Clinical impact of remnant lymphatic invasion on the recurrence of esophageal squamous cell carcinoma after esophagectomy with neoadjuvant chemotherapy

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Abstract. For stage II and III esophageal squamous cell carcinoma (ESCC), neoadjuvant chemotherapy (NAC) followed by esophagectomy is recommended in the Japanese guidelines for the diagnosis and treatment of esophageal cancer. However, recurrence of ESCC is common regardless of the NAC regimen and surgical method, and NAC demonstrates limited efficacy against recurrence. Therefore, the present study was conducted to identify risk factors of recurrence of ESCC with surgery after NAC. The outcomes of 51 patients who underwent esophagectomy for ESCC after NAC from 2010 to 2017 at Kyushu University Hospital were retrospectively analyzed. A total of 52 patients with ESCC without NAC followed by esophagectomy from 2001 to 2017 were selected for comparison. Among patients who underwent NAC followed by surgery, only lymphatic invasion (LY; hazard ratio, 2.761; 95% CI, 1.86-6.43, P=0.018) was an independent factor significantly associated with 3-year recurrence-free survival in the multivariate analysis. In patients with pathologic lymph node metastasis (pN) and no LY after NAC, there was significantly less recurrence compared with patients with pN and LY (P=0.0085), whereas in patients without LY after NAC, the presence of pN was not significantly associated with recurrence (P=0.2401). There were significantly fewer LY (+) patients in the NAC (+) group (P=0.0158) compared with those in the NAC (-) group. The presence of LY was an independent risk factor for recurrence of ESCC after esophagectomy following NAC. Overall, adjuvant treatment after surgery may be required in cases with remnant LY after NAC.

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Abbreviations: ESCC, esophageal squamous cell carcinoma; RFS, recurrence-free survival; NAC, neoadjuvant chemotherapy; CRT, chemoradiotherapy; LVI, lymphovascular invasion; UICC, Union for International Cancer Control; R, residual tumor; EGD, esophagogastroduodenoscopy; CT, contrast-enhanced computed tomography; PET, positron emission tomography; 3-FL, three-field regional lymph node dissection; HE, hematoxylin-eosin; V, venous invasion; LY, lymphatic invasion; EVG, Elastica van Gieson; pN, pathological lymph node metastasis

Key words: esophageal squamous cell carcinoma, neoadjuvant chemotherapy, recurrence factor, lymphatic invasion

Introduction

Esophageal cancer is the seventh most common cancer worldwide (1). In Japan, more than 85% of esophageal cancers are esophageal squamous cell carcinoma (ESCC) (2). Neoadjuvant therapy including chemotherapy and/or radiation therapy is recommended for advanced esophageal cancer to improve patient prognosis by downstaging tumors (3-6) and controlling local and distant micrometastasis (7,8). Despite advances in neoadjuvant therapy, surgical technique and patient selection, the 5-year recurrence-free survival (RFS) rate after neoadjuvant therapy followed by esophagectomy is approximately 35-55% (9,10). In Japan, the Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus 2017 (11,12) recommend neoadjuvant chemotherapy (NAC), not neoadjuvant chemoradiotherapy (CRT), as preoperative therapy for advanced ESCC before esophagectomy. In addition, adjuvant therapy in cases with NAC is not recommended after surgery (9). However, the impact of surgery after NAC on recurrence is limited in ESCC patients (9,13).

Several risk factors for recurrence (e.g., clinical or pathological lymph node metastasis, lymphovascular invasion (LVI), perineural invasion, and extracapsular invasion) have been identified in cases with neoadjuvant CRT (14-16). In such analysis of ESCC patients who underwent neoadjuvant CRT and esophagectomy, LVI was indicated as an independent risk factor for recurrence (14-16). Advanced stage indicators including T and N in pathological diagnosis are also risk factors for recurrence of ESCC following curative resection with or without neoadjuvant therapy (17-21). However, the risk

factors for recurrence after esophagectomy with NAC alone for ESCC have not been clarified so far.

The present study aimed to identify the post-NAC specific recurrence factors for ESCC. We analyzed the clinicopathological factors focusing on patients treated with NAC alone followed by esophagectomy.

