Impact of Interval Between Neoadjuvant Chemoradiation and Surgery Upon Morbidity and Survival of Patients with Squamous Cell Carcinoma of Thoracic Esophagus

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Abstract. *Background/Aim:* The present study aimed to determine the effects of intervals between neoadjuvant chemoradiotherapy (nCRT) and esophagectomy on therapeutic outcomes in patients with locally advanced esophageal squamous cell carcinoma (ESCC). *Patients and Methods:* We analyzed data from 134 consecutive patients who were diagnosed with locally advanced ESCC of the thoracic esophagus and were treated by nCRT followed by esophagectomy between September 2003 and September 2015. We assigned the patients to groups A and B according to whether they underwent esophagectomy ≤ 8 or >8 weeks after nCRT. *Results:* The two groups were comparable in terms of age, gender, performance status, comorbidities, tumor location, clinical stage, R0 resection rates and pathological responses to nCRT. The incidences of pneumonia and respiratory failure were significantly higher in group B ($p=0.03$, $p=0.009$, respectively). Recurrence-free (RFS) and overall (OS) survival rates did not significantly differ between the two groups. However, RFS was significantly poorer among patients with R0 resection ($p=0.04$) and those of cStages III and IV ($p=0.009$) in group B. *Conclusion:* Esophagectomy should proceed within eight weeks after nCRT from the viewpoints of respiratory morbidity and impact of RFS on patients with R0 resection.

Esophageal squamous cell carcinoma (ESCC) is one of the most aggressive among cancers of the gastrointestinal tract.

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Therefore, a longer delay from diagnosis to treatment can result in disease progression and higher perioperative morbidity and mortality (1, 2). An intensive trimodal approach comprising chemotherapy, radiotherapy and surgery is required to control the local progression of advanced esophageal cancer and improve the survival of patients (3, 4). Neoadjuvant chemoradiotherapy (nCRT) might reduce the tumor burden and increase the rate of complete resections.

A 6-8-week interval between nCRT and surgery is commonly accepted for esophageal cancer because it allows patients to recover from the side-effects of chemoradiation (5). On the other hand, the interval between neoadjuvant treatment and surgery has been implicated as an important factor in rectal adenocarcinoma, and thus a longer interval (>8 weeks) can be even more beneficial (6, 7). The effect of radiation is maximized, tumors shrink and rates of pathological complete responses (pCR) increase. However, prolonging the delay before surgery might promote tumor regrowth that will increase risk of recurrence and in theory, the benefit of tumor downstaging after nCRT will be abolished. Furthermore, longer intervals between nCRT and surgery might increase the incidence of radiation-induced fibrosis, and result in surgical complexity and more postoperative complications.

Three retrospective studies of the intervals between nCRT completion and esophagectomy investigated only ESCC (8-10). The results of these studies were inconsistent, and the optimal timing for esophagectomy was not established.

Esophagectomy for esophageal cancer has usually proceeded within eight weeks after the completion of radiation therapy in many studies of nCRT. Therefore, the postoperative courses and prognoses of the patients who underwent esophagectomy at >8 weeks after nCRT have not been investigated in detail. The present study aimed to determine the effects of intervals of <8 or >8 weeks between nCRT and surgery on short- and long-term therapeutic outcomes.

Patients and Methods

Patients. This retrospective study included 134 consecutive patients with locally advanced thoracic ESCC without visible primary-tumor infiltration of adjacent structures (cT4), who underwent nCRT followed by esophagectomy at our institution between September 2003 and September 2015. The patients underwent a physical examination, standard laboratory tests, chest radiography, and had performance status (PS) 0 or 1 according to the definitions of the Eastern Cooperative Oncology Group (11). Tumors were clinically staged based on the findings of biopsies, endoscopic ultrasonography radiography of the upper gastrointestinal tract and helical computed tomography (CT) from the neck to the abdomen. They were also systematically assessed after 2006 by ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography imaging. Tumors were staged according to the 7th edition of the Union for International Cancer Control (UICC) by consensus at meetings regarding multimodal images (12). Patients underwent nCRT and were followed by esophagectomy if the cancer in the thoracic esophagus was resectable, or if a tumor was more deeply invasive than cT2, positive for lymph node (LN) metastasis or resectable supraclavicular LN metastasis (cM1 LYM).

