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Original Article

Outcome and Prognostic Analysis of Salvage Esophagectomy for Clinical T4b Esophageal Squamous Cell Carcinoma after Definite Chemoradiotherapy

Yu Chen[1], Chien-Ming Lo[1], Yu-Ming Wang[2], Li-Chun Chen[1], Shau-Hsuan Li[3], Hung-I Lu[1]*

[1]Department of Thoracic & Cardiovascular Surgery, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan
[2]Department of Radiation Oncology, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan
[3]Department of Hematology-Oncology, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan

Abstract

Background: Definite chemoradiotherapy (dCRT) followed by surgery is a treatment option for clinical T4b esophageal squamous cell carcinoma (ESCC). However, the feasibility and safety of salvage esophagectomy for clinical T4b patients after dCRT remains unclear. This study aimed to analyze the outcomes and prognostic factors of salvage esophagectomy for cT4b ESCC after dCRT. **Materials and Methods:** From 2008 to 2017, a total of 21 patients who underwent salvage esophagectomy after dCRT for initially unresectable disease at the author's institution were assessed. The study retrospectively reviewed the baseline characteristics of these cases and evaluated the prognostic factors and surgical outcomes. **Results:** Among the study group, R0 resection was achieved in 9 patients (43%). The rate of major complications classified as Clavien-Dindo classification (CDc) Grade IIIb or higher was 24.0%. The overall survival (OS) and disease-free survival (DFS) rates were 46% and 25% at 3 years, respectively. Univariate analysis showed that the patients who had R0 resection had a significantly better OS ($P = 0.012$, 78% vs. 25%) and DFS ($P = 0.025$, 39% vs. 18%) compared to those with R1/2 resection. The patients with minor complications (CDc ≤ IIIa) had a better OS ($P = 0.002$, 61% vs. 0%) compared to the group with major complications (CDc ≥ IIIb). The pathological results with earlier T (ypT0-2) were better than with advanced T (ypT3-4) for 3-year OS ($P = 0.042$, 83% vs. 30%) and 3-year DFS ($P = 0.018$, 53% vs. 13%). In multivariate analysis, R0 resection ($P = 0.042$, 95% confidence interval [CI] 1.051–15.617) and CDc ≤ IIIa ($P = 0.019$, 95% CI 1.286–16.023) were associated with a significantly better prognosis with regards to 3-year OS, and R0 resection was associated with a significantly better prognosis with regards to 3-year DFS ($P = 0.0339$, 95% CI 1.108–13.136). **Conclusion:** The results showed that in salvage esophagectomy for T4b ESCC patients after dCRT, R0 resection and CDc ≤ IIIa were favorable prognostic factors. The surgical complications were still high, but this was acceptable in view of the potential long-term survival after salvage esophagectomy. Carefully selecting candidates remains an important issue before surgery.

Keywords: Definite chemoradiotherapy, esophageal squamous cell carcinoma, salvage esophagectomy

Address for correspondence: Dr. Hung-I Lu, Department of Thoracic and Cardiovascular Surgery, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, No. 123, Dapi Rd., Niaosong Dist., Kaohsiung City 833, Taiwan.
E-mail: luhungi@yahoo.com.tw

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Introduction

The biological aggressiveness of esophageal cancer with the lack of serosa in the esophagus facilitates the invasion of esophageal tumors to adjacent organs, including the trachea, lungs, heart and aorta. In the latest version of the American Joint Committee on Cancer (AJCC) Cancer manual, "T4b tumors" are classified as being unresectable if they invade the aorta, vertebral body or major airways.[1] Definite chemoradiotherapy (dCRT) for esophageal squamous cell carcinoma (ESCC) is a treatment option that may achieve a complete response (CR), even for patients with unresectable tumors.[2-6] However, the incidence rate of locoregional recurrence after dCRT for patients with cT4b esophageal cancer is >50%.[7,8] Tumor regrowth is also frequently observed in the post-treatment course of cT4b patients after dCRT, even in those who achieved a clinical CR. The results of dCRT for cT4b patients are poor, with a 3-year survival rate rarely exceeding 20%–25%.[9,10]

In order to improve outcomes, new strategies such as new chemotherapy regimens or higher radiation doses have been proposed.[2,4,5] Salvage esophagectomy is also considered to be a treatment options in cases of persistent or recurrent disease for operable patients after dCRT. Some studies have demonstrated that dCRT followed by surgery leads to a higher survival rate in patients with cT4b ESCC. However, the incidence of surgery-related complications associated with increasing morbidity and mortality remains high.[11-16] Therefore, identifying suitable patients who would benefit from salvage esophagectomy is very important.

