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Efficacy and Safety of Neoadjuvant Chemoradiotherapy Following Esophagectomy with Japanese-style Extended 3-Field Lymphadenectomy for Thoracic Esophageal Cancer

SATORU MOTOYAMA, YUSUKE SATO, TOMOHIKO SASAKI, AKIYUKI WAKITA, YUTA KAWAKITA, JIAJIA LIU, YUSHI NAGAKI, HAJIME SAITO, KAZUHIRO IMAI, HAYATO KONNO, KAORI T. MIZUSAWA and YOSHIHIRO MINAMIYA

Esophageal Surgery, Akita University Hospital, Akita, Japan

Abstract. *Aim: We investigated the safety of adding Japanese-style extended 3-field lymphadenectomy in patients treated with neoadjuvant chemoradiotherapy (NACRT) for thoracic esophageal squamous cell carcinoma (TESCC). Furthermore, the efficacy of NACRT, as shown by the pathological and metabolic responses were determined. Patients and Methods: One hundred consecutive patients with cStage II-IV TESSC were enrolled. We analyzed the adverse events related to NACRT and surgical complications following surgery. Pathological responses to NACRT and the association between pCR and [^{18}F]-fluorodeoxyglucose positron-emission tomography (FDG-PET) evaluation were investigated. Results: Adding Japanese-style extended 3-field lymph node dissection after NACRT did not increase serious surgical complications. Seventy-four percent of patients experienced grade 2-3 pathological response, with 25% achieving pCR. There was a significant relationship between the change from positive to negative findings on FDG-PET/CT and pCR. Conclusion: Transthoracic esophagectomy with Japanese-style extended 3-field lymph node dissection after NACRT is a safe and powerful treatment.*

Thoracic esophageal squamous cell carcinoma (TESCC) is a highly aggressive cancer characterized by a poor prognosis and rapid clinical progression (1, 2). Moreover, lymph node metastases distribute widely, from the neck to the abdomen, as a result of a complex peri-esophageal lymphatic network. Micrometastases or very small metastatic lymph nodes are invisible, making it nearly impossible to make a complete diagnosis. The potential presence of such metastasis prompts surgeons to be aggressive with respect to lymph node dissection. Therefore, extended lymphadenectomy in the neck, mediastinum and upper abdomen, so-called three-field lymphadenectomy is standard practice in Japan (1). On the other hand, TESCC often responds well to chemotherapy and radiotherapy, therefore, adding radiotherapy to chemotherapy increases the efficacy of local control (3, 4). For this reason, preoperative neo-adjuvant chemoradiotherapy (NACRT) followed by esophagectomy has been a mainstay of treatment for advanced TESCC in Europe, the United States and parts of Asia (5-9). In Japan, by contrast, based on the results of a Japan Clinical Oncology Group trial comparing neo-adjuvant chemotherapy (NAC) and postoperative adjuvant chemotherapy (JCOG 9907), NAC with cisplatin and 5-fluorouracil (5-FU) is the standard for cStage II-III TESCC at this point (10).

Surgeons have recognized that Japanese-style extended 3-fieled lymphadenectomy with esophagectomy is a full treatment for local control, although adding this powerful Japanese-style surgical treatment to NACRT brings a considerable risk for patients. However, in the JCOG 9907 study, 25% of patients who had a single locoregional tumor recurrence after NAC with cisplatin and 5-FU plus esophagectomy had that recurrence despite extensive lymphadenectomy.

We started using a treatment strategy that entailed NACRT followed by esophagectomy for cStage II-IV TESCC with a greater than T3 tumor or with lymph node involvement in 2009. In the present study, we report on the safety of treating patients with NACRT followed by esophagectomy and Japanese style extended 3-field lymphadenectomy in 100 consecutive cases. Moreover, the efficacy of NACRT as shown by the pathological response and evaluation using

Correspondence to: Satoru Motoyama, Esophageal Surgery, Akita University Hospital, 1-1-1 Hondo, Akita 010-8543, Japan. Tel: +81 188846132, Fax: +81 188362615, e-mail: motoyama@doc.med.akita-u.ac.jp

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[^{18}F]-fluorodeoxyglucose positron-emission tomography/computed tomography (FDG-PET/CT) was investigated.

