Received: 9 February 2023 | Revised: 20 May 2023 | Accepted: 28 May 2023

DOI: 10.1002/ags3.12706

AGSurg Annals of Gastroenterological Surgery Open Access WILEY

ORIGINAL ARTICLE

Preoperative neoadjuvant chemoradiotherapy provides borderline resectable thoracic esophageal cancer with equivalent treatment results as clinically T3 thoracic esophageal cancer

Akiyuki Wakita[1,2] | Satoru Motoyama[3] | Yusuke Sato[1,2] | Yushi Nagaki[1,2] | Hiromu Fujita[1,2] | Kohei Kemuriyama[1,2] | Kenjiro Hayashi[1,2] | Kazuhiro Imai[2] | Hiroshi Nanjo[4] | Yoshihiro Minamiya[1,2]

[1]Division of Esophageal Surgery, Akita University Hospital, Akita, Japan

[2]Department of Thoracic Surgery, Akita University Graduate School of Medicine, Akita, Japan

[3]Department of Gastroenterological Surgery, Japanese Red Cross Akita Hospital, Akita, Japan

[4]Division of Clinical Pathology, Akita University Hospital, Akita, Japan

Correspondence
Akiyuki Wakita, Department of Thoracic Surgery, Akita University Graduate School of Medicine, 1-1-1 Hondo, Akita, 010-8543, Japan.
Email: wakita@gipc.akita-u.ac.jp

Abstract

Aim: Because the optimal treatment strategy for borderline resectable (cT3br) thoracic esophageal cancer patients remains unclear, it is of great interest whether preoperative neoadjuvant therapy for cT3br could achieve results comparable to those seen with resectable T3 cancer (cT3r). We speculated that preoperative neoadjuvant chemoradiotherapy (NACRT) would be particularly effective in cT3br thoracic esophageal cancer patients and compared to cT3br and cT3r.

Methods: Of 186 cT3 thoracic esophageal cancer patients treated with intended NACRT, 162 received radical esophagectomy. More than 97% were squamous cell carcinomas. Patients were partitioned into two groups according to whether invasion of adjacent organs was suspected (cT3br and cT3r). Treatment outcomes and survival were analyzed.

Results: Sixty-eight patients (36.6%) were classified as cT3br and 118 (63.4%) as cT3r. The cT3br group had significantly more tumors in the upper and middle mediastinum ($p < 0.0001$) and more cases with cM1 (lymph node) ($p = 0.0104$) than the cT3r group. In addition, the cT3br patients receiving esophagectomy exhibited a significantly lower pathological complete response rate than the cT3r patients ($p = 0.0374$). However, the R0 resection rate did not differ between the cT3br and cT3r patients ($p = 0.0978$), and the two groups treated with intended NACRT had similar 5-year overall (OS) and disease-specific survival (DSS) ($p = 0.3831$ and $p = 0.9020$). In addition, the incidence and patterns of recurrence did not differ between the cT3br and cT3r patients receiving esophagectomy ($p = 0.8109$ and $p = 0.3128$).

Conclusions: Preoperative neoadjuvant chemoradiotherapy appears to be a promising treatment for patients with borderline resectable thoracic esophageal squamous cell carcinoma.

KEYWORDS
borderline resectable esophageal cancer, pathological complete response, preoperative neoadjuvant chemoradiotherapy, survival

1 | INTRODUCTION

Thoracic esophageal squamous cell carcinoma (ESCC) is an aggressive upper gastrointestinal malignancy characterized by rapid progression and a poor prognosis.[1–3] This is in part because lymph node metastasis widely distributes from the neck to the abdomen. However, although surgical resection is the mainstay of treatment for locally advanced esophageal cancer, the prognosis after monotherapy remains poor. Therefore, locally advanced esophageal cancer also requires perioperative adjuvant chemotherapy and radiotherapy to improve survival.[4–12] In Western countries and China, preoperative neoadjuvant chemoradiotherapy (NACRT) is regarded as the standard treatment for locally advanced esophageal cancer.[8,9]

We have applied preoperative neoadjuvant chemoradiotherapy (NACRT) followed by esophagectomy for cStage II-IV thoracic ESCC with tumors greater than cT3 or with lymph node involvement.[13,14] NACRT exerts a substantial antitumor effect, with grade 2–3 pathological responses of the cancer in 75% of eligible patients and a pathological complete response (pCR) in both the tumor and lymph nodes in 25% of eligible patients.[13,14] The recent JCOG1109 trial comparing preoperative neoadjuvant chemotherapy with cisplatin plus 5-fluorouracil (CF), docetaxel, cisplatin plus 5-fluorouracil (DCF), and preoperative neoadjuvant chemoradiotherapy with cisplatin, 5-fluorouracil (CF-RT) demonstrated preoperative neoadjuvant DCF as Japan's standard preoperative treatment for locally advanced thoracic ESCC.[15] [Correction added on 14 July 2023, after first online publication: the acronyms CF, DCF and CF-RT have been spelled out on first use]. As for DCF therapy, there were more cases than CF-RT in which treatment could not be completed due to tumor growth. Furthermore, the JCOG1109 trial did not include cT3br cases.[15]

Several vital organs surround the esophagus within the mediastinum, including the trachea, aorta, and pulmonary veins. This makes developing an effective treatment strategy for thoracic esophageal cancer challenging. Preoperative neoadjuvant treatments followed by esophagectomy are applied for resectable locally advanced esophageal cancer, while definitive chemoradiotherapy is the primary treatment for cases with unresectable invasion of adjacent organs.[16,17] Unfortunately, it is often difficult to accurately determine whether a tumor can be completely resected, and an optimal, comprehensive treatment strategy for borderline resectable cancers (i.e., those with probable organ invasion) remains unclear. The 12th edition of the Japanese Classification of Esophageal Cancer, published in 2022, newly describes a classification of cT3br cancer.[18] Preoperative DCF therapy is not always appropriate for this cT3br thoracic ESCC, and NACRT would also be a treatment option.[19]

We conducted the present study by dividing the patients into cT3br and cT3r following the new classification and comparing their outcomes retrospectively to clarify the efficacy of NACRT followed by esophagectomy for patients with tumors suspected of invading adjacent organs.