The current study aimed to clarify the prognostic factors associated with postoperative mortality, morbidity and survival for salvage esophagectomy in clinical T4b patients after dCRT.

Materials and Methods

Patient selection

The current study was approved by the Chang Gung Medical Foundation Institutional Review Board (IRB No. 202000319B0), and the review board waived the need for written informed consent. We retrospectively reviewed the medical records of patients with esophageal cancer between January 2008 and December 2017. The inclusion criteria were: (1) Clinical T4b esophageal cancer with any N stage; (2) biopsy-proven ESCC; (3) underwent dCRT; and (4) underwent salvage esophagectomy. The exclusion criteria were: (1) Metastasis; (2) previous, synchronous, and/or metachronous cancers; (3) cancer involving the cervical esophagus; and (4) previous surgical intervention for other benign esophageal diseases.

Diagnosis and staging

All tumors were staged based on the eighth edition of the AJCC (8^{th} AJCC) criteria. The tumor assessment included complete history-taking, physical examination, complete blood counts, chemistry profiles, chest radiography, esophagogastroduodenoscopy with biopsy, endoscopic ultrasonography (EUS), and computed tomography (CT) scan with contrast of the chest and upper abdomen. Whole-body ^{18}F-fluorodeoxyglucose positron-emission tomography with CT (PET-CT) scans were performed in some of the patients.

The diagnostic criteria of clinical T4b were as follows: (1) Tracheobronchial invasion defined by confirmation of the bronchoscopic biopsy or macroscopic view with rigid encasement of indentation by CT; (2) aortic invasion was defined if CT or EUS showed more than 90 degree contact with the obliteration of the fat plane between the esophageal tumor and the aorta; and (3) vertebral body or vital organ invasion (heart or pulmonary artery) was defined by CT. The clinical stage was confirmed in our multidisciplinary cancer meeting.[17]

Treatment protocols

All patients newly diagnosed with clinical T4b ESCC were discussed in the multidisciplinary cancer meeting. The primary treatment was dCRT.

For local radiotherapy (RT), a customized thermoplastic immobilization device was used for each patient. Then, all patients underwent CT-based simulation and were treated using the three-dimensional conformal RT technique or intensity-modulated RT technique using 6-or 10-MV photons. For target delineation, the gross target volume was defined as the gross tumor and gross lymph nodes on CT scan and/or PET-CT images. The clinical target volume (CTV) comprehensively covered the whole esophagus and the regional lymph nodes. The planned target volume (PTV) was expanded from the CTV by 1.0–2.0 cm margins in all directions. The total dose to the PTV was 50–50.4 Gy in 25–28 daily fractions. For patients with gross lymph nodes in the supraclavicular area, a boosted dose to the lymph nodes was added of 10–16 Gy in 5–8 daily fractions.

Chemotherapy was performed concurrently with RT, and consisted of cisplatin (75 mg/m^2; 4-h drip) on day 1, and 5-fluorouracil (1000 mg/m^2; continuous infusion) on days 1–4 every 4 weeks.