Materials and methods

Patients. We retrospectively reviewed the records of 111 consecutive patients who underwent curative operation for ESCC at the Department of Surgery and Oncology, Kyushu University Hospital between April 2010 and July 2017 (Fig. 1). The tumor staging was classified according to the Japanese Classification of Esophageal Cancer, 11th Edition (22,23). There are no big differences in the definitions of the T and M categories between the Japanese staging system and the staging system of the Union for International Cancer Control (UICC) (24), but there is a big difference in N category. The UICC system defines the N category according to the number of metastatic lymph nodes, while the Japanese system determines the N category on the basis of the location of the main tumor and the metastatic lymph nodes. Demographic, clinical, surgical, pathological, postoperative, and survival data were collected from the prospectively entered clinical database of the department. Only patients identified as ESCC on record were included. Patients who did not receive NAC or patients with no record of residual tumor (R) and who had R were excluded. After the application of these criteria, 51 patients were extracted as the NAC (+) group. We included an NAC (-) group (Fig. 2) and compared this data with the NAC (+) group. We retrospectively reviewed the records of 232 consecutive patients who underwent curative operation for ESCC between December 2001 and July 2017. Among the patients without NAC, pathological T0N0 or T1N0 cases were excluded to align the background of both groups. Patients with no R record and patients with R were also excluded. After application of the criteria, 52 patients were extracted as the NAC (-) group.

This study was approved by the institutional review board of the Kyushu University Hospital (approval no. 22002-00) and written informed consent was waived owing to the retrospective analysis of the study.

Diagnosis and treatment. Clinical diagnosis was determined by barium swallow, esophagogastroduodenoscopy (EGD), endoscopic ultrasound, contrast-enhanced computed tomography (CT), and whole-body positron emission tomography (PET). Clinical stage II and III patients underwent NAC followed by esophagectomy.

The NAC regimen consisted of 80 mg/m^2 of cisplatin administered intravenously on day 1 followed by continuous intravenous infusion of 800 mg/m^2 5-fluorouracil on days 1 through 5. Most patients were administered the medication for two cycles every 4 weeks. NAC was discontinued if the patient experienced any issues (e.g., side effects such as severe allergy, febrile neutropenia, and renal function disorder). At approximately 4 weeks after the last round of NAC, the patients underwent surgery. To assess medical operability, cardiac and pulmonary functions were evaluated by electrocardiography, echocardiography, and pulmonary function tests. All patients had an American Society of Anesthesiologists physical status of I or II. The operation for ESCC in this study was a subtotal esophagectomy with three-field regional lymph node dissection (3-FL) regardless of the use of thoracoscope and laparoscope.

All surgically resected specimens were stained using hematoxylin-eosin (HE). When the findings of HE-stained sections were not sufficient to identify venous invasion (V) and lymphatic invasion (LY), Elastica van Gieson (EVG) and D2-40 (413451, 1:5 dilution, Nichirei Biosciences Inc.) staining were

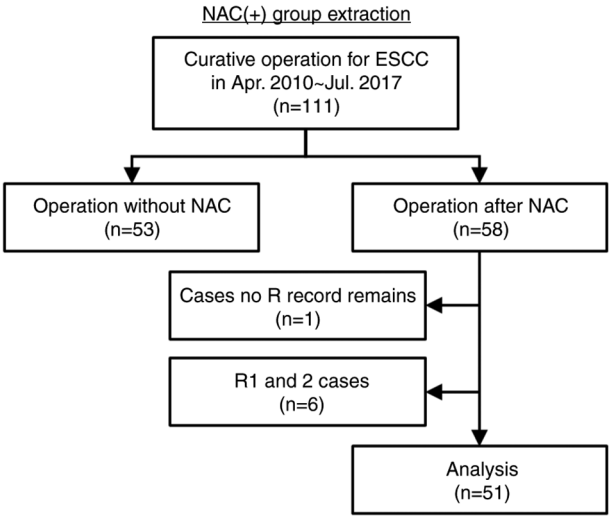

Figure 1. Diagram of case selection. Diagnosis was based on the Japanese Classification of Esophageal Cancer (11th Edition) edited by the Japan Esophageal Society (22,23). ESCC, esophageal squamous cell carcinoma; NAC, neoadjuvant chemotherapy; R, residual tumor.