2 | METHODS

2.1 | Patients

Between 2010 and 2021, we administered NACRT to 186 Japanese patients with locally advanced thoracic ESCC at Akita University Hospital. Their primary tumor was diagnosed as cT3, and lymph node metastasis was limited to regional lymph nodes, including supraclavicular lymph nodes. The CONSORT diagram for patients receiving NACRT is shown in Figure 1. Among the 186 patients, we determined 68 (36.6%) to be cT3br and 118 (63.4%) to be cT3r. Twenty-four patients were excluded from the study after NACRT, and the remaining 58 cT3br patients and 104 cT3r patients received radical esophagectomy with 2–3 regional lymph node dissection (Figure 1).

A multidisciplinary tumor board for esophageal cancer composed of gastroenterologists, surgeons, radiologists, oncologists, and pharmacists determined clinical-stage and treatment strategies according to the TNM classification. The disease was classified according to the Japanese Classification of Esophageal Cancer (11th edition),[20,21] and the International Union Against Cancer tumor-node-metastasis (TNM) Classification of Malignant Tumors (7th edition).[22] All patients fulfilled the Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0–1. The Ethics Committee of Akita University Graduate School of Medicine approved this study (No. 2617). Informed consent was obtained from all patients for using their information in this article. All experiments were performed in accordance with the Helsinki Declaration.

2.2 | Evaluation of tumor depth and definition of borderline resectable tumor

Primary tumor depth was classified according to the degree of invasion using the Japanese Classification of Esophageal Cancer (11th edition).[20,21] T3 is defined as tumors invading adventitia and not invading adjacent structures. Within T3, we further classified primary tumors into borderline resectable tumors (cT3br) and resectable tumors (cT3r). Borderline resectable is defined as no T4 findings on imaging studies; if T4 is determined, non-operative treatment is performed.

We defined cT3br thoracic ESCC in accordance with the Japanese Classification of Esophageal Cancer (12th edition).[18] The representative cases of cT3br and cT3r thoracic ESCC are shown in Figure 2. A diagnosis of tracheal or bronchial invasion was made when there

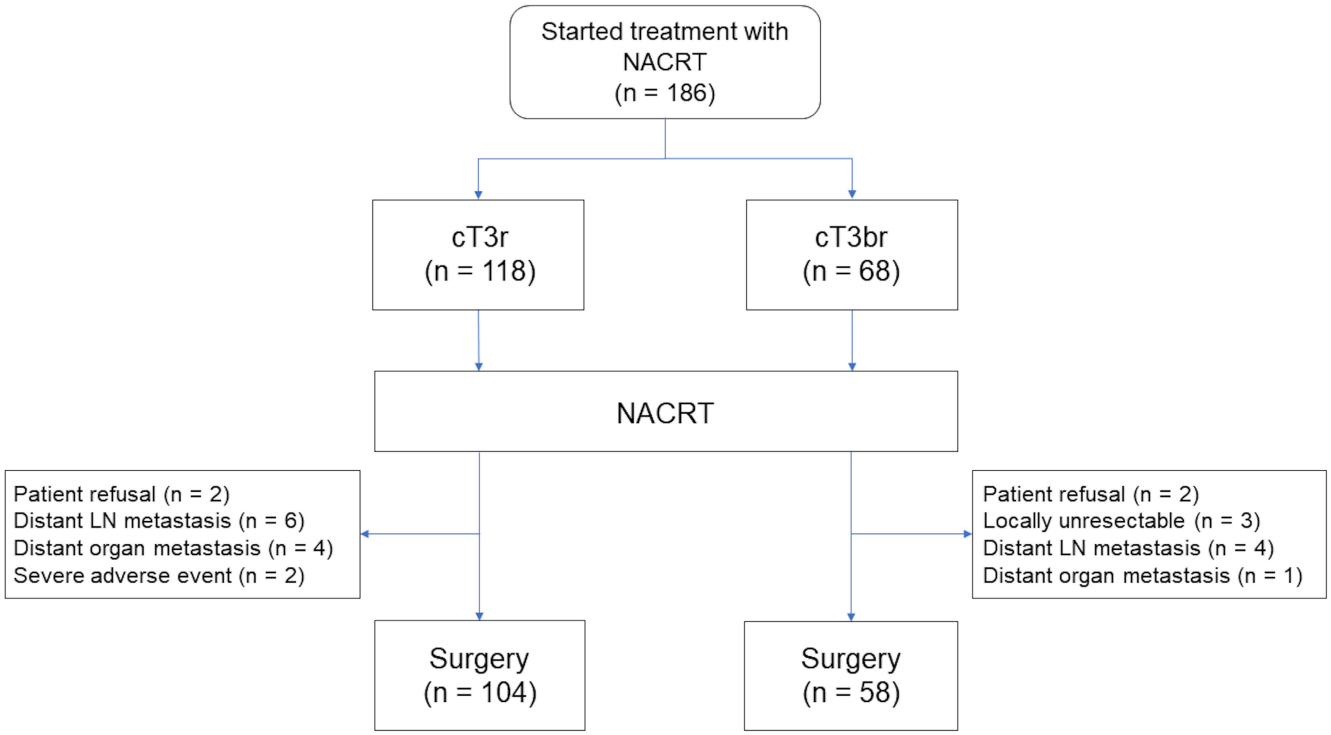

FIGURE 1 CONSORT diagram for cT3 thoracic ESCC patients undergoing NACRT.