After dCRT, the patients were reevaluated to check the treatment outcome and discussed again in the multidisciplinary cancer meeting. Salvage esophagectomy was performed on patients when the following criteria were met: (1) Locally residual disease after dCRT or local recurrence during surveillance without distant metastasis; (2) images showed possibly resectable lesions as judged by the thoracic surgeon in charge; (3) Eastern Cooperative Oncology Group performance status: 0-1; and (4) American Society of Anesthesiologists physical status classifications: I ~ II. Transthoracic esophagectomy with two-field lymph node dissection was the most common surgical procedure. The

thoracic approach was via video-assisted thoracoscopic surgery (VATS) or thoracotomy, and the abdominal approach was via laparoscopy or minimal laparotomy. We mostly used gastric tubes for reconstruction. The reconstruction route was mainly via the posterior mediastinal or retro-sternal route, and was decided according to the length of the gastric tube and the condition of blood supply.

Statistical analysis

Overall survival (OS) and disease-free survival (DFS) were analyzed using the Kaplan–Meier method. The prognostic factors involved in OS and DFS were evaluated using the log-rank test. In univariate analysis, variables associated with OS and DFS were identified using backward Cox proportional hazards models. Variables identified using simple Cox proportional hazards models were selected for potential association with survival. Variables with a $P < 0.1$ in the univariate analysis were included in multifactorial Cox proportional hazard models. In the multivariate analysis, a $P < 0.05$ was considered to be significant. Statistical analysis was performed using MedCalc Statistical Software version 19.0.3 (MedCalc Software bvba, Ostend, Belgium).

Results

Patient and tumor characteristics

From 2008 to 2017, 963 cases were diagnosed with ESCC in our institution. Among them, 249 patients were cT4bNxM0 and 226 cases received dCRT. Twenty-one cases with a post-dCRT biopsy-proven residual tumor or recurrence during surveillance were included in this study. The patient characteristics and the tumor characteristics are presented in Table 1. All patients were male, and 19 (90%) had used betel nut. With regards to body weight changes, 11 patients (52%) gained body weight after dCRT, and 10 patients lost body weight (48%). The clinical N classifications were 7 N1, 12 N2, and 2 N3 stage (33%, 57%, and 10%, respectively).

Table 1: Clinic features of 21 patients with 8th American Joint Committee on Cancer clinical T4b esophageal squamous cell carcinoma

	Number of cases (%)
Gender	
Male	21 (100)
Female	0
Age (years/old)	
<52	8 (38)
≥52	13 (62)
Habits	
Alcohol	21 (100)
Betel-nut	19 (90)
Cigarette	20 (95)
Body weight change after dCRT	
Loss	10 (48)
Gain	11 (52)
Primary tumor location	
Upper	2 (10)
Middle	14 (67)
Lower	5 (24)
Clinical N classification	
N1	7 (33)
N2	12 (57)
N3	2 (10)

AJCC: American Joint Committee on Cancer, dCRT: Definite chemoradiotherapy

The tumor characteristics are shown in Table 2. Seven patients (33%) with T4b invasion were diagnosed by both EUS and CT of the chest, 7 patients (33%) were diagnosed by EUS alone, and 7 patients (33%) were diagnosed by CT of the chest alone. Two patients underwent a bronchoscopic biopsy with positive results. Some bulky or extensive tumors ($n = 9$, 43%) invaded multiple nearby structures, and the others ($n = 12$, 57%) invaded only single structures. The involved structures were the descending aorta ($n = 17$, 81%), carina or bronchus ($n = 7$, 33%), trachea ($n = 5$, 24%), and left atrium or pulmonary vessels ($n = 2$, 10%).

Perioperative outcomes

The perioperative outcomes are presented in Table 3. In terms of surgical approach, thoracoscopic surgery (VATS) was performed in 17 cases (81%) and thoracotomy was performed in 4 cases (19%). Three-field esophagectomy was performed in 19 cases (90%), and the Ivor-Lewis procedure was performed in 2 cases (10%). Reconstruction with gastric tubes was performed in all cases. The gastric tubes were reconstructed from a posterior-mediastinal route in 16 cases (76%) and from a retro-sternal route in 5 cases (24%).

