The response to NAC has been evaluated by anatomic criteria, such as response evaluation criteria in solid tumors (RECIST) or the World Health Organization (WHO) criteria.[8–10] However, in RECIST 1.1, only LNs with short-axis lengths >15 mm are considered measurable, so RECIST may not be appropriate for evaluation of LNM in TESCC with small metastatic foci.[8,11] In addition, the esophageal tumor is a nonmeasurable lesion by the RECIST definition. In contrast, the advantage of metabolic response assessment by ^{18}F-fluorodeoxy glucose (FDG)-PET for esophageal cancer has been reported in many clinical trials.[12–14] Using FDG-PET, esophageal primary tumors can be assessed; however, reliable response criteria have not been established, especially for LNMs.

The number of pLNMs is the most important known prognostic marker for TESCC following treatment, but the relationship between pLNM number and LN metabolism after NAC as measured by FDG uptake is still unclear.[15,16] We performed this study to test the prognostic significance of FDG uptake in LNs after NAC for patients with TESCC and PET-positive LNs and to define the optimal NAC response criteria for evaluation of TESCC patients with LNM.

PATIENTS AND METHODS

Study Design and Patients

This was a prospective, nonrandomized, single-institution, clinical study and was approved by the High-Degree Advanced Medical Committee of Osaka University Hospital. We performed NAC followed by surgery at Osaka University Hospital for 51 consecutive patients with cT3 or lower TESCC and PET-positive LNs within a three-field region who met the eligibility criteria described in our previous report.[7] Informed consent was obtained from all patients. Initial and repeat conventional staging by barium esophagography, gastroesophageal endoscopy, and neck, thoracic, and abdominal computed tomography (CT) followed by FDG-PET were performed approximately 2 weeks before administration and after the completion of NAC for tumor staging according to the sixth edition of the tumor-node-metastasis classification of the AJCC/UICC.[17,18] Some patients also underwent magnetic resonance imaging, endoscopic ultrasonography, and/or bronchoscopy to obtain further information. Surgical resection was conducted within 2 weeks of the second FDG-PET.

PET Imaging and Response Evaluation

PET was performed using a dedicated PET scanner (HEADTOME/SET 2,400 W, Shimadzu Co., Kyoto, Japan) as reported previously.[19,20] The acquired PET images were combined with the CT images utilizing a commercially available digital software program (T-B Fusion; Shimadzu).[19] A maximum standardized FDG uptake value (SUVmax) $\geq$2.5 was defined as positive because FDG uptake of SUVmax <2.5 is invisible. Patients with an FDG uptake of SUVmax $\geq$2.5 in the region coinciding with the primary tumor and in LNs on the CT image were diagnosed as PET-T positive and PET-N positive, respectively. The clinical responses of the primary tumor and LNs were evaluated by CT 2 weeks after the completion of chemotherapy according to WHO criteria.[9,10] Metabolic responses were evaluated by FDG-PET and CT in the same period. Patients with a complete metabolic response in the primary tumor were classified as posttreatment PET-T negative (post-PET-T negative), which was reported to have a close association with grade $\geq$2 histological response and better postoperative survival, and those with a complete metabolic response in LNs were classified as posttreatment PET-N negative (post-PET-N negative).[21] All assessments were performed by one radiologist and two surgeons that specialize in esophageal cancer.

Neoadjuvant Chemotherapy

Chemotherapy was administered for 2 cycles preoperatively. The regimen consisted of daily 5-fluorouracil (700 mg/m^2/day) for 7 days by continuous intravenous infusion plus doxorubicin (35 mg/m^2) and cisplatin (70 mg/m^2) by intravenous bolus on day 1.[22] The courses were repeated twice every 28 days according to the hematological, digestive, and renal tolerance of the patient.

Surgical Treatment

All patients underwent transthoracic subtotal esophagectomy with esophageal reconstruction using a gastric tube (45 patients) or a pedicled jejunum (6 patients due to simultaneous total gastrectomy or history of distal gastrectomy). A three-field lymphadenectomy was performed for patients with supraclavicular or recurrent laryngeal nerve LNMs, either for preoperative staging or rapid intraoperative diagnosis, and for patients with a primary tumor located in the upper third of the thoracic esophagus.[23,24]

Histopathological Examination

Conventional histological examinations were performed for all harvested LNs in all cases after being dissected separately from the specimen and classified. The pathological responses were classified into five main categories according to the guidelines for clinical and pathological studies on carcinoma of the esophagus by the Japan Esophageal Society: Grade 3, complete disappearance of cancer cells; Grade 2, more than 2/3 disappearance; Grade

1b, <2/3 to >1/3 disappearance; Grade 1a, <1/3 disappearance; Grade 0, no disappearance.[25]

Follow-up

All patients with an R0 resection were followed-up without postoperative adjuvant treatment until recurrence was detected. The surviving patients were followed-up as outpatients every 3–6 months for the first 5 years, and then on an annual basis. CT scans of the neck, chest, and abdomen were performed twice a year, and endoscopy was performed once a year. Recurrent disease was classified as local (vicinity of the tumor), regional (surgical field), or distant (all other sites).