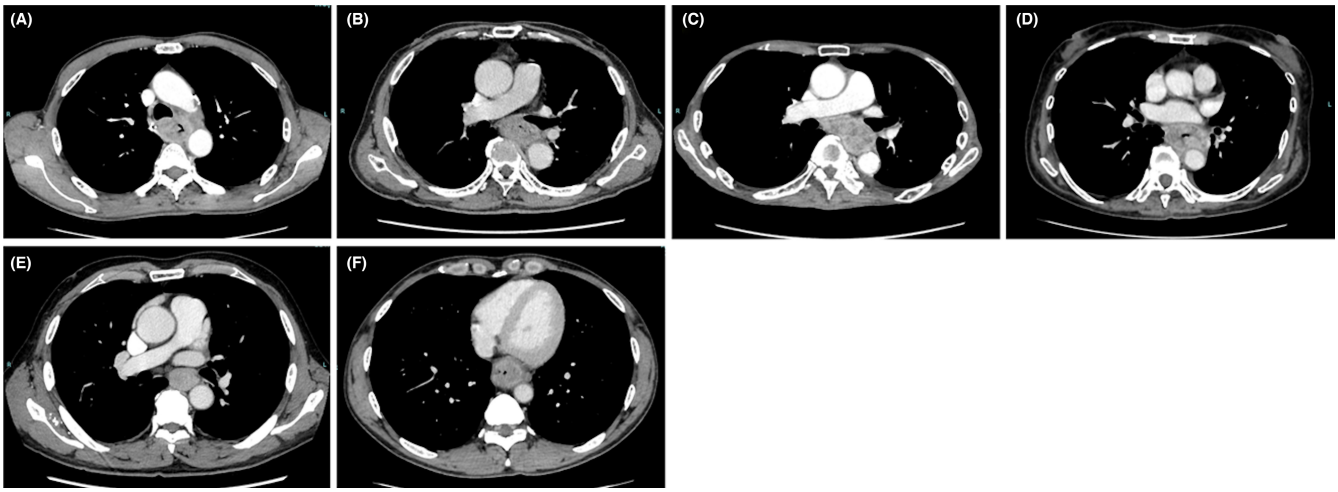

FIGURE 2 Representative CT findings for patients with (A–D): borderline resectable (cT3br) or (E, F): resectable (cT3r) esophageal cancers.

was an irregular boundary between the primary tumor or a metastatic lymph node and the airway, accompanied by compression, displacement, and luminal narrowing on computed tomography (CT). In addition, irregularity of the airway lumen on bronchoscopy was considered indicative of invasion.[18] A diagnosis of aortic invasion was made when the primary tumor or a metastatic lymph node was in extensive contact with the aorta (contact length of 20 mm or more with a contact angle of 90°–110°; or a contact length of 10 mm or more with a contact angle of over 110°) or when there was deformation or irregularity of the aortic wall. A lesion that disfigured and encircled the aorta was also considered to have invaded the vessel.[18] We defined cT3br as tumors in which organ invasion could not be determined with certainty.

2.3 | Preoperative neoadjuvant chemoradiotherapy

Chemotherapy using cisplatin and 5-fluorouracil was conducted following the JCOG9204[23] and JCOG9907[24] trials. Briefly, 80 mg/m^2 cisplatin was administrated on day 1, and 800 mg/m^2

5-fluorouracil was administered as a continuous infusion from day 1 to day 5. This protocol was repeated twice with 3- to 5-week intervals in between.

High-energy X-rays (10 MV) were used, and all patients underwent three-dimensional radiotherapy. The gross tumor volume (GTV) was set both in the primary tumor and metastatic lymph nodes. The clinical target volume (CTV) was set with an approximately 1 cm margin around the GTV and the planning target volume (PTV) with a 5 mm margin around the CTV. Concurrent radiotherapy was administered 5 days a week at 1.8 Gy/day for a total radiation dose of 41.4 Gy in 23 fractions.[14] Patients in the cT3br group whose tumors were deemed unresectable after 41.4 Gy were directly assigned for definitive CRT.

2.4 | Surgery

The patients underwent right transthoracic or thoracoscopic (including robot-assisted thoracoscopic) esophagectomy with two- or three-field lymph node dissection. Three-field lymph node dissection entails dissection of the mediastinal (involving the periesophageal region and areas around the trachea and bilateral main bronchus), abdominal (involving the perigastric region and areas around the celiac axis), and cervical (involving the bilateral periesophageal region and supraclavicular region) nodes. Cervical lymph node dissection was omitted for elderly patients aged 75 years or older and patients with physical disadvantages such as respiratory dysfunction. We commonly perform reconstruction by inserting a gastric tube via the posterior mediastinal or the retrosternal route.[13,14] All harvested lymph nodes were sectioned, stained with hematoxylin and eosin, and examined by experienced pathologists.

2.5 | Follow-up

All patients were followed every 2 months for 5 years after surgery. During those periods, the patients underwent physical examination, blood tests (including for tumor markers), chest X-rays, panendoscopy, and neck/chest/abdominal computed tomography. Computed tomography was carried out every 4 months for the first 2 years and at least yearly thereafter. Panendoscopy was performed when there were symptoms of local recurrence; otherwise, panendoscopy was performed once annually.

2.6 | Pathological response

The pathological response was evaluated according to the Pathological criteria for the effects of radiation and/or chemotherapy described in the Japanese Classification of Esophageal Cancer (11th edition).[20,21] Grade 0, no recognized cytological or histological therapeutic effect; Grade 1, slightly effective with apparently viable cancer cells accounting for at least one-third of the tumor tissue; Grade 2, moderately effective with viable cancer cells accounting for less than one-third of the tumor tissue; Grade 3, markedly effective with no evidence of viable cancer cells. A pathologically complete response was determined only when there was no evidence of viable cells in the primary lesion and lymph nodes.