Pulmonary complications were the most common (7 pneumonia, 5 pleural effusion, and 2 acute respiratory distress syndrome [ARDS]), followed by arrythmia ($n = 7$), infection ($n = 6$), anastomosis leakage ($n = 5$), injury of recurrent laryngeal nerve ($n = 2$), chylothorax ($n = 2$), and esophago-pleural fistula ($n = 1$). The minor complication (Clavien-Dindo classification [CD] Grade IIIa or lower) rate was 76%, and the major complication (CD

Table 2: Details about T4b invasion

	Number of cases (%)
Diagnosis tool of T4b invasion	
EUS alone	7 (33)
CT alone	7 (33)
Both EUS and CT	7 (33)
Bronchoscopy	2 (10)
T4b invaded location	
Descending aorta	17 (81)
Carina or bronchus	7 (33)
Trachea	5 (24)
Left atrium and pulmonary vessel	2 (10)
Single invaded location	12 (57)
Multiple invaded locations	9 (43)

EUS: Endoscopic ultrasound, CT: Computed tomography

Grade IIIb or higher) rate was 24%. There were 2 deaths (10%) within 30 days after surgery.

Table 3: Peri-operative outcomes

	Number of cases (%)
OP approach	
Thoracoscopic (VATS)	17 (81)
Thoracotomy	4 (19)
OP time (min)	
<600	13 (62)
≥600	8 (38)
Clavien-Dindo classification	
≤IIIa	16 (76)
≥IIIb	5 (24)
30-day mortality	
Absence	19 (90)
Presence	2 (10)
Complications	
Pulmonary complications	10 (48)
Pneumonia	7 (33)
Pleural effusion (post intervention)	5 (24)
ARDS	2 (10)
Arrythmia	7 (33)
Infection (other than pneumonia)	6 (29)
Anastomosis leakage	5 (24)
Recurrent laryngeal nerve injury	2 (10)
Chylothorax	2 (10)
Esophago-pleural fistula	1 (5)

OP: Operation, VATS: Video-assisted thoracic surgery, ARDS: Acute respiratory distress syndrome

Pathological results and long-term prognostic factors

The pathological results are shown in Table 4. With regards to the primary tumor, 2 cases (10%) presented with no primary tumor but positive lymph nodes (T0N+). For the other cases with a primary tumor, 11 cases (52%) were down-staged (T1b: 1; T2: 3; T3: 6; T4a: 1; 5%, 14%, 29%, and 5%, respectively) and 8 cases (38%) were still T4b. Concerning the surgical margin, 9 cases (43%) were R0 resection and 12 cases (57%) were R1 (defined as surgical margin < 1 mm) or R2 resection. The medium OS and DFS were 25 months and 8.8 months, respectively.

The prognostic factors are presented in Figure 1 and Table 5. Six cases with earlier T (ypT 0-2) had a significantly better prognosis than 15 cases with advance T (ypT 3-4) for 3-year OS (P = 0.042, 83% vs. 30%) and 3-year DFS (P = 0.018, 53% vs. 13%). Nine cases with R0 resection had a significantly better prognosis than 12 cases with R1/R2 resection (3-year OS: P = 0.012, 78% vs. 25%; 3-year DFS: P = 0.025, 39% vs. 18%). Sixteen cases with minor complications had a better prognosis than 5 cases with major complications (3-year OS: P = 0.002, 61% vs. 0%; 3-year DFS: P = 0.08, 30% vs. 0%). In the multivariate analysis of the prognostic factors listed above, R0 resection had a significantly better 3-year OS (P = 0.042, 95% confidence interval [CI] 1.051–15.617) and 3-year DFS (p 0.034, 95% CI 1.108–13.136). The patients with minor complications had a significantly better 3-year OS (P = 0.019, 95% CI 1.286–16.023).