The patients were assigned to groups according to the interval between nCRT and surgery. Patients in groups A and B underwent surgery at intervals of ≤8 and >8 weeks after completing nCRT. Short- and long-term therapeutic outcomes such as perioperative findings, pathological characteristics and survival were compared. The Institutional Review Board at Hiroshima University approved this study.

Neoadjuvant chemoradiotherapy and surgery. The nCRT comprised concurrent radiotherapy (40 Gy) and chemotherapy with 5-fluorouracil plus either docetaxel or cisplatin, or both, as described (4, 13-16). Cisplatin was replaced with nedaplatin for patients with renal dysfunction. Five fractions per week of external beam radiotherapy with 10-MV X-rays were applied over four weeks (total dose, 40 Gy). Three-dimensional treatment was planned using a CT simulator. The radiation field for upper thoracic tumors included the region from the supraclavicular and mediastinal LN to the carina. The field for mid-thoracic or lower thoracic tumors included the mediastinal and perigastric LN, and the supraclavicular fossa was included if upper mediastinal nodes were positive. The primary tumor was assessed with a craniocaudal margin of 2 cm (4, 13-16).

All patients underwent open transthoracic or thoroscopic esophagectomy and at least two-field (thoracic and abdominal) LN dissection between four and 24 weeks after completing nCRT. Esophageal cancer in the upper and middle third of the thoracic esophagus or LN metastasis in the superior mediastinum was inevitably treated by three-field LN dissection including cervical lymphadenectomy. The gastric tube or colonic conduit was subsequently lifted *via* the posterior mediastinal or retrosternal route for cervical anastomosis with the esophagus.

Follow-up. All patients who underwent esophagectomy were followed-up at three- to four-monthly intervals from the day of surgery for the first two years, then every six months thereafter. The neck, chest and abdomen were assessed by CT at three- to four-monthly intervals for the first two years and every six months thereafter and the upper gastrointestinal tract was examined

Table I. Demographic and clinical characteristics of patients.

Clinical factors	All patients (n=134)	Interval between nCRT and surgery		p-Value
		≤8 weeks (n=106)	>8 weeks (n=28)	
Age (y)*				
≤65	72	55 (51.9)	17 (60.7)	0.5
>65	62	51 (48.1)	11 (39.3)	
Gender				
Male	116	91 (85.8)	25 (89.3)	0.8
Female	18	15 (14.2)	3 (10.7)	
Performance status				
0	119	94 (88.7)	25 (89.3)	1
1	15	12 (11.3)	3 (10.7)	
Cardiovascular comorbidity				
No	81	64 (60.4)	17 (60.7)	1
Yes	53	42 (39.6)	11 (39.3)	
Respiratory comorbidity				
No	104	84 (79.2)	20 (71.4)	0.5
Yes	30	22 (20.8)	8 (28.6)	
Diabetes mellitus				
No	116	90 (84.9)	26 (92.9)	0.4
Yes	18	16 (15.1)	2 (7.1)	
Tumor location				
Supracarinal	27	23 (21.7)	4 (14.3)	0.4
Infracarinal	107	83 (78.3)	24 (85.7)	
Clinical T category				
1	3	3 (2.8)	0	0.2
2	18	17 (16.0)	1 (3.6)	
3	113	86 (81.1)	27 (96.4)	
Clinical N category				
0	27	20 (18.9)	7 (25.0)	0.6
1-2	107	86 (81.1)	21 (75.0)	
Clinical M category				
0	119	92 (86.8)	27 (96.4)	0.2
1	15	14 (13.2)	1 (3.6)	
Clinical stage				
1	5	5 (4.7)	0	0.3
2	30	22 (20.8)	8 (28.6)	
3	84	65 (61.3)	19 (67.9)	
4	15	14 (13.2)	1 (3.6)	

nCRT: Neoadjuvant chemoradiotherapy. Data are shown as numbers or n (%).

annually by endoscopy. All patients completed the follow-up until February 2017 or death.

Statistical analysis. Data are expressed as numbers (%), frequency, or means and standard deviation (SD). Frequencies were compared using χ^2 tests for categorical variables and small samples were assessed using Fisher exact tests. Continuous variables were compared using *t*-tests.