2.7 | Statistical analysis

Patients were divided into two groups according to the clinical depth of their tumors (cT3br or cT3r). The median and frequency were used to summarize the characteristics of the patients in those two groups. The Wilcoxon test (for continuous variables), Pearson's chi-square test, or Fisher's exact probability test (for categorical variables) was used to evaluate differences between groups. OS was determined from the surgery date to the patient's death or the last clinical attendance. DSS was measured as the length of time from the surgery date to the patient's death from esophageal cancer or the last clinical contact. Survival curves were constructed using the Kaplan–Meier method, and differences between curves were analyzed using the log-rank test. All analyses were performed using JMP 12 (SAS Institute Inc.) and yielded two-sided p-values. Values of $p<0.05$ were considered statistically significant.

3 | RESULTS

3.1 | Patients treated with intended preoperative neoadjuvant chemoradiotherapy

We treated 68 cT3br and 118 cT3r thoracic esophageal cancer patients with NACRT. Table 1 summarizes their clinicopathological features separately. The median age at NACRT was 64.5 years (range 46–77) in the cT3br group and 66 years (range 43–76) in the cT3r group. Squamous cell carcinoma (SCC) histological type (cT3br: 97.0% vs. cT3r: 97.5%; $p=0.5076$) was the predominant cancer in both groups. Tumor location significantly differed between the two groups, with more tumors in the upper and middle mediastinum in the cT3br group and more in the lower mediastinum in the cT3r group ($p<0.0001$). Among the 68 cT3br patients, the borderline resectable site was the primary tumor in 63 (92.6%) patients and lymph nodes in six (8.8%) patients. In 54 (79.4%) patients, findings were suggestive of tracheal invasion, while in 35 (51.5%) patients, findings were suggestive of aortic invasion. With respect to clinical staging, the cT3br group had significantly more cases with supraclavicular lymph node metastasis (cM1-lymph node) (cT3br: 19.1% vs. cT3r: 6.8%; $p=0.0104$). Of the 68 cT3br patients, two with a complete response refused surgery, three had locally unresectable tumors, four developed distant lymph node metastasis, and one developed distant organ metastasis (Figure 1). Of the 118 cT3r patients, two with a complete response refused surgery, six developed distant lymph node metastasis, and four developed distant organ metastasis. In addition, two cT3r patients did not receive their planned radical surgery due to severe adverse events (renal failure and sepsis) (Figure 1).

TABLE 1 Clinical and pathological characteristics of cT3br and cT3r thoracic esophageal cancer patients treated with intended NACRT.

Variable	cT3br ($n=68$)	cT3r ($n=118$)	p
Age, median (range)	64.5 (46–77)	66 (43–76)	0.9492
Gender			
Male	58 (85.3%)	105 (89.0%)	0.4617
Female	10 (14.7%)	13 (11.0%)	
Histology			
SCC	66 (97.0%)	115 (97.5%)	0.5076
Basaloid SCC	1 (1.5%)	2 (1.7%)	
Adeno-squamous	0	1 (0.8%)	
Carcinosarcoma	1 (1.5%)	0	
Tumor location			
Upper	23 (33.8%)	16 (13.6%)	**<0.0001**
Middle	42 (61.8%)	45 (38.1%)	
Lower	3 (4.4%)	57 (48.3%)	
Tumor site suspected of invasion			
Main tumor	63 (92.6%)	NA	
Lymph node	6 (8.8%)	NA	
Organ suspected of invasion			
Trachea	54 (79.4%)	NA	
Aorta	35 (51.5%)	NA	
Pericardia	2 (2.9%)	NA	
Liver	1 (1.5%)	NA	
Clinical N stage (Japanese classification 11th)			
0	6 (8.8%)	19 (16.1%)	0.3213
1	20 (29.4%)	41 (34.7%)	
2	29 (42.7%)	40 (33.9%)	
3	11 (16.2%)	12 (10.2%)	
4	2 (2.9%)	6 (5.1%)	
Clinical N stage (UICC 7th)			
0	6 (8.8%)	20 (17.0%)	0.2932
1	41 (60.3%)	62 (52.5%)	
2	21 (30.9%)	34 (28.8%)	
3	0	2 (1.7%)	
Clinical M1 (Lymph node; UICC 7th)			
0	55 (80.9%)	110 (93.2%)	**0.0104**
1	13 (19.1%)	8 (6.8%)	
Clinical Stage (Japanese classification 11th)			
2	6 (8.8%)	18 (15.3%)	0.5859
3	60 (88.2%)	95 (80.5%)	
4a	2 (3.0%)	5 (4.2%)	
Clinical stage (UICC 7th)			
IIA	6 (8.8%)	19 (16.1%)	0.0640
IIIA	33 (48.5%)	57 (48.3%)	
IIIB	16 (23.5%)	32 (27.1%)	
IIIC	0	2 (1.7%)	
IV	13 (19.2%)	8 (6.8%)	
Reasons to cancel esophagectomy			
Patient's refusal	2 (2.9%)	2 (1.7%)	0.1514
Locally unresectable	3 (4.4%)	0	
Distant lymph node metastasis	4 (5.9%)	6 (5.1%)	
Distant organ metastasis	1 (1.5%)	4 (3.4%)	
Severe adverse event	0	2 (1.7%)	
Outcome			
Alive	38 (55.9%)	68 (57.6%)	0.9565
Deceased from EC	21 (30.9%)	34 (28.8%)	
Deceased from other diseases	9 (13.2%)	16 (13.6%)	

Note: Statistically significant values ($p<0.05$) are given in bold.
Abbreviations: EC, esophageal cancer; SCC, squamous cell carcinoma.