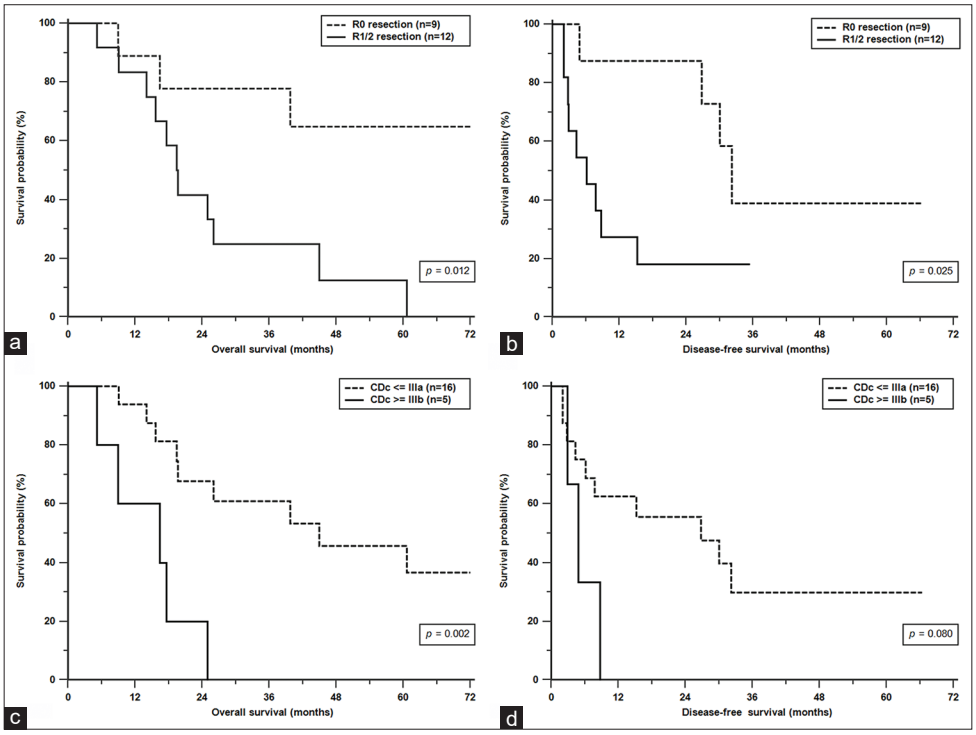

Figure 1: Kaplan-Meier curves according to resection margin and Clavien-Dindo classification. (a) Overall survival according to the resection margin; (b) Disease-free survival according to the resection margin; (c) Overall survival according to the Clavien-Dindo classification; (d) Disease-free survival according to the Clavien-Dindo classification

Table 4: American Joint Committee on Cancer 8th pathological outcomes

Parameters	Number of cases (%)
ypT	
T0N+	2 (10)
T1-2	4 (19)
T3-4	15 (71)
Surgical margin	
R0 resection	9 (43)
R1/2 resection	12 (57)
ypN	
N0	14 (67)
N+	7 (33)
Lymph nodes	
Dissected lymph nodes; medium (mean, range)	19 (19, 5-32)
ypStage	
I	2 (10)
II	4 (19)
III	7 (33)
IV	8 (38)
OS (months), medium (range)	25 (5.2-73.5)
DFS (months), medium (range)	8.8 (0.5-66.4)
Site of recurrence	
Locoregional	6 (29)
Distant	3 (14)
Both	4 (19)

OS: Overall survival, DFS: Disease-free survival

Discussion

In the current study, we demonstrated that salvage esophagectomy is still associated with a higher incidence of postoperative complications, despite recent advances in perioperative management. We also evaluated the prognostic factors and clinical outcomes of salvage esophagectomy of T4b esophageal cancer after dCRT, and found that R0 resection and minor postoperative complications were independent prognostic factors.

Salvage esophagectomy after dCRT has been reported to be associated with higher postoperative morbidity and mortality rates than regular esophageal cancer surgery.[11,18,19] This is mostly related to tissue fibrosis after high-dose radiation treatment, and thus the procedure often causes more bleeding or surrounding tracheobronchial damage. Therefore, surgeons may omit radical lymph node dissection or adopt intensive peri-operative management to reduce the complication rate. In this study, 2 patients died within 30 postoperative day (10%), both due to ARDS. In addition, the pulmonary complication rate was much higher than that for our regular esophageal cancer surgery. Several studies have reported that postoperative severe complications of CDc ≥ IIIb remain an independent factor for a poor prognosis after salvage esophagectomy.[20,21] In these studies, respiratory complications represent the most common form of postoperative morbidity. Therefore, reducing the incidence of severe postoperative pulmonary complications is important in patients receiving salvage esophagectomy to achieve a better prognosis. In our institution, we adjusted the radiation field of low-dose exposure to the lung parenchyma to decrease the incidence of radiation pneumonitis in 2014. The anesthesiologists have also used goal-directed fluid therapy (GDT) for the past years.[22-27] Our team have routinely monitored intra-operative fluid status and stroke volume using a FloTrac™ system since 2015. With GDT, the incidence of ARDS seems to be lower than before, however we need more data to check the effect on other complications and surgical mortality.