Recurrence was defined as any unequivocal occurrence of new cancer foci in a disease-free patient. Recurrence-free survival (RFS) was defined as the interval between the day of surgery and a first event (cancer recurrence or death from any cause) or the last follow-

Table II. Perioperative factors and histopathological findings.

Surgical factors	All patients (n=134)	Interval between CRT and surgery		<i>p</i> -Value
		≤8 weeks (n=106)	>8 weeks (n=28)	
Surgical procedure				
Thoracotomy	120	96 (90.6)	24 (85.7)	0.5
Thoracoscopy	14	10 (9.4)	4 (14.3)	
Lymphadenectomy				
2-field	45	34 (32.1)	11 (39.3)	0.5
3-field	89	72 (67.9)	17 (60.7)	
Surgical duration (min)	426 (300-787)	430 (310-787)	408 (300-543)	0.07
Blood loss (ml)	420 (134-3030)	405 (134-3030)	465 (200-2300)	0.8
Blood transfusion				
No	95	79 (74.5)	16 (57.1)	0.1
Yes	39	27 (25.5)	12 (42.9)	
Resection margin				
R0	124	98 (92.5)	26 (92.9)	1
R1-2	10	8 (7.5)	2 (7.1)	
Pathological findings				
ypT0 status				
Yes	48	39 (36.8)	9 (32.1)	0.8
No	86	67 (63.2)	19 (67.9)	
Number of LN harvested	47±22	46±20	50±27	0.5
Number of invaded LN	1.4±3.1	1.5±3.4	1.0±1.5	0.4
ypN category				
0	73	57 (53.8)	16 (57.1)	0.8
1-3	61	49 (46.2)	12 (42.9)	
Pathological CR				
Yes	38	32 (30.2)	6 (21.4)	0.5
No	96	74 (69.8)	22 (78.6)	
Response to CRT				
G2-3	101	81 (76.4)	20 (71.4)	0.6
G0-1	33	25 (23.6)	8 (28.6)	

Data are shown as numbers, n (%), means±SD or as medians with ranges. CR: Complete response; LN: lymph nodes; nCRT: neoadjuvant chemoradiotherapy; SD: standard deviation.

up. Overall survival (OS) was defined as the interval between the day of surgery and death or the last follow-up. Rates of RFS and OS were calculated from Kaplan–Meier curves and statistically evaluated using log rank tests. Probability (*p*) was considered statistically significant at <0.05. Data were statistically analyzed using EZR (version 1.36) (Saitama Medical Center, Jichi Medical University, Saitama, Japan) (17), a graphical user interface for the modified version of R (The R Foundation for Statistical Computing, Vienna, Austria).

Results

General characteristics of the enrolled patients. Table I summarizes the basic demographic and clinical characteristics of the 134 patients (male, n=116 (86.6%); age, >65 years;

Table III. Postoperative course according to interval between nCRT and surgery.

Postoperative course	All patients (n=134)	Interval between nCRT and Surgery		<i>p</i> -Value
		≤8 weeks (n=106)	>8 weeks (n=28)	
Pneumonia				
No	108	90 (84.9)	18 (64.3)	0.03
Yes	26	16 (15.1)	10 (35.7)	
Respiratory failure (reintubation)				
No	117	97 (91.5)	20 (71.4)	0.009
Yes	17	9 (8.5)	8 (28.6)	
Recurrent laryngeal nerve palsy				
No	111	85 (80.2)	26 (92.9)	0.2
Yes	23	21 (19.8)	2 (7.1)	
Anastomotic leak				
No	100	79 (74.5)	21 (75.0)	1
Yes	34	27 (25.5)	7 (25.0)	
Any morbidity				
No	72	58 (54.7)	14 (50.0)	0.7
Yes	62	48 (45.3)	14 (50.0)	
90 days surgical mortality				
No	132	104 (98.1)	28 (100)	1
Yes	2	2 (1.9)	0	
Median postoperative hospital stay, (range) days	28 (14-394)	26.5 (14-225)	31.5 (17-394)	0.7
Recurrence				
No	79	65 (61.3)	14 (50.0)	0.3
Yes	55	41 (38.7)	14 (50.0)	
Overall survival (%)				
3 years		60.1	62.7	50.0
5 years		53.7	55.6	