3.2 | Effects of tumor depth on survival

Figure 3A,B show the Kaplan–Meier analysis of the cT3br and cT3r patients treated with intended NACRT. No significant difference in 5-year OS (cT3br: 56.8% vs. cT3r: 50.4%; $p=0.3831$) or 5-year DSS (cT3br: 63.3% vs. cT3r: 63.1%; $p=0.9020$) was detected between the two groups. We also analyzed the cT3br patients' survival taking into consideration the organs suspected of being invaded. The 5-year OS was 52.5% for patients with suspected tracheal invasion and 64.8% for patients with suspected aortic invasion (data not shown).

The incidence of recurrence and recurrence patterns after esophagectomy of the cT3br patients did not significantly differ from those of the cT3r patients ($p=0.8109$ and $p=0.3128$). Nineteen cT3br patients (32.8%) relapsed. There was locoregional recurrence in seven patients (12.1%), distant lymph node recurrence in one patient (1.7%), and distant organ recurrence in 11 patients (19.0%). Of the 19 relapsed patients, distant organ recurrence accounted for 57.9% of recurrences, with lung metastasis being the most frequent (Table 2). Length of survival after recurrence was 13.6 months (1.6–46.0 months) for the cT3br patients versus 11.0 months (1.7–51.8 months) for the cT3r patients (data not shown; $p=0.6220$).

3.3 | Association between tumor depth and surgical outcomes

Table 2 summarizes the surgical outcomes of the cT3br and cT3r patients. The operation time of the cT3br patients was shorter than the cT3r patients (cT3br: 566.5 min vs. cT3r: 611 min; $p=0.0108$), but there was no difference in blood loss volume between the cT3br and cT3r patients (cT3br: 495.5 mL vs. cT3r: 479.5 mL; $p=0.5798$).

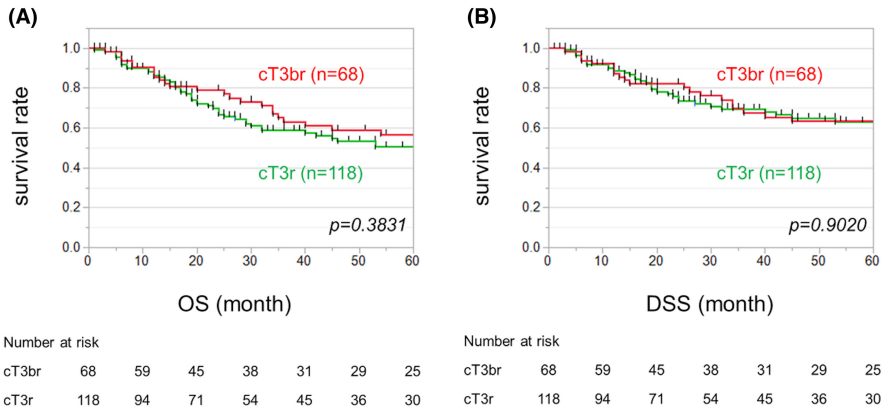

FIGURE 3 Kaplan–Meier curves assessing (A): 5-year overall survival (OS) and (B): 5-year disease-specific survival (DSS) among patients with borderline resectable (cT3br) and resectable (cT3r) tumors treated with intended NACRT. No significant differences were seen between the two groups.

Although the cT3br patients had significantly more thoracotomy cases ($p=0.0003$), there were no significant differences in the dissection field, the number of harvested lymph nodes, or the incidence of postoperative complications between the cT3br and cT3r patients. The final pathological results revealed the cT3br patients to have significantly greater tumor depth ($p=0.0294$) and more organ invasion (cT3br: 10.4% vs. cT3r: 2.0%; $p=0.0408$). Three patients exhibited invasion of the trachea, two had invasion of the lung, and one had invasion of the pericardium. Two cT3r patients exhibited organ invasion: one with pericardium invasion and another with diaphragm invasion. The R0 resection rate did not differ between the cT3br and cT3r patients (cT3br: 94.8% vs. cT3r: 99.0%; $p=0.0978$), though the pCR rate of the cT3br patients was significantly lower (cT3br: 12.1% vs. cT3r: 26.0%; $p=0.0374$). Three of the cT3br patients (5.2%) and one cT3r patient (1.0%) retained residual tumors (R1-2 resection).

4 | DISCUSSION

This study assessed the outcomes of cT3br thoracic ESCC patients treated with NACRT followed by esophagectomy. Significantly more patients were diagnosed with cM1 (lymph node) in the cT3br group than in the cT3r group. Pathological examinations also showed that the pCR rate of cT3br patients was lower than that of cT3r patients. However, there was no significant difference in the incidence of residual tumors or survival rate between the cT3br and cT3r patients.

The phase III CROSS trial showed that NACRT significantly prolonged OS compared to surgery alone.[8] This result made NACRT the standard treatment for locally advanced esophageal cancer in Western countries. However, we are reluctant to apply the results of the CROSS trial to ESCC patients because the majority of patients in that trial had adenocarcinoma, and the chemotherapy regimens differed from those used in Japan. A phase III trial of thoracic ESCC in China also showed a survival benefit with significantly longer OS and DFS with NACRT versus surgery alone.[9] Furthermore, the NACRT group had a substantially better R0 resection rate and a higher pCR rate than the surgery alone group, indicating that NACRT has benefits for local control.[9]

The JCOG1109 trial was designed to identify the optimal preoperative treatment for locally advanced thoracic ESCC. The trial compared CF-RT and DCF to CF therapy and demonstrated that DCF therapy should be the standard neoadjuvant treatment for locally advanced cStage II-III thoracic ESCC patients. DCF therapy showed significant advantages over CF therapy for OS. Although the pCR rate was higher with CF-RT than the other treatments, survival rates with CF-RT failed to show a substantial difference versus CF therapy.[15] [Correction added on 14 July 2023, after first online publication: "…survival rates with CR-RT…" in the preceding sentence has been corrected to "…survival rates with CF-RT…"]. Interestingly, subgroup analysis showed an advantage of CF-RT therapy for upper mediastinal tumors.[15] Thus, CF-RT therapy with more robust local control is an option for upper mediastinal tumors with a high risk of invading adjacent organs. However, because that study did not examine cT3br cases, optimal treatment for borderline resectable esophageal cancer is yet to be established.