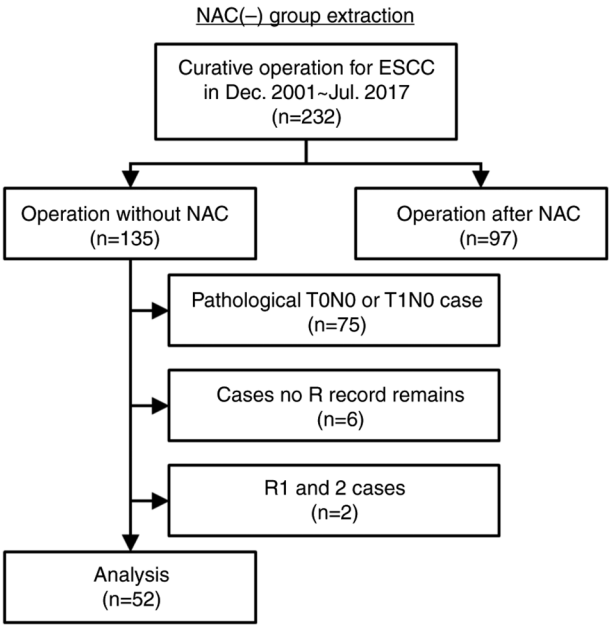

Figure 2. Diagram of case selection for the NAC(-) group. Diagnosis was based on the Japanese Classification of Esophageal Cancer (11th Edition) edited by the Japan Esophageal Society (22,23). ESCC, esophageal squamous cell carcinoma; NAC, neoadjuvant chemotherapy; T, depth of tumor invasion; N, grading of lymph node metastasis; R, residual tumor.

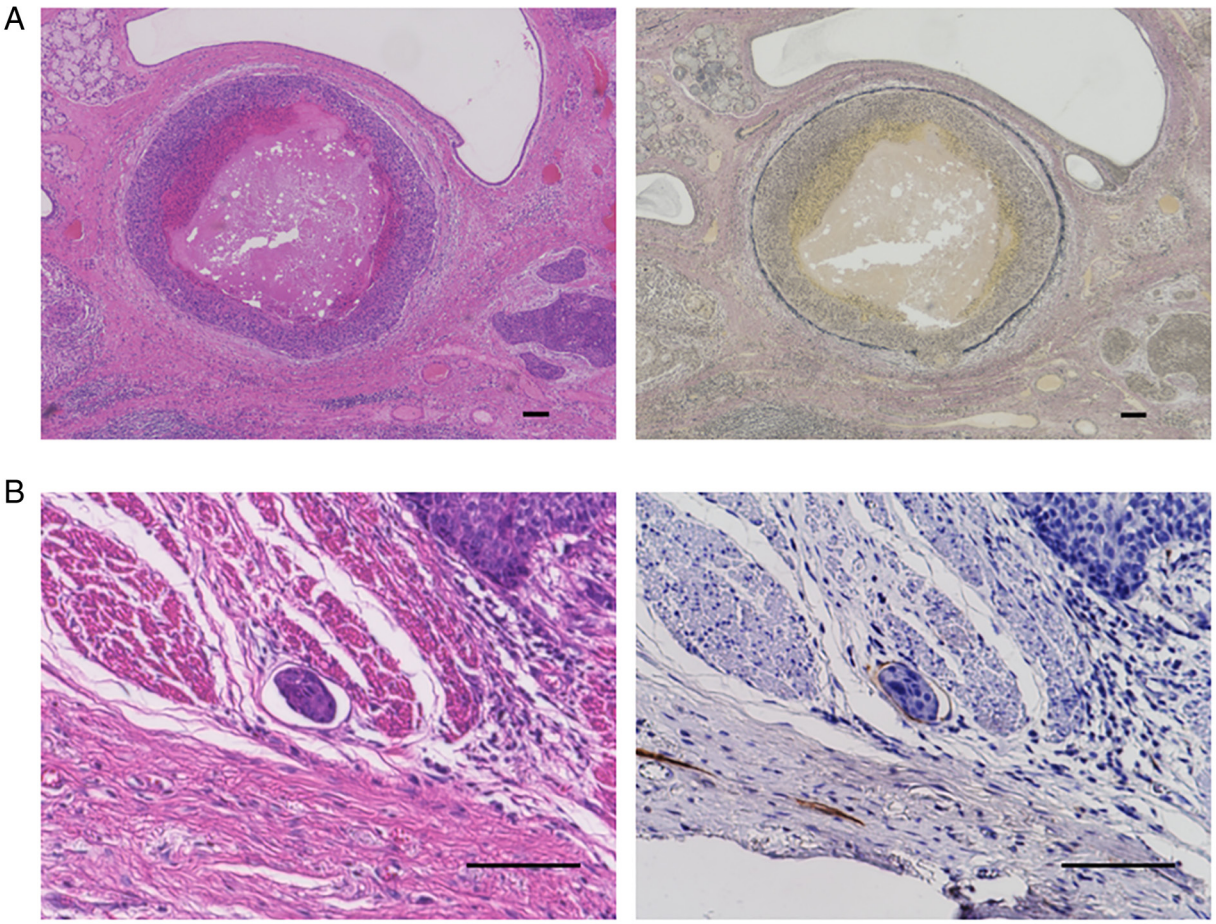

Figure 3. Representative images of special staining compared with HE staining. (A) EVG (magnification, x40) and (B) D2-40 (magnification, x200). HE and EVG/D2-40-stained images of the diagnosed area are shown side by side. Scale bars, 100 μm. HE, hematoxylin-eosin; EVG, Elastica van Gieson.

