

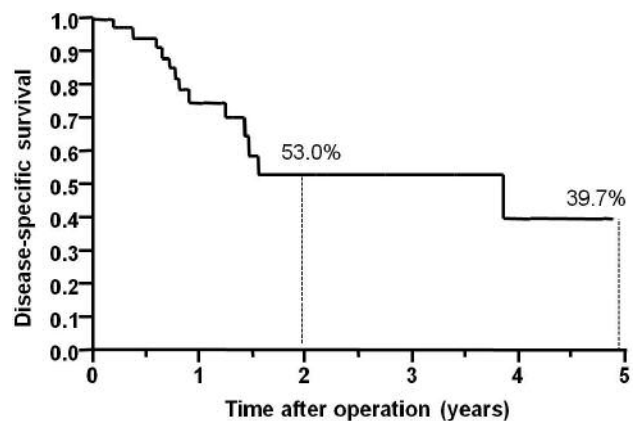


Figure 1. Disease-specific survival at 2 and 5 years postoperatively of the whole patient group was 53.0% and 39.7%, respectively.

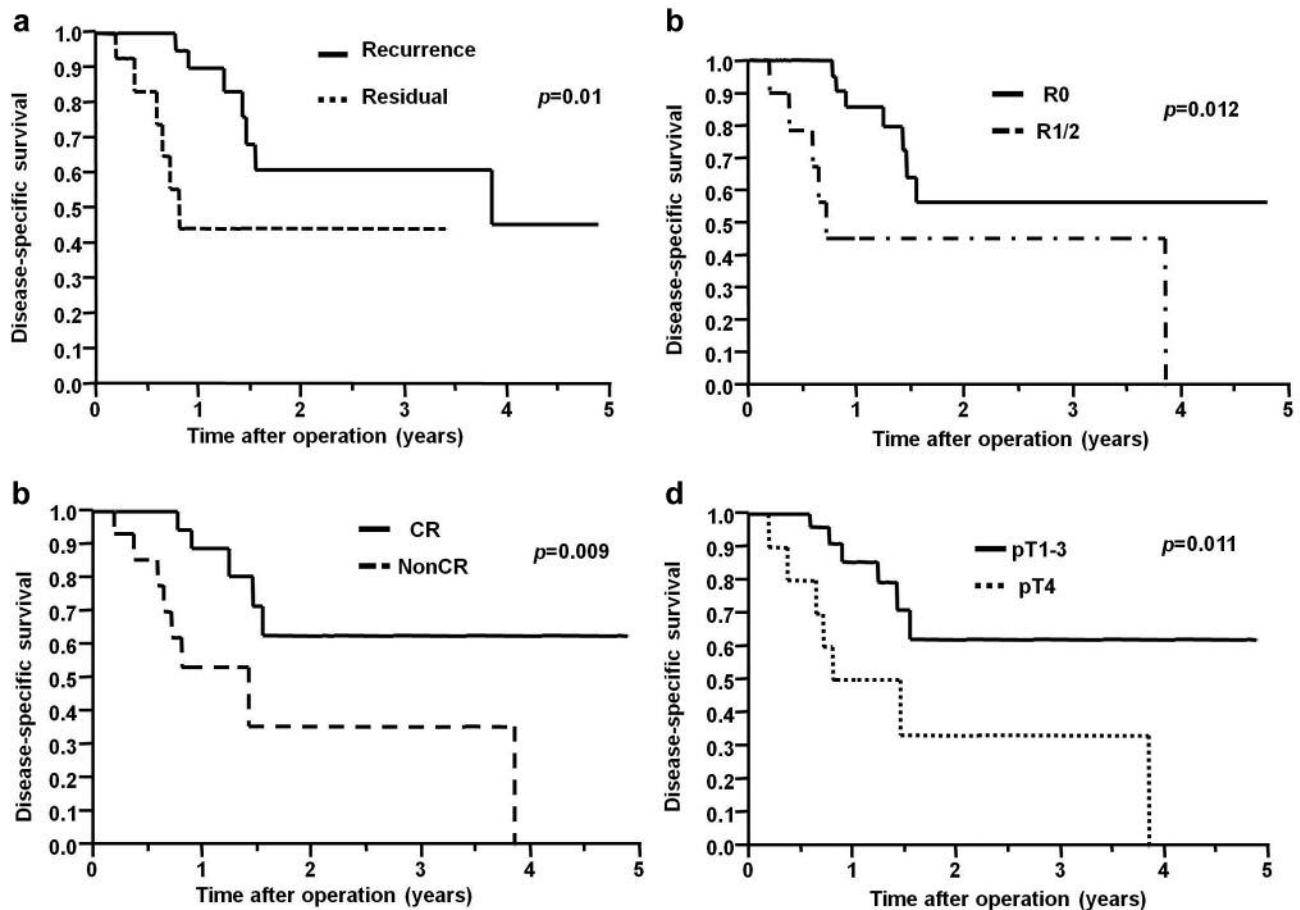


Figure 2. Disease-specific survival (DSS) at 3 years postoperatively. a: DSS of cases of recurrence and clinical residual tumor were 60.7% and 40.7%, respectively ( $p=0.01$ ). b: DSS of complete response (CR) cases and non-CR cases were 62.6% and 35.6%, respectively ( $p=0.009$ ). c: DSS of R0 and R1/2 cases were 56.2% and 45.0%, respectively ( $p=0.012$ ). d: DSS of pT1-3 cases and pT4 cases were 62.2% and 33.3%, respectively ( $p=0.011$ ).