Statistical Analysis

Group differences in noncontinuous data were evaluated by χ^2 and Mann-Whitney U tests, and continuous data were compared by Student's t test. RFS and overall survival (OS) were calculated from day 1 of the first NAC to the date of the first evidence of relapse and the date of death, respectively, and were compared by the log-rank test. Risk factors were analyzed by Cox's proportional hazards regression model. Differences were considered statistically significant for p values <0.05.

RESULTS

Patient Characteristics and Posttreatment PET-N Response

Of the 51 TESCC patients enrolled in this study, 30 were post-PET-N negative and 21 post-PET-N positive after NAC (Table 1). No significant differences in pretreatment clinical factors were observed between the two groups except tumor location and histological type. The post-PET-N negative group showed better clinical responses, lower average SUVmax in primary tumors, and a significantly higher post-PET-T negative rate, resulting in a significantly higher downstage rate (24/30 = 80.0 vs. 6/21 = 28.6 %; $p = 0.0007$) than the post-PET-N positive group. R0 resection was conducted in all patients except 1 (R2) due to invasion of the right and left pulmonary veins. A tumor pathological response of Grade 2 or 3 was observed in seven patients of the post-PET-N negative group, but in no post-PET-N positive patients.

Number of Pathological LNMs and Posttreatment PET-N Response

The average number of pLNMs was significantly higher in the post-PET-N positive group than the post-PET-N negative group (5.7 vs. 1.9, $p = 0.0004$). In addition, ten patients in the post-PET-N negative group exhibited no pathological LNMs in any of their harvested LNs.

The 5-year RFS rate for all patients was 49.0 %. The rate decreased progressively with the number of pLNMs (0: 88.9 %, 1–2: 63.6 %, 3–6: 10.0 %, ≥7: 12.5 %), with an extremely poor survival rate in patients with ≥3 pLNMs (Supplemental Fig. E1). The proportion of patients with ≤2 pLNMs was substantially higher in the post-PET-N negative group than the post-PET-N positive group (86.7 vs. 28.6 %; $p < 0.0001$; Fig. 1). Consequently, we defined responders and nonresponders as the post-PET-N negative and positive patients, respectively.

Response Evaluation to NAC and Survival

The median follow-up of censored patients was 81.5 (range 48.2–120.9) months. The comprehensive clinical response of both tumor and LNs significantly correlated with survival (Fig. 2a), whereas post-PET-N evaluation distinguished responders from nonresponders to NAC with greater statistical significance, yielding 5-year RFS rates of 69.0 and 20.0 %, respectively ($p = 0.0001$; Fig. 2b), and 5-year OS rates of 69.0 and 26.8 % ($p = 0.0003$, data not shown).

Comprehensive evaluation using the combination of post-PET-N and -T response clearly stratified patients by RFS in the order double negative (highest RFS 77.8 %), T single positive, N single positive, and double positive (lowest RFS, 14.3 %; Fig. 2c). Post-PET-N negative patients showed superior RFS rates than post-PET-N positive patients independent of post-PET-T status.

Post-PET-N Response and Failure Patterns

Tumor recurrence was observed in 75.0 % of the post-PET-N positive group, a recurrence rate 2.8 times higher than for the post-PET-N negative group ($p = 0.001$); in particular, the rate of distant metastasis was significantly higher ($p = 0.001$), showing more than double the frequencies of M1LYM and hematogenous metastases compared to the post-PET-N negative group (Table 2).

Preoperative Risk Factors for Tumor Recurrence after Surgery

A univariate analysis of preoperative risk factors for RFS showed significant associations with the initial cStage (III/IV vs. 0/I/IIA/IIB), total clinical response, post-PET-T status, and post-PET-N status (Table 3). A multivariate analysis using four significant risk factors from the univariate analysis plus the initial number of PET-positive LNs ($p < 0.1$) as independent variables identified post-

TABLE 1 Patient characteristics and posttreatment PET-N diagnosis

		Post-