performed for the diagnosis (Fig. 3). An automated immunohistochemistry system BOND-III (13B2X10268B30001, Leica Biosystems) was used for D2-40. According to the protocols of this system, the sections were incubated with BOND Epitope Retrieval Solution 2 (AR9640, Leica Biosystems) at 100˚C for 10 min, 3% H_2O_2 at room temperature for 5 min, D2-40 at room temperature for 15 min, and BOND Polymer Refine Detection (DS9800, Leica Biosystems) including DAB. The stained specimens were confirmed by two or more pathologists, and the postoperative diagnosis was determined according to the Japanese classification (22,23).

Follow-up examinations were performed for 5 years after operation using tumor marker measurements every 3 months, contrast-enhanced CT every 6 months, and EGD every year.

Statistical analyses. Statistical analysis was performed using JMP® 15 (SAS Institute Inc.). The 3-year RFS was calculated from the date of the operation to the date of recurrence, and patients without recurrence 3 years after operation were censored at that time. Overall survival (OS) was calculated from the date of the operation to the date of death. Patients who were lost to follow-up were also censored at the date of last contact. Univariate analysis for 3-year RFS and OS were estimated with the Kaplan-Meier method and compared using the log-rank test. The variables with P<0.05 in univariate analysis were included in the multivariate models. Multivariate analysis for 3-year RFS was performed using a Cox proportional hazards model. Student's t-test and ANOVA were used for the comparison of continuous variables. Pearson's χ^2 test was used to compare categorical variables. The threshold for significance was P<0.05.

Results

Patient characteristics. A total of 51 patients were eligible for inclusion in the NAC (+) group (Fig. 1). Table I shows the detailed clinical and pathological characteristics of the included patients. Japanese guidelines indicate that NAC should be performed for only stage II and III patients (11,12). However, post-NAC preoperative diagnosis included 3 (6%) stage I patients. Furthermore, 2 (4%) patients were stage 0, 4 (8%) patients were stage I, and 3 (6%) patients were stage IV in pathological diagnosis. Among the 51 total patients, 15 (29%) patients had LY.

Survival analysis in the NAC (+) group. Kaplan-Meier analysis showed that lymph node metastasis in pathological diagnosis (pN) (P=0.0290) and LY (P=0.0031) were significantly associated with 3-year RFS in patients who underwent NAC (Table II). The Kaplan-Meier curves of RFS according to the status of postoperative diagnosis are shown in Fig. 4. There was no significant difference in OS between LY-positive

Table I. Characteristics of patients in the NAC (+) group (n=51).

Characteristics	Number of patients
Age, years	
Median (range)	64 (44-79)
Sex [n (%)]	
Male/Female	41 (80)/10 (20)
Location [n (%)]	
Ce/Ut/Mt/Lt/Ae	2 (4)/2 (4)/30 (59)/16 (31)/1 (2)
Post-NAC diagnosis [n (%)]	
T	
1a/1b/2/3	1 (2)/15 (29)/15 (29)/20 (40)
N	
0/1/2/3	14 (27)/13 (25)/15 (29)/9 (18)
Stage	
I/II/III	3 (6)/24 (47)/24 (47)
Operative time, min	
Median (range)	615 (340-935)
Blood loss, g	
Median (range)	100 (21-524)
Pathological diagnosis [n (%)]	
T	
0/1a/1b/2/3	1 (2)/4 (8)/15 (29)/10 (20)/21 (41)
N	
0/1/2/3/4	13 (25)/7 (14)/24 (47)/5 (10)/2 (4)
Stage	
0/I/II/III/IV	2 (4)/4 (8)/20 (40)/23 (45)/2 (4)
V	
(-)/(+)	42 (82)/9 (18)
LY	
(-)/(+)	36 (71)/15 (29)

NAC, neoadjuvant chemotherapy; Ce, cervical esophagus; Ut, upper thoracic esophagus; Mt, middle thoracic esophagus; Lt, lower thoracic esophagus; Ae, abdominal esophagus; T, depth of tumor invasion; N, grading of lymph node metastasis; V, venous invasion; LY, lymphatic invasion.