Patients and Methods

Patients. This study was approved by the Ethics Committee of Akita University Graduate School of Medicine (no. 547). Additional informed consent was obtained from all patients for whom identifying information is included in this article. The study participants were 100 consecutive Japanese patients treated with preoperative NACRT followed by esophagectomy with Japanese-style extended 3-field lymph node dissection for cStage II-IV TESSC at Akita University Hospital between 2009 and 2016. This treatment was recommended for patients with either a greater than T3 tumor or regional lymph node involvement, including supraclavicular lymph node metastasis, and with Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-1.

Clinical staging. For all patients, the esophageal cancer stage, including diagnosis of lymph node metastasis, was defined at a conference attended by radiologists, physicians and surgeons according to the International Union Against Cancer tumor-node-metastasis (TNM) Classification of Malignant Tumors (seventh edition) (11). Regional nodes were considered positive for malignancy when they were round or ovoid shaped with short axes ≥10 mm in thin-sliced CT. When ultrasonography of the neck lymph nodes showed well-defined boundary echo, weak or sonolucent internal echo or strong with notching internal echo, we considered this as metastasis in the lymph node.

NACRT. Chemotherapy consisted of protracted infusion of 5-FU (800 mg/m^2/day) on days 1-5 and cisplatin or nedaplatin (80 mg/m^2/day) on day 1. This protocol was repeated twice with 3- to 5-week intervals in between. High-energy X-rays (10 MV) were used for radiotherapy. All patients underwent 3-dimensional radiotherapy planning. The radiotherapy target was set around the gross tumor volume and metastatic lymph nodes. Concurrent radiotherapy consisted of 2 Gy/day for 5 days each week, with a total radiation dose of 40 Gy/20 fractions.

Grading of adverse events of NACRT was according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (11).

[^{18}F]-FDG-PET/CT. Patients were clinically staged using systematic FDG-PET/CT imaging before NACRT and 3-4 weeks after NACRT, before surgery. Patients received an intravenous injection of 185 MBq/kg FDG (FDGscan; Nihon Medi-Physics, Tokyo, Japan) and then rested for 1 hour before scanning. All images were acquired using a combined PET/CT scanner (Discovery ST Elite 16; GE Healthcare, Chicago, IL, USA). The detailed methods of examination in FDG-PET/CT were as described previously (12). We defined the maximum standardized uptake value (SUV_{max}) as positive when SUV_{max} was 2.5 and more, and as negative when it was less than 2.5.

Surgery. Esophagectomies were scheduled more than 3 weeks after completing NACRT, by which time patients had no grade 2 or more adverse events. Esophagectomy with extended 3-field lymph node dissection (bilateral neck including supraclavicular lymph node, and mediastinal and abdominal lymph nodes) under right thoracotomy was performed as the standard operative method in this study. However, thoracoscopic esophagectomy and robotic-assisted thoracoscopic esophagectomy for patients after NACRT were introduced late during the study period. Surgical complications were evaluated using the Clavien-Dindo classification (13).

Pathological response. The pathological response of the primary tumor was graded using response evaluation criteria for the effects of radiation, chemotherapy or both, as published by the Japanese Esophageal Society: 0: no recognized cytological or histological therapeutic effect; 1: slightly effective, with apparently viable cancer cells accounting for at least one-third of the tumor tissue; 2: moderately effective with viable cancer cells accounting for less than one- third of the tumor tissue; and 3: markedly effective, with no evidence of viable cancer cells (14, 15). A pathological complete response (pCR) was considered to have been achieved when there was no evidence of viable cancer cells in the tumor or lymph nodes.

Evaluations of safety and efficacy. We analyzed the adverse events related to NACRT and surgical complications following surgery to determine the safety of this treatment. Pathological responses to NACRT were determined in resected tumors and lymph nodes as an indicator of the efficacy of NACRT. In addition, the association between pCR and PET/CT evaluation was investigated.

Statistical analysis. Continuous variables are presented as the median (minimum-maximum). Differences between groups were analyzed using Fisher's exact probability test. All statistical analyses were performed using JMP10 (SAS Institute, Cary, NC, USA) and yielded two-sided *p*-values. Values of $p<0.05$ were considered statistically significant.

Results

The patient population included 86 (86%) males and 14 (14%) females with a median age of 65 (range=43-77) years. The patient characteristics are shown in Table I. There were 86 patients (86%) with cT3 tumors, and 1 (1%) with a cT4 (left main bronchus) tumor. Ninety-two (92%) patients had 2 (range=1-7) involved lymph nodes. Three patients had posterior thoracic para-aortic lymph node metastasis (N0. 112aoP in 11th Japanese Classification of Esophageal Cancer) (12, 13).