Data are shown as numbers or n (%) unless otherwise indicated. nCRT: Neoadjuvant chemoradiotherapy.

histology, squamous cell carcinoma) who were included in this study. The pretreatment clinical stages (cStage) of cancer were IB, II, III, and IV in 5 (3.7%), 30 (22.4%), 84 (62.7%) and 15 (11.2%) patients, respectively. The mean interval from nCRT completion to surgical intervention was 49 days (range=20-163 days, median, 44.5). Patients were assigned to groups A or B based on intervals between nCRT and surgery of ≤8 (n=106) or >8 weeks (n=28). The groups did not differ significantly in terms of age, gender, performance status, comorbidities, tumor location, and clinical TNM stage.

Perioperative factors and histopathological findings. Table II shows surgical factors and pathological findings. The surgical procedures comprised esophagectomy *via* thoracotomy and three-field lymphadenectomy for 120 (90%) and 89 (66%) patients, respectively. The surgical duration tended to be longer for group A, but the value did

not reach statistical significance ($p=0.07$). The surgical procedures, regions of lymphadenectomy, amount of blood loss and need for blood transfusion also did not significantly differ between the groups. Ten patients were also treated by esophagectomy with a positive resection margin (R1: 2, R2: 8), but the incidence of this did not significantly differ between the groups. Primary tumors in 48 (35.8%) patients disappeared, and a pathological complete response (ypT0N0M0: pCR) due to nCRT was achieved in 38 (28.4%) patients. These pathological responses to nCRT were similar between the groups. The numbers of harvested lymph nodes did not significantly differ between the groups and thus, neither did the degree of difficulty associated with lymphadenectomy.

Postoperative morbidity and mortality. The overall 90-day surgical mortality was 1.5% (2/134), with no significant differences between the groups. The overall morbidity rate was 46.3%. The incidences of pneumonia and respiratory failure accompanied by re-intubation were significantly higher in group B ($p=0.03$, $p=0.009$, respectively). Rates of recurrent laryngeal nerve palsy and anastomotic leakage (Table III), as well as the length of postoperative hospital stays were comparable between the groups.

Recurrence and survival. Cancer recurred in 55 (41.0%) patients after a median interval of 6.5 (range=0-95) months. The recurrence rates were 38.7% and 50.0% in groups A and in B, respectively ($p=0.3$). The median OS was 39.5 (range=1.3-152.6) months. Table III, Figure 1A and B show that neither OS nor RFS significantly differed between the groups ($p=0.2$ for both). The prognosis tended to be poorer for patients with R0 resection in group B than in group A, but OS did not significantly differ between them ($p=0.08$; Figure 1C). However, RFS significantly differed between patients with R0 resection in groups A and B (67% vs. 50%, $p=0.04$; Figure 1D). Likewise, OS in patients with cStage III and IV who underwent R0 resection did not significantly differ between the groups (Figure 1E, $p=0.09$), but RFS was significantly poorer in group B (Figure 1F, $p=0.009$).

Discussion

Esophageal squamous cell carcinoma is one of the most aggressive cancers of the gastrointestinal tract. An intensive trimodal approach is needed to improve the survival of patients with locally advanced esophageal cancer (3, 5). The reported range of 5-year survival rates is 30%-50% for locally advanced esophageal cancer after trimodal therapy (3, 4, 18). Esophagectomy has usually proceeded between six and eight weeks after the completion of radiation therapy in many studies of nCRT and esophageal cancer, because it allows patients to recover from the side effects of nCRT (5).

On the other hand, the interval between neoadjuvant treatment and surgery has been implicated as an important factor in rectal adenocarcinoma, indicating that an interval longer than eight weeks might be even more beneficial (6, 7). This is because the effect of radiation is maximized, tumor shrinkage increases and rates of pCR are higher. However, tumor regrowth might occur after excessive surgical delays.