Table II. Univariate analysis for 3-year RFS of NAC (+) group (n=51).

Characteristics	n (%)	Mean RFS (months)	3-year RFS rate (%)	P-value
Total	51 (100)	18	48	
Age, years				0.5750
≤64	27 (53)	18	42	
>64	24 (47)	11	55	
Sex				0.2373
Male	41 (80)	19	50	
Female	10 (20)	12	38	
Location				0.4116
Ce, Ut, Mt	34 (67)	18	42	
Lt, Ae	17 (33)	14	60	
Post-NAC diagnosis				
T				0.2185
T0, 1	16 (31)	21	57	
T2-4	35 (69)	15	44	
N				0.6029
N0	14 (27)	16	42	
N1-4	37 (73)	18	50	
Operative time, min				0.1703
≤600	23 (45)	11	64	
>600	28 (55)	18	36	
Blood loss, g				0.2593
≤100	27 (53)	17	40	
>100	24 (47)	19	59	
Pathological diagnosis				
T				0.5599
T0, 1	21 (41)	20	50	
T2-4	30 (59)	15	47	
N				0.0290
N0	13 (25)	22	81	
N1-4	38 (75)	16	38	
V				0.0570
(-)	42 (82)	19	54	
(+)	8 (18)	14	15	
LY				0.0031
(-)	36 (71)	19	61	
(+)	15 (29)	14	16	

RSF, recurrence-free survival; NAC, neoadjuvant chemotherapy; Ce, cervical esophagus; Ut, upper thoracic esophagus; Mt, middle thoracic esophagus; Lt, lower thoracic esophagus; Ae, abdominal esophagus; T, depth of tumor invasion; N, grading of lymph node metastasis; V, venous invasion; LY, lymphatic invasion.

and -negative patients during the 3-year observation period (P=0.0747) (Fig. S1). In the multivariate analysis, the independent factors significantly associated with 3-year RFS in patients with esophagectomy after NAC were only LY (hazard ratio: 2.761; 95% CI: 1.86-6.43, P=0.018) (Table III). In the patients without LY (n=36), there was no significant difference in 3-year RFS according to the presence and absence of pN (P=0.2401) (Fig. 5A). However, in patients with pN (n=38), a significant increase in the recurrence rate was observed in patients with LY compared with those without LY (P=0.0085) (Fig. 5B).

Comparison of characteristics between NAC (-) and (+) groups. We established the NAC (-) group (n=52) (Fig. 2) and compared the characteristics of patients in the NAC (-) and (+) groups (Table IV). The NAC (+) group included significantly more advanced cases in clinical N (P<0.0001), and stage