## Discussion

Definitive CRT without planned surgery has been recently widely used as a therapeutic option for locally advanced esophageal cancer. Salvage esophagectomy can offer the chance of prolonged survival for patients who have locoregional failure after definitive CRT. Previous reports showed morbidity rates ranging from 50-79% (7, 14-19), and the rate of treatment-related deaths was reported to be 10.3% (20).

In our study, postoperative complications occurred in 50% of cases, and treatment-related deaths occurred in 5.0%. Our data were similar to the findings of previous reports, although the number of cases was limited in each report. Miyata *et al.* reported rates of anastomotic leakage and pulmonary complications of 39% and 30%, respectively (12). Our data compare acceptably with those of previous studies.

From univariate analysis, we demonstrated that being female, clinical residual tumor, non-CR, pT4, and pathological residual tumor (R1+R2) were significant unfavorable prognostic factors after salvage esophagectomy regarding disease-specific survival. Previous reports have also shown prognostic factors for patients undergoing salvage esophagectomy. Miyata *et al.* found that pretreatment T and N status, pathological T-stage, and operative curability were significant prognostic factors (12), and Swisher *et al.* reported early-stage pathology, prolonged time to relapse, and R0 resection were significant favorable factors for survival in univariate analysis (15). Moreover, Watanabe *et al.* reported response to CRT, time to relapse, pathological T-stage, and residual disease were prognostic factors, as the result of univariate analysis (19). It was unclear why being female was a significant unfavorable prognostic factor in our study. This may be due to the small number of cases. Factors

of pathological T-stage and R0 resection were common in each report including ours, although the number of cases was small in each report.

From multivariate analysis, Morita *et al.* revealed that incomplete resection was an independent unfavorable prognostic factor for survival (21). Wang *et al.* also reported that CR, R0 resection, pathological N and M tumor categories, and total mediastinal dissection with more than 15 dissected nodes were independent prognostic factors (22). These common results show that R0 resection is the most important favorable prognostic factor for achieving long-term survival after salvage esophagectomy. We performed multivariate analysis for disease-specific survival, based on univariate analysis, and clinical residual tumor was an independent unfavorable prognostic factor after salvage esophagectomy. R0 resection was not an independent unfavorable prognostic factor of disease-specific survival in our study. This may be because the rate of death from other illnesses in the group with incomplete resection was high as compared with the rate in the group with complete resection after salvage esophagectomy. From our results, CR after primary treatment was the most important factor for patients. A more powerful regimen of chemotherapy will prolong disease-specific survival because clinical residual tumor was an independent unfavorable prognostic factor after salvage esophagectomy.

We previously reported a phase I/II study of docetaxel, cisplatin, and 5-fluorouracil combination chemoradiotherapy (DCF-RT) in patients with advanced esophageal cancer (23). DCF-RT ensures safety and feasibility by adequately managing myelotoxicity with recommended doses. As a result, we have concluded that this protocol might produce a high CR rate and a favorable prognosis as compared with standard CRT for advanced esophageal cancer. However, that study is limited by the small number of patients that were included. A DCF regimen was performed in a small number of patients in this study. Sufficient analysis could not be performed for each regimen. Higuchi *et al.* also reported that definitive CRT with DCF demonstrated a high CR rate of 52.4%, although this regimen frequency caused myelosuppression and esophagitis. The development of novel regimens may improve curability, and CR after definitive CRT is the most important factor for improved disease-specific survival of patients with esophageal cancer who were given CRT (24).

As salvage esophagectomy after definitive CRT is generally associated with considerable morbidity, and long-term survival is mostly achieved in patients with early-stage disease who are likely to achieve R0 resection, it is necessary to identify these candidate patients accurately. Moreover, we showed that after salvage esophagectomy many patients died from pneumonia. For survival after salvage esophagectomy, not only management of postoperative morbidity and curative operation but also long-term rigorous outpatient management, including

respiratory rehabilitation to reduce pneumonia, is necessary. In conclusion, salvage esophagectomy is a feasible and requisite multimodal therapy option for patients who have recurrent or residual esophageal cancer after CRT, although it must be diagnosed cautiously for proper indications. In particular, recurrence after definitive CRT had favorable indicators for salvage esophagectomy because improved perioperative management leads to reduced morbidity after surgery.

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