Previous reports on borderline resectable esophageal cancers analyzed limited populations undergoing esophagectomy. Ikeda and colleagues analyzed 37 potential or actual cT4 ESCC patients initially treated with CRT. Among them, 13 patients underwent esophagectomy, and R0 resection was achieved in 12 of those patients. Eight patients exhibited grade 2 histopathologic effect, while one patient achieved grade 3.[25] Suzuki and colleagues analyzed 50 borderline resectable ESCC patients initially treated with CRT. Among those patients, R0 resection was achieved in 44% (22/50), and 10% (5/50) achieved pCR.[26]

Our study compared cT3 thoracic esophageal cancer patients with (cT3br) and without (cT3r) suspicion of invasion of adjacent organs. Because our study focused on cT3 cases, the pCR rate is lower than that in the JCOG1109 trial. We should note that there was no difference in the R0 resection rate (cT3br: 94.8% vs. cT3r: 99.0%; $p=0.0978$) between the cT3br and cT3r patients, even though the cT3br patients had a significantly lower pCR rate than the cT3r patients (cT3br: 12.1% vs. cT3r: 26.0%; $p=0.0374$). In addition, the survival rate between the two groups treated with intended NACRT did not differ (5-year OS: $p=0.3831$ and 5-year DSS: $p=0.9020$). For eight (11.8%) cT3br patients treated with intended NACRT, esophagectomy had to be canceled due to disease progression. Moreover, among all cT3 patients scheduled for NACRT, 18 (9.7%) withdrew their planned treatment due to disease progression, which is comparable to the rate seen in the preoperative neoadjuvant DCF arm of JCOG1109.[15] These results

TABLE 2 Surgical outcomes among cT3br and cT3r thoracic esophageal cancer patients treated with NACRT followed by esophagectomy.

Variable	cT3br ($n=58$)	cT3r ($n=104$)	p
Operation time (min) median (range)	566.5 (418–928)	611 (386–902)	**0.0108**
Blood loss (mL) median (range)	495.5 (115–3217)	479.5 (86–3366)	0.5798
Thoracic procedure			
Thoracoscopic (including robot-assisted)	14 (24.1%)	56 (53.9%)	**0.0003**
Open	44 (75.9%)	48 (46.1%)	
Dissected fields			
Two-field	4 (6.9%)	10 (9.6%)	0.5549
Three-field	54 (93.1%)	94 (90.4%)	
Number of harvested LNs median (range)	50.5 (8–91)	50 (12–97)	0.6014
Anastomotic leakage			
Present	7 (12.1%)	15 (14.4%)	0.6750
Absent	51 (87.9%)	89 (85.6%)	
Recurrent laryngeal nerve palsy (CD ≧ 1)			
Present	19 (32.8%)	38 (36.5%)	0.6291
Absent	39 (67.2%)	66 (63.5%)	
Pneumonia			
Present	2 (3.4%)	4 (3.8%)	0.8977
Absent	56 (96.6%)	100 (96.2%)	
Chylothorax			
Present	1 (1.7%)	3 (2.9%)	0.6482
Absent	57 (98.3%)	101 (97.1%)	
Pathological T stage			
0	12 (20.7%)	34 (32.7%)	**0.0294**
1	6 (10.3%)	18 (17.3%)	
2	7 (12.0%)	17 (16.4%)	
3	27 (46.6%)	33 (31.7%)	
4a	3 (5.2%)	2 (1.9%)	
4b	3 (5.2%)	0	
Pathological organ invasion			
None	52 (89.6%)	102 (98.0%)	**0.0408**
Diaphragm	0	1 (1.0%)	
Lung	2 (3.5%)	0	
Pericardium	1 (1.7%)	1 (1.0%)	
Trachea	3 (5.2%)	0	
Pathological N Stage (Japanese classification 11th)			
0	26 (44.8%)	64 (61.5%)	0.3364
1	11 (19.0%)	15 (14.4%)	
2	17 (29.3%)	19 (18.3%)	
3	3 (5.2%)	4 (3.9%)	
4	1 (1.7%)	2 (1.9%)	
Pathological N stage (UICC 7th)			
0	28 (48.3%)	66 (63.4%)	0.1853
1	18 (31.0%)	27 (26.0%)	
2	10 (17.2%)	10 (9.6%)	
3	2 (3.5%)	1 (1.0%)	
Pathological M1 (Lymph node; UICC 7th)			
0	52 (89.7%)	98 (94.2%)	0.2864
1	6 (10.3%)	6 (5.8%)	
Pathological CR			
pCR	7 (12.1%)	27 (26.0%)	**0.0374**
Non-pCR	51 (87.9%)	77 (74.0%)	
Residual tumor			
R1-2	3 (5.2%)	1 (1.0%)	0.0978
R0	55 (94.8%)	103 (99.0%)	
Recurrence after surgery			
None	39 (67.2%)	68 (65.4%)	0.3128
Loco-regional	7 (12.1%)	6 (5.8%)	
Distant LN	1 (1.7%)	6 (5.8%)	
Distant organ	11 (19.0%)	24 (23.0%)	

Note: Statistically significant values ($p<0.05$) are given in bold.
Abbreviations: CD, Clavian–Dindo; LN, lymph node.