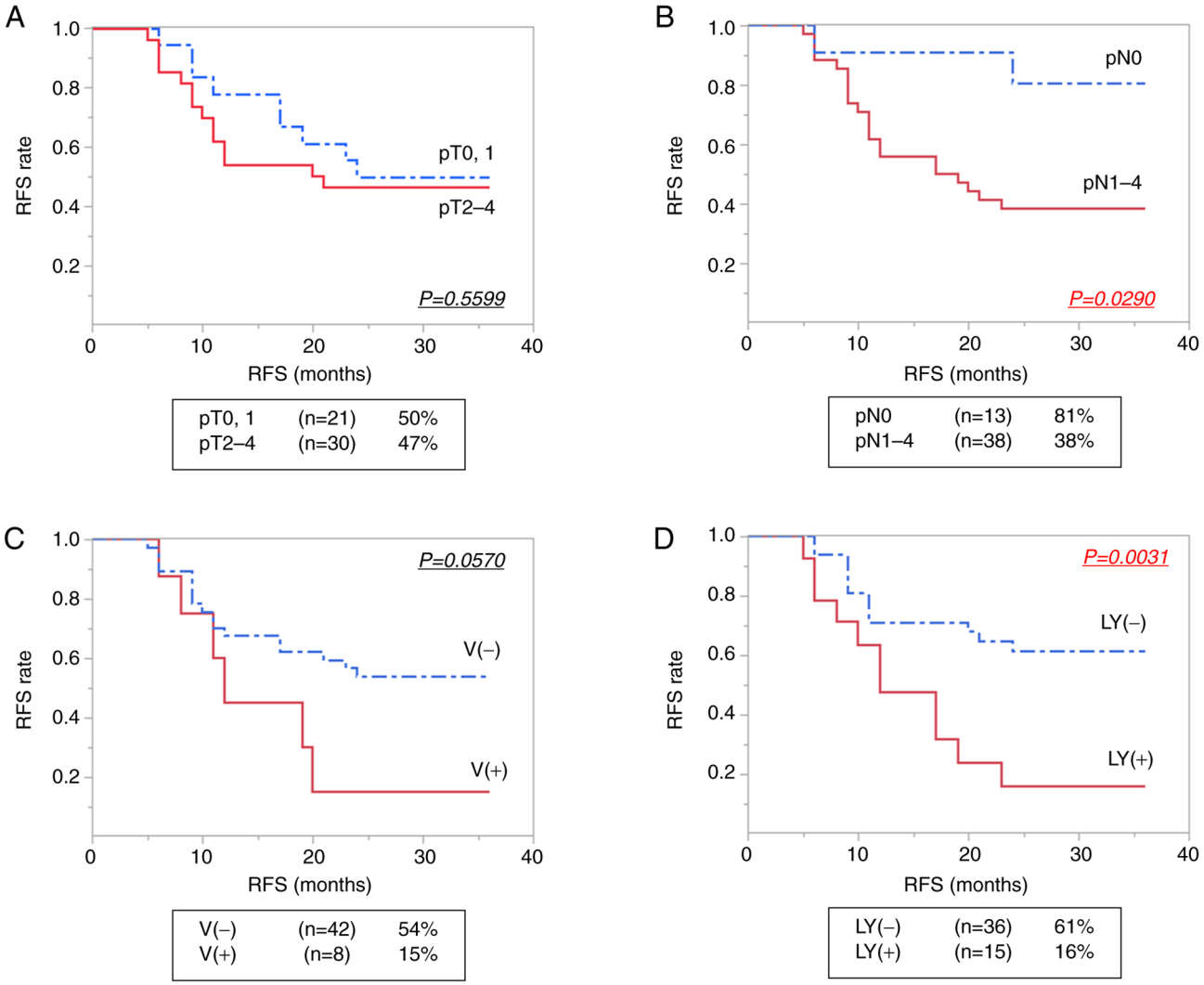

Figure 4. Kaplan-Meier estimates of 3-year RFS in NAC (+) patients. (A) pT0, 1 and pT2-4 subgroups, (B) pN0 and pN1-4 subgroups, and according to the presence of (C) V and (D) LY. The 3-year RFS rate is shown as a percentage in the square. All factors were diagnosed based on the Japanese Classification of Esophageal Cancer (11th Edition) edited by the Japan Esophageal Society (22,23). RFS, recurrence-free survival; NAC, neoadjuvant chemotherapy; pT, depth of tumor invasion; pN, grading of lymph node metastasis; V, venous invasion; LY, lymphatic invasion.

(P<0.0001) than the NAC (-) group. In contrast, pathological results showed that there were significantly fewer LY (+) cases in the NAC (+) group than those in the NAC (-) group (P=0.0158). No significant difference in pN was observed between patients with or without NAC (P=0.0680).

Discussion

This study investigated the clinicopathological factors of patients treated with curative operation for ESCC after NAC, with the aim of identifying NAC-specific recurrence factors. Previous studies showed that R is a well-known recurrence factor regardless of NAC (25-28), and thus we excluded cases with R from this analysis. The results showed that LY in pathological examination were significantly associated with recurrence. Our results also showed that LY was a significant recurrence factor among patients with pN, although the presence of pN was not significantly correlated with the recurrence rate among patients without LY.

Previous studies have shown that LVI is an independent risk factor for recurrence after preoperative CRT and esophagectomy in patients with ESCC (14-16). Yoshida *et al* (29) reported that V was an independent risk factor for early recurrence within 6 months of resectable advanced ESCC following NAC, and Zhang *et al* (30) demonstrated that simultaneous LY and V were significantly correlated with postoperative recurrence for ESCC without neoadjuvant or adjuvant therapy. However, no report has examined the clinical significance of LY as distinguished from V in cases of NAC only rather than neoadjuvant CRT. This is the first study that has focused on LY, and our results show that LY is an independent recurrence factor in patients treated with esophagectomy after NAC alone.