Table 5: Results of univariate log-rank analysis of prognostic factors for overall survival and disease-free survival in 21 patients with esophageal squamous cell carcinoma

Factors	Number of patients	OS		DFS	
		3-year OS rate (%)	*P*	3-year DFS rate (%)	*P*
Age (years/old)			0.597		0.058
<52	8	25		0	
≥52	13	60		43	
ypT			0.042		0.018
T0-2	6	83		53	
T3-4	15	30		13	
ypN			0.159		0.377
N0	14	32		28	
N1	6	13		40	
N2	1	0		0	
ypstage			0.190		0.152
I	2	50		100	
II	4	38		50	
III	7	7e1		33	
IV	8	25		13	
Clinical N			0.163		0.250
N1	7	69		54	
N2+3	14	36		17	
OP time (min)			0.421		0.916
<600	13	51		24	
≥600	8	38		14	
Surgical margin			0.012		0.025
R0 resection	9	78		39	
R1/2 resection	12	25		18	
Anastomosis leak			0.162		0.556
Absence	16	42		21	
Presence	5	60		40	
Pulmonary complication			0.085		0.485
Absence	11	64		27	
Presence	10	27		38	
Clavien-Dindo classification			0.002		0.080
≤IIIa	16	61		30	
≥IIIb	5	00		00	

OP: Operation, OS: Overall survival, DFS: Disease-free survival

Several previous studies have demonstrated that incomplete resection was an independent factor for a poor prognosis after salvage surgery.[21,28-30] In our data, patients with R0 resection had a significantly better survival outcome compared to those with R1/R2 resection (3-year OS, 78% vs. 25%). However, it was difficult to correctly predict whether or not the resection was curative after high-dose radiation treatment due to difficultly in identifying the tissue plane between fibrotic tissue and residual cancer. The most commonly invaded location in our series was the descending aorta (81%). With advances in vascular stent-grafting, some aggressive procedures may be considered to reach R0 resection. Nakajima *et al*. performed salvage esophagectomy combined with partial aortic wall resection following thoracic endovascular aortic repair (TEVAR) for 4 patients, and none of them died due to local recurrence.[31] Cong *et al*. performed aortic segment replacement in 47 patients, and reported no in-hospital mortality with 1-, 3-, and 5-year OS rates of 80.9%, 44.7%, and 21.3%, respectively.[32] In clinical T4b cases after dCRT, it is often difficult to determine whether or not R0 resection is possible preoperatively using current imaging studies and diagnostic tools. Consideration of using stent-grafting for equivocal aorta invasion after dCRT by imaging studies may facilitate a curative resection.

There are several limitations in this investigation. First, this is small and retrospective study conducted in a single center. Second, the study period was relatively long, and thus the diagnostic tools and treatment strategy for clinical T4b ESCC patients varied during the study period. Third, the selection bias of this study is that the decision to perform salvage esophagectomy was largely affected by patient's performance status. Fourth, the accuracy rate of current diagnostic tools for T4b are limited, and mis-staging may have affected the oncological outcomes.[17]

Conclusion

In salvage esophagectomy for cT4b ESCC patients after dCRT, R0 resection and minor postoperative complications were favorable prognostic factors. Salvage esophagectomy was a feasible treatment option with potential long-term survival. However, the surgical complication rate was still higher compared with regular esophageal cancer surgery, especially pulmonary complications. Carefully selecting candidates remains an important issue before surgery.

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Conflicts of interest

There are no conflicts of interest.

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