Three retrospective studies have investigated the impact of intervals between nCRT and esophagectomy on ESCC (8-10). Ruol *et al.* investigated 129 patients with ESCC and concluded that intervals between nCRT and surgery of ≤ 30 , 31 to 60 and 61 to 91 days were not associated with rates of R0 resection, pCR, postoperative mortality, and overall survival (8). Chiu *et al.* studied 276 patients with ESCC and found that intervals of ≤ 8 and >8 weeks were not associated with the rate of pCR and OS (9). Wang *et al.* reviewed 665 patients with ESCC and associated early surgery (<30 days) after nCRT with reduced rates of surgical margin positivity (10). Our findings revealed that the interval between nCRT and esophagectomy was not associated with rates of R0 resection, responses to nCRT, surgical mortality and survival. However, rates of surgical morbidity such as pneumonia and respiratory failure accompanied by re-intubation were significantly higher in group B that underwent surgery after a longer interval.

Ruol *et al.* indicated that rates of overall morbidity and anastomotic complications were comparable among three groups (8). Chiu *et al.* also found that rates of complications did not significantly differ between longer and shorter intervals after nCRT according to the Clavien-Dindo classification. However, none of the three studies (8-10) compared morbidity limited to respiratory complications (9). Respiratory morbidity is generally influenced by the background of the patients, namely age, preoperative smoking history, degree of emphysema, preoperative PS and postoperative recurrent laryngeal nerve palsy. Risk for developing radiation-induced pneumonitis increases at several months after radiation therapy (19). Radiotherapy might have equally powerful influences on pulmonary stroma and

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Figure 1. Five-year survival curves for all patients based on intervals of ≤ 8 (group A) and >8 (group B) weeks between nCRT completion and esophagectomy. Five-year OS (A) and RFS (B) rates of groups A and B were 56% vs. 46% ($p=0.2$) and 61% vs. 50% ($p=0.2$), respectively. Five-year OS (C) and RFS (D) rates of patients with R0 resection in groups A and B were 60% vs. 46% ($p=0.08$) and 67% vs. 50% ($p=0.04$), respectively. (E) Five-year OS (E) and RFS (F) rates of patients with cStage III and IV cancer and R0 resection in groups A and B were 53% vs. 42% ($p=0.09$) and 64% vs. 37% ($p=0.009$), respectively. OS: Overall survival; RFS: recurrence-free survival.

parenchyma. Furthermore, radiotherapy might be harmful to the mechanism of phlegm discharge by the trachea after a certain amount of time has elapsed after treatment. Therefore, pulmonary complications might increase during a prolonged interval between nCRT completion and esophagectomy.

On the other hand, the present study found that RFS significantly declined among patients with R0 resection and those with cStage III and IV cancer when the interval between nCRT and surgery exceeded eight weeks. These findings might have been associated with the increased onset of pneumonitis in the group that underwent surgery at >8 weeks after nCRT. Some studies have associated postoperative complications with a poor prognosis of esophageal cancer (20, 21). Among them, Lerut *et al.* identified a significant correlation between pulmonary infection and the early recurrence of cancer of the esophagus and gastroesophageal junction. Yamashita *et al.* similarly associated postoperative pulmonary infection with an unfavorable prognosis among patients with esophageal cancer who underwent neoadjuvant chemotherapy.

Furthermore, an author of the present study (Y. Ibuki) demonstrated elevated levels of post-operative C-reactive protein (CRP) associated with poor RFS in patients with esophageal cancer (22). Persistent inflammation could cause cancer to develop, and IL-6 that mainly regulates CRP synthesis, is thought to play important roles through activities such as stimulating angiogenesis and inhibiting cancer from undergoing apoptosis. A persistent inflammatory state in the presence of postoperative occult residual cancer would be more likely to cause cancer progression and recurrence. Host immunosuppression and stimulated residual cancer cell growth induced by severe complications might, at least in part, explain the mechanisms of the relationship between pneumonia and a poor prognosis of ESCC (23).

Chiu *et al.* also indicated that the incidence of residual cancer increased and OS worsened when surgery proceeded at longer intervals after nCRT for good responders (9). Even from the viewpoint of micrometastasis control, longer intervals between nCRT and esophagectomy might worsen prognosis. These findings might require validation through prospective and randomized studies.

In conclusion, esophagectomy should proceed within eight weeks after nCRT from the viewpoint of respiratory morbidity and impact on RFS among patients with R0 resection.

Conflicts of Interest

None.

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