Previous studies have also shown that advanced stage indicators including T and N in pathological examination are risk factors for the recurrence of ESCC following curative resection (17-21). Wang *et al* (18) reported that patients with pN had a much higher recurrence rate than patients without pN. However, in the present multivariate analysis, pN was

Table III. Multivariate analysis for 3-year RFS of the NAC (+) group.

Variables	Hazard ratio	95% CI	P-value
pN (pN1-4 vs. pN0)	3.567	0.819-15.5	0.090
LY [LY (+) vs. LY (-)]	2.761	1.86-6.43	0.018

RSF, recurrence-free survival; NAC, neoadjuvant chemotherapy; pN, pathological grading of lymph node metastasis; LY, lymphatic invasion.

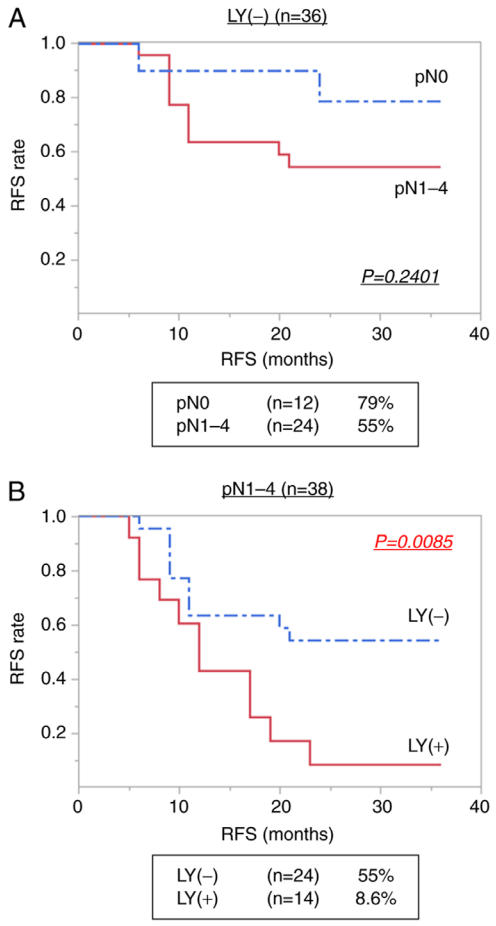

Figure 5. Kaplan-Meier estimates of 3-year RFS in NAC (+) patients. (A) RFS of LY (-) cases with and without pN. (B) RFS of pN (+) cases with and without LY. All factors were diagnosed based on the Japanese Classification of Esophageal Cancer (11th Edition) edited by the Japan Esophageal Society (22,23). RFS, recurrence-free survival; NAC, neoadjuvant chemotherapy; pN, grading of lymph node metastasis; LY, lymphatic invasion.

not an independent risk factor for recurrence. Furthermore, the presence or absence of pN was not significantly related to recurrence among the patients without LY. In contrast, LY was significantly associated with the recurrence rate in patients with pN. The fact that pN was not a significant factor for recurrence in our study may be related to the surgical method specific to Japan. In Japan, 3-FL is the standard method for lymph node dissection in esophageal cancer operation, in line with the esophageal cancer practice guidelines of Japan (11,12). The widespread use of 3-FL in Japan is due to

Table IV. Comparison of characteristics between the NAC (-) and (+) groups.

Characteristics	NAC(-) (n=52)	NAC(+) (n=51)	P-value
Age, years			
Median (range)	69 (34-83)	64 (44-79)	0.2243
Sex			
Male/Female	46/6	41/10	0.2583
Location			
Ce/Ut/Mt/Lt/Ae	2/6/29/11/3	2/2/30/16/1	0.4138
Clinical or post-NAC diagnosis			
T			
1a/1b/2/3	1/23/17/8	1/15/15/20	0.0747
1/2, 3	24/25	16/35	0.0724
N			
0/1/2/3	37/7/5/0	14/13/15/9	<0.0001
0/1-3	37/12	14/37	<0.0001
Stage			
I/II/III	21/20/8	3/24/24	<0.0001
Operative time, min			
Median (range)	596 (293-984)	615 (340-935)	0.8074
Blood loss, g			
Median (range)	215 (60-1370)	100 (21-524)	<0.0001
Pathological diagnosis			
T			
0/1a/1b/2/3/4a	0/6/18/9/19	1/4/15/10/21	0.7696
0, 1/2-4	24/28	21/30	0.6106
N			
0/1/2/3/4	6/21/19/5/1	13/7/24/5/2	0.0330
0/1-4	6/46	13/38	0.0680
Stage			
0/I/II/III/IV	0/1/29/21/1	1/3/16/29/2	0.1180
V			
(-)/(+)	39/13	42/8	0.2611
LY			
(-)/(+)	24/27	36/15	0.0158