The NACRT and adverse events are shown in Table II. The median duration of the NACRT was 37 (range=11-62) days. The chemotherapy was nedaplatin + 5FU for 79 (79%) patients. NACRT was completed in 85 (85%) patients. The reasons NACRT was incomplete in 15 patients were bone marrow suppression, hyponatremia with symptoms, renal dysfunction, sepsis, gastric ulcer, osteomyelitis of the mandible, and patient's wishes. Greater than grade 3 adverse events included decreases in white blood cell or neutrophil counts, anemia, decreased platelet counts and hyponatremia. All greater than grade 3 adverse events occurred in 52 (52%) patients.

The fraction of patients in whom the SUV_{max} changed from positive to negative on FDG-PET/CT is shown in Table

Table I. *Patient backgrounds and pathological findings.*

	Value
Cases, n	100
Age, median (range), years	65 (43-77)
Gender, n (%)	
Male	86 (86%)
Female	14 (14%)
Tumor location, n (%)	
Upper	19 (19%)
Middle	49 (49%)
Lower, abdominal	32 (32%)
cT, n (%)	
T1b	5 (5%)
T2	8 (8%)
T3	86 (86%)
T4	1 (1%)
cN, n (%)	
Negative	8 (8%)
Positive	92 (92%)
Involved lymph nodes, median (range), n	2 (0-7)
cM, n(%)	
M0	87 (87%)
M1 (distant lymph nodes)	13 (13%)
cStage, n (%)	
IIA	8 (8%)
IIB	12 (12%)
IIIA	38 (38%)
IIIB	27 (27%)
IIIC	2 (2%)
IV	13 (13%)
pT, n (%)	
T0	32 (32%)
T1	17 (17%)
T2	11 (11%)
T3	37 (37%)
T4	3 (3%)
pN, n (%)	
N0	58 (58%)
N1	25 (25%)
N2	16 (16%)
N3	1 (1%)
pCR both tumor and lymph nodes, n (%)	25 (25%)
Histological CRT response, n (%)	
Grade 1	26 (26%)
Grade 2	42 (42%)
Grade 3	32 (32%)

CRT: Chemoradiotherapy, pCR: pathological complete response.

Table II. *Neoadjuvant chemoradiotherapy (NACRT) and adverse events.*

	Value
Treatment duration, median (range), days	37 (11-62)
Chemotherapy, n (%)	
5-FU + cisplatin	21 (21%)
5-FU + nedaplatin	79 (79%)
Radiotherapy, n (%)	
40 Gy	97 (97%)
<40 Gy	3 (3%)
Treatment, n (%)	
Complete	85 (85%)
Incomplete	15 (15%)
Reason for incomplete NACRT, n (%)	
Bone marrow suppression	8 (8%)
Hyponatremia	2 (2%)
Renal dysfunction	1 (1%)
Sepsis	1 (1%)
Gastric ulcer	1 (1%)
Osteomyelitis of the mandible	1 (1%)
Patient's wishes	1 (1%)
Adversed effect (grade 3-4), n (%)	
White blood cell count decreased	49 (49%)
Anemia	4 (4%)
Platelet count decreased	3 (3%)
Hyponatremia	9 (9%)

5-FU: 5-Fluorouracil.

III. After NACRT, 38% (29/76) of patients had changed from positive to negative for tumors on FDG-PET/CT. Eighty-three percent (43/52) of patients previously positive for lymph node involvement were negative on FDG-PET/CT.

The surgery and surgical complications are shown in Table IV. Postoperative complications included anastomotic leakage (CD >I) in 10 (10%) patients, recurrent nerve palsy (CD >I) in 35 (35%) patients, chylothorax (CD >I) in 4 (4%) patients, pneumonia (CD > III) in 18 (18%) patients, and Sepsis after surgery in 2 (2%) patients). The median hospital stay was 26.5 (range=16-168) days. A patient died in the hospital on 169 days after surgery by multi organ failures consist of sepsis (fungus), renal failure, acute respiratory distress syndrome and encephalitis.

The pathological findings for patients receiving NACRT followed by esophagectomy are shown in Table I. Among the 100 patients, 32 (32%) were pT0, 58 (58%) were pN0, and 25 (25%) were pCR for both the tumor and lymph nodes. The histological responses to NACRT in the tumor were grade 3 in 32 (32%), grade 2 in 42 (42%), and grade 1 in 26 (26%) patients.