suggest that NACRT exerts sufficient local control even in cases where the tumors are suspected of invading adjacent organs and provides an opportunity for radical surgery. There was also no significant difference in the incidence of recurrence between the cT3br and cT3r patients. The treatment outcome for patients with cT3br thoracic ESCC may depend on whether or not R0 resection is achieved. Therefore, NACRT, which offers more substantial local control, should be the preferred treatment strategy for cT3br thoracic ESCC. Nineteen cT3br patients (32.8%) relapsed after esophagectomy, and 12 (20.7%) had a recurrence in distal lymph nodes or organs. Taking measures against distal lymph node and organ recurrences is indispensable, as the strength of NACRT as systemic treatment is inferior to that of DCF therapy. In past trials, nivolumab, a fully human monoclonal anti-programmed death 1 antibody, has shown efficacy in cases of previously treated advanced gastroesophageal adenocarcinoma or SCC, significantly prolonging survival compared to conventional chemotherapy.[27] Kelly and colleagues reported the survival benefit of postoperative adjuvant nivolumab therapy for locally advanced esophageal cancer and esophagogastric junction cancer treated with NACRT followed by esophagectomy. They also reported that the risk of distant recurrence or death was reduced by 26%, and prolonged distant metastasis-free survival was 10.7 months.[28] Based on their results, we believe that postoperative adjuvant nivolumab therapy for cT3br patients treated with NACRT will be an effective countermeasure against distant recurrence.

Nine patients (13.2%) in the cT3br group died from other diseases. In the FFCD9901 trial, postoperative mortality was three-fold higher among patients receiving NACRT than those receiving surgery alone, thus offering no survival benefit.[29] Similarly, von Dobeln and colleagues reported that NACRT lacks a survival benefit, despite providing a better tumor response than neoadjuvant chemotherapy.[30] It is necessary to devise ways to minimize the damage to

surrounding tissue caused by radiotherapy. It has been suggested that intensity-modulated radiotherapy can reduce the dose to normal tissues and thus reduce the incidences of lung- and heart-related complications and mortality as compared to conventional three-dimensional conformal radiotherapy.[31–33]

One limitation of this study is that it is a single-center, retrospective study with a relatively small population. In addition, the diagnostic criteria used to distinguish cT3br from cT3r are generally vague and subjective. There are also no data on preoperative neoadjuvant chemotherapy comparing cT3br and cT3r.

5 | CONCLUSION

Borderline resectable thoracic esophageal cancer (cT3br) treated with NACRT showed comparable R0 resection and survival rates, even though the pCR rate was lower than that achieved with resectable esophageal cancer (cT3r). Preoperative NACRT may still be a promising treatment for locally advanced thoracic esophageal squamous cell carcinoma with suspected invasion of adjacent organs.

AUTHOR CONTRIBUTIONS

Conception and design: AW; Acquisition of data: AW, SM, YS, YN, HF, KK, KH, KI, and HN; Analysis and interpretation of data: AW; Drafting of the manuscript: AW; Critical revision of the manuscript: SM, YS, and YM; Statistical analysis: AW, Study supervision: SM, YS, and YM. All authors listed have contributed substantially to the design, data collection and analysis, and manuscript editing.

FUNDING INFORMATION

This work was supported, in part, by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Science, Sports and the Japan Science and Technology Agency.

ETHICS STATEMENT

The protocol for this research has been approved by a suitably constituted Ethics Committee of the institution and it confirms to the provisions of the Declaration of Helsinki. Committee of Akita University Graduate School of Medicine, Approved No. 2617. Informed consent was obtained from all patients.
Approval of the research protocol: N/A.
Registry and the registration No. of the study/trial: N/A.
Animal studies: N/A.

CONFLICT OF INTEREST STATEMENT

All authors declare no actual or potential financial conflicts of interest.

ORCID

Akiyuki Wakita https://orcid.org/0000-0002-3446-6840
Yusuke Sato https://orcid.org/0000-0002-2729-7284

REFERENCES

1. Chen MF, Yang YH, Lai CH, Chen PC, Chen WC. Outcome of patients with esophageal cancer: a nationwide analysis. Ann Surg Oncol. 2013 Sep;20(9):3023–30.
2. Abnet CC, Arnold M, Wei WQ. Epidemiology of esophageal squamous cell carcinoma. Gastroenterology. 2018 Jan;154(2):360–73.
3. Watanabe M, Toh Y, Ishihara R, et al. Comprehensive registry of esophageal cancer in Japan, 2014. Esophagus. 2022;19(1):1–26.
4. Walsh TN, Noonan N, Hollywood D, Kelly A, Keeling N, Hennessy TP. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N Engl J Med. 1996;335(7):462–7.
5. Kelsen DP, Ginsberg R, Pajak TF, Sheahan DG, Gunderson L, Mortimer J, et al. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. N Engl J Med. 1998;339(27):1979–84.
6. Medical Research Council Oesophageal Cancer Working Group. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. Lancet. 2002;359(9319):1727–33.
7. Cunningham D, Allum WH, Stenning SP, et al. MAGIC trial participants. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355(1):11–20.
8. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366(22):2074–84.
9. Yang H, Liu H, Chen Y, et al. Neoadjuvant chemoradiotherapy followed by surgery versus surgery alone for locally advanced squamous cell carcinoma of the esophagus (NEOCRTEC5010): a phase III multicenter, randomized, open-label clinical trial. J Clin Oncol. 2018;36(27):2796–803.
10. Tanaka Y, Yoshida K, Suetsugu T, Imai T, Matsuhashi N, Yamaguchi K. Recent advancements in esophageal cancer treatment in Japan. Ann Gastroenterol Surg. 2018;2(4):253–65.
11. Mayanagi S, Irino T, Kawakubo H, Kitagawa Y. Neoadjuvant treatment strategy for locally advanced thoracic esophageal cancer. Ann Gastroenterol Surg. 2019;3(3):269–75.
12. Saeki H, Sohda M, Sakai M, Sano A, Shirabe K. Role of surgery in multidisciplinary treatment strategies for locally advanced esophageal squamous cell carcinoma. Ann Gastroenterol Surg. 2020;4(5):490–7.
13. Motoyama S, Sato Y, Sasaki T, Wakita A, Kawakita Y, Liu J, et al. Efficacy and safety of neoadjuvant chemoradiotherapy following esophagectomy with Japanese-style extended 3-field lymphadenectomy for thoracic esophageal cancer. Anticancer Res. 2017;37(10):5837–43.
14. Sato Y, Motoyama S, Wada Y, Wakita A, Kawakita Y, Nagaki Y, et al. Neoadjuvant chemoradiotherapy followed by esophagectomy with three-field lymph node dissection for thoracic esophageal squamous cell carcinoma patients with clinical stage III and with supraclavicular lymph node metastasis. Cancers (Basel). 2021;13(5):983.
15. Kato K, Ito Y, Daiko H, et al. A randomized controlled phase III trial comparing two chemotherapy regimen and chemoradiotherapy regimen as neoadjuvant treatment for locally advanced esophageal cancer, JCOG1109 NExT study. J Clin Oncol. 2022;40(4_suppl):238–8.
16. Ishida K, Ando N, Yamamoto S, Ide H, Shinoda M. Phase II study of cisplatin and 5-fluorouracil with concurrent radiotherapy in advanced squamous cell carcinoma of the esophagus: a Japan esophageal oncology group (JEOG)/Japan clinical oncology group trial (JCOG9516). Jpn J Clin Oncol. 2004;34(10):615–9.
17. Ochi M, Murakami Y, Nishibuchi I, Kubo K, Imano N, Takeuchi Y, et al. Long-term results of definitive chemoradiotherapy for unresectable locally advanced esophageal squamous cell carcinoma. J Radiat Res. 2021;62(1):142–8.