NAC, neoadjuvant chemotherapy; Clinical or post-NAC diagnosis, in NAC (+) group, post-NAC diagnosis is shown; Ce, cervical esophagus; Ut, upper thoracic esophagus; Mt, middle thoracic esophagus; Lt, lower thoracic esophagus; Ae, abdominal esophagus; T, depth of tumor invasion; N, grading of lymph node metastasis; V, venous invasion; LY, lymphatic invasion.

the rapid increase in the number of laparoscopic esophagectomy for esophageal cancer in recent years (31). Meta-analyses and studies comparing 3-FL and 2-FL reported a tendency

for a better prognosis of the 3-FL group (32-38). Ye *et al* (35) reported that 3-FL provides a better 5-year survival rate than 2-FL for thoracic esophageal cancer with lymph node metastasis. In the present study, pN was not a risk factor in NAC cases, indicating that 3-FL possibly decreased the significance of lymph node metastasis in the risk of recurrence. Taken together, the present data suggests that remnant LY, rather than remnant lymph node metastasis, is a critical risk factor for recurrence in patients who underwent esophagectomy with 3-FL after NAC.

The main purpose of neoadjuvant therapy is to downstage the primary tumor to facilitate complete resection (3-6) and to reduce micrometastasis that cause local or systemic recurrence (7,8). Pathological tumor regression and the number of involved lymph nodes have been reported to be significantly associated with the prognosis of the patients who have received neoadjuvant CRT for esophageal cancer (6,39-44). However, the prognostic impact of pathological LY status in patients with esophageal cancer who have undergone NAC has not been fully investigated. In the present study, LY was significantly less frequent in patients with NAC than in patients without NAC. These data suggest that NAC contributes to regulate LY, which is a type of microinvasion, and remnant LY after NAC may reflect the limited control of micrometastasis in patients with NAC.

It is sometimes difficult to identify LVI and to distinguish LY from V based only on the findings of HE-stained sections (45). Immunohistochemistry with D2-40 and EVG staining has been reported to be useful for evaluate LVI (46). In the present study, we identified LY and V using D2-40 and EVG staining, respectively, when the findings of HE-stained sections were not sufficient to identify LY and V. Therefore, our results may differ from reports that only evaluated cases by HE staining. For further examination, all cases should be subjected to stain with D2-40 and EVG to evaluate LVI accurately.

This study has several limitations. First, it was a retrospective study of a small number of patients that was conducted at a single institution. Selection bias was also present in the extraction of the NAC (-) group. Moreover, we did not establish criteria for NAC dosage reduction during the study period. The administration and dosage of NAC were ultimately decided by the attending physicians depending on the patient's condition and/or willingness, and thus the NAC (+) group in our study included patients with both full-dose and lowered-dose NAC. Therefore, further prospective multi-institutional studies with larger populations are required to assess the true impact of remnant LY for ESCC patients with NAC following esophagectomy. In addition, the preoperative diagnosis may differ between our report and reports from other countries because imaging examinations including endoscopic ultrasound and PET are frequently used in Japan.

We found that the presence of LY in pathological examination was an independent risk factor for recurrence of ESCC after esophagectomy with 3-FL following NAC. The present data also showed that patients with NAC had significantly less LY than those without NAC, although the NAC group included more advanced cases in clinical diagnosis than the non-NAC group. These data suggest that the remnant LY after NAC reflects the insufficient control of micrometastasis. Therefore, adjuvant treatment after surgery may be desirable in cases with remnant LY after NAC.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

SO, KO and MN contributed to the conception and design of work. JK and YO contributed to the pathological examination. SO and KO confirm the authenticity of all the raw data. SO, KO, KS, TM, JK, KT, MS, KoN, YM, NI, KiN, YO and MN contributed to the data analysis and interpretation, read and approved of the final version to be published, agreed to be accountable for all aspects of the work and ensured that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

This study was performed in line with the principles of the Declaration of Helsinki. Approval for this study was obtained from the institutional review board of the Kyushu University Hospital (approval no. 22002-00). The requirement of written informed consent to participate was waived in accordance with the standards of the institutional review board, and an opt-out method was used at our institution due to the retrospective analysis of de-identified data.

Patient consent for publication

Informed consent for publication was obtained from all individual participants included in the study.

Competing interests

The authors declare that they have no competing interests.

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