There was a significant relationship between the change from positive to negative findings for tumors on FDG-PET/CT and pCR (p=0.0173) (Table V). However, there was no relationship between the change in the FDG-PET/CT result for lymph node involvement and pCR (p>0.999).

Discussion

In this study, we demonstrated that transthoracic esophagectomy with Japanese-style extended 3-field lymph node dissection after NACRT (40 Gy) is safe, without

Table III. *Fraction of patients in whom the SUV_{max} changed from positive to negative on [^{18}F]-fluorodeoxyglucose positron-emission tomography/computed tomography (FDG-PET/CT).*

Group	n	%
Evaluated with FDG-PET/CT before NACRT	91	91%
Evaluated with FDG-PET/CT before and after NACRT	76	76%
Tumor		
Positive on FDG-PET/CT before treatment	91/91	100%
Evaluated with FDG-PET/CT after NACRT among the PET-positive patients, n	76	
Changed from positive to negative after NACRT	29/76	38%
Remained positive after NACRT	47/76	62%
Lymph nodes		
Positive on FDG-PET/CT before treatment	60/91	66%
Negative on FDG-PET/CT before treatment	31/91	34%
Evaluated with FDG-PET/CT after NACRT among the PET-positive patients, n	52	
Changed from positive to negative after NACRT	43/52	83%
Remained positive after NACRT	9/52	17%

NACRT: Neoadjuvant chemoradiotherapy.

increasing serious surgical complications. The local control by NACRT was strong, with 74% of patients with cStage II-IV disease experiencing grade 2-3 pathological response in the tumor and 25% achieving pCR in both tumor and lymph nodes. For tumors, the change from positive to negative on FDG-PET/CT was significantly positively associated with pCR.

The JCOG 9907 study for cStage II-III TESCC brought the standard treatment strategy of NAC with cisplatin and 5-FU plus esophagectomy to Japan (10). However, the response rate associated with this regimen was less than 40%, and at least 25% of patients experienced locoregional recurrence. Moreover, subgroup analysis revealed no survival benefit for patients with T3 or cStage III tumors; more powerful neoadjuvant treatment was necessary for such cancer. Thus, the JCOG 1109 study, a three-arm phase III trial of neoadjuvant 5-FU plus cisplatin *vs*. 5-FU with cisplatin and docetaxel *vs*. 5-FU plus cisplatin and 41.4 Gy radiation was begun (16).

A large-scale meta-analysis that included the CROSS trial (17) demonstrated the advantage of NACRT plus esophagectomy for patients with resectable esophageal cancer (18). In the CROSS trial, pCR in both the tumor and lymph nodes was achieved in 49% of patients with TESCC or esophago-gastric junctional squamous cell carcinoma. In the latest randomized controlled trial to compare NAC with NACRT for thoracic esophageal cancer or esophago-gastric junctional cancer, subgroup analysis revealed that NACRT resulted in a higher pCR rate among patients with squamous cell carcinoma (42%) (19). The pCR rate of 49% in the CROSS trial is much higher than our rate of 25%. Our study included patients with more advanced cancer, as 80% had cStage III-IV, 92% had clinical lymph node metastases, and all were positive for tumors on PET/CT. On the other hand, Tong *et al*. reported that 31% of patients achieved pCR among 175 patients recruited in Hong Kong (8). They also showed that male gender, a high percentage of residual viable cells, and positive nodal status were independent predictors of poor prognosis in a Cox regression analysis.

The most common adverse event after NACRT in our study was bone marrow suppression (grade 2-3), which occurred in more than 50% of patients. More severe adverse events did not occur. Hyponatremia occurred in nine patients, but this also occurred during chemotherapy with cisplatin/nedaplatin alone due to overhydration. Does NACRT result in more morbidity and mortality after esophagectomy, and does NACRT make esophagectomy technically more difficult? The higher rates of recurrent laryngeal nerve palsy and pulmonary complications are a concern. In our series, the occurrence rate for recurrent nerve palsy was high (35%). Radiotherapy may result in more fibrosis with obscured tissue planes. Difficulty in dissecting the tumor from its bed was evident, as was difficulty in the lymphadenectomy around the recurrent laryngeal nerves, which increased vocal cord palsy rates. In the CROSS trial, however, the complication and mortality rates among patients treated with NACRT plus esophagectomy did not differ from those for patients treated with surgery alone. Depending on the location of the tumor and irradiated field (remnant esophagus or the proximal stomach), and the timing of the surgery, the occurrence rates for anastomotic leak, recurrent nerve palsy and/or pulmonary complications appear to vary widely.