18. Japan Esophageal Society, editor. Japanese classification of esophageal cancer. 12th ed. Tokyo: Kanehara; 2022.
19. Japan Esophageal Society, editor. Guidelines for diagnosis and treatment of carcinoma of the esophagus 2022. Vol 2022. Tokyo: Kanehara; 2022.
20. Japan Esophageal Society. Japanese classification of esophageal cancer, 11th edition: part I. Esophagus. 2017;14(1):1–36.
21. Japan Esophageal Society. Japanese classification of esophageal cancer, 11th edition: part II and III. Esophagus. 2017;14(1):37–65.
22. Sobin LH, Gospodarowicz MK, Wittekind C, editors. TNM classification of malignant Tumours. International Union against Cancer. 7th ed. Oxford: Wiley-Blackwell; 2009 Skin Tumours.
23. Ando N, Iizuka T, Ide H, et al. Surgery plus chemotherapy compared with surgery alone for localized squamous cell carcinoma of the thoracic esophagus: a Japan clinical oncology group study—JCOG9204. J Clin Oncol. 2003;21(24):4592–6.
24. Ando N, Kato H, Igaki H, Shinoda M, Ozawa S, Shimizu H, et al. A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). Ann Surg Oncol. 2012;19(1):68–74.
25. Ikeda K, Ishida K, Sato N, Koeda K, Aoki K, Kimura Y, et al. Chemoradiotherapy followed by surgery for thoracic esophageal cancer potentially or actually involving adjacent organs. Dis Esophagus. 2001;14(3–4):197–201.
26. Suzuki T, Okamura A, Watanabe M, Mine S, Imamura Y, Asari T, et al. Neoadjuvant chemoradiotherapy with cisplatin plus fluorouracil for borderline Resectable esophageal squamous cell carcinoma. Ann Surg Oncol. 2020;27(5):1510–7.
27. Kato K, Cho BC, Takahashi M, Okada M, Lin CY, Chin K, et al. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2019;20(11):1506–17.
28. Kelly RJ, Ajani JA, Kuzdzal J, et al. Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer. N Engl J Med. 2021;384(13):1191–203.
29. Mariette C, Dahan L, Mornex F, Maillard E, Thomas PA, Meunier B, et al. Surgery alone versus chemoradiotherapy followed by surgery for stage I and II esophageal cancer: final analysis of randomized controlled phase III trial FFCD 9901. J Clin Oncol. 2014;32(23):2416–22.
30. von Döbeln GA, Klevebro F, Jacobsen AB, et al. Neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the esophagus or gastroesophageal junction: long-term results of a randomized clinical trial. Dis Esophagus. 2019;32(2).
31. Nutting CM, Bedford JL, Cosgrove VP, Tait DM, Dearnaley DP, Webb S. A comparison of conformal and intensity-modulated techniques for oesophageal radiotherapy. Radiother Oncol. 2001;61(2):157–63.
32. Chandra A, Guerrero TM, Liu HH, Tucker SL, Liao Z, Wang X, et al. Feasibility of using intensity-modulated radiotherapy to improve lung sparing in treatment planning for distal esophageal cancer. Radiother Oncol. 2005;77(3):247–53.
33. Lin SH, Wang L, Myles B, Thall PF, Hofstetter WL, Swisher SG, et al. Propensity score-based comparison of long-term outcomes with 3-dimensional conformal radiotherapy vs intensity-modulated radiotherapy for esophageal cancer. Int J Radiat Oncol Biol Phys. 2012;84(5):1078–85.

How to cite this article: Wakita A, Motoyama S, Sato Y, Nagaki Y, Fujita H, Kemuriyama K, et al. Preoperative neoadjuvant chemoradiotherapy provides borderline resectable thoracic esophageal cancer with equivalent treatment results as clinically T3 thoracic esophageal cancer. Ann Gastroenterol Surg. 2023;7:904–912. https://doi.org/10.1002/ags3.12706