NACRT reportedly damages the left ventricle, as radiation therapy inevitably irradiates the heart (20). Although one patient in our study died 31 months after their initial treatment, possibly due to a cardiac event, no other patients

Table IV. *Surgery and surgical complications*.

	Value
Interval between NACRT and esophagectomy, median (range), days	38.5 (21-95)
Surgery, n (%)	
Open thoracotomy	77 (77%)
Thoracoscopic	17 (17%)
Robot-assisted thoracoscopic	6 (6%)
Operation time, median (range), min	554 (386-928)
Blood loss, median (range), ml	560.5 (115-3366)
Reconstruction, n (%)	
Gastric tube	90 (90%)
Pedicled colon	10 (10%)
Number of dissected lymph nodes, median (range)	50 (19-97)
Complications, n (%)	
Anastomotic leak (CD >I)	10 (10%)
Recurrent nerve palsy (CD >I)	35 (35%)
Chylothorax (CD >I)	4 (4%)
Pneumonia (CD >III)	18 (18%)
Sepsis	2 (2%)
Hospital stay, median (range), days	26.5 (16-168)
Hospital death, n (%)	1 (1%)*

NACRT: Neoadjuvant chemoradiotherapy, CD: Clavien–Dindo classification. *Died 168 days after surgery due to multiple organ failure.

Table V. *Relationship between the change from positive to negative findings on [^{18}F]-fluorodeoxyglucose positron-emission tomography/computed tomography (FDG-PET/CT) and pathological complete response (pCR).*

Tissue	pCR, n	pNon-CR, n	*p*-Value
Tumor			
Changed to negative on FDG-PET/CT	13	16	0.0173*
Remained positive on FDG-PET/CT	7	33	
Lymph nodes			
Changed to negative on FDG-PET/CT	14	29	>0.999
Remained positive on FDG-PET/CT	3	6	

*Significant difference.

experienced heart trouble. Restrictive ventilatory impairment that necessitated ventilator support occurred as a late stage (more than 1 year after surgery) complication in three patients. In two of these patients, anastomotic leakage with mediastinitis necessitated re-operation. In the third patient, liver metastasis was treated with intensity-modulated radiation therapy, after which the patient suffered restrictive ventilatory impairment. Although we cannot precisely define the factors that led to restrictive ventilatory impairment, it appears to be related to the aforementioned complications. Postoperative complications and toxicity in patients undergoing NAC is also reportedly associated with skeletal muscle loss (21). We found that NACRT led to loss of skeletal muscle volume, but NACRT did not reduce skeletal muscle volume any more than did NAC (22).

The most suitable interval between NACRT and surgery is not yet well defined. In a meta-analysis published in 2015, intervals greater than the standard 7-8 weeks did not increase the pCR rate, but were disadvantageous for long-term survival (23). Shapiro *et al*. (24) and Shaikh *et al*. (25) reported that a prolonged interval between NACRT and surgery increased the probability of a pCR, but was associated with a slightly higher likelihood of postoperative complications, although disease-free or overall survival were unaffected. At present, we set the interval between NACRT and surgery to be within 8 weeks. Postoperative complications and toxicity in patients undergoing NAC are also reportedly associated with skeletal muscle loss (26).

FDG-PET/CT evaluation was useful for predicting pCR among patients who received NACRT. The rate of change from positive to negative findings on FDG-PET/CT after NACRT was 38% for the main tumor and 83% for lymph nodes. We discovered that the change from positive to negative finding for tumors on FDG-PET/CT were significantly associated with pCR. Recently, we reported that the rate of decrease of the value of SUV_{max} in the tumor on FDG-PET/CT is a valuable predictor of survival (12). Hamai *et al*. also showed that the optimal cutoff for SUV_{max} is 2.7 and that the rate of decrease predictive of a pCR is 75% (27). Individual tumors can exhibit widely differing susceptibilities to chemotherapy and radiotherapy, with some patients showing no response or experiencing adverse effects (28, 29). Consequently, identification of reliable biomarkers of chemoradiosensitivity that could be evaluated before treatment would be highly desirable. Until then, we will use FDG-PET/CT as a method for predicting prognosis in patients treated with NACRT plus surgery, but imaging will be evaluated only after treatment is administered.

In conclusion, we found that transthoracic esophagectomy with Japanese-style extended 3-field lymph node dissection after NACRT is safe. The efficacy of NACRT is strong, with a 74% grade 2-3 pathological response and 25% pCR for both the tumor and lymph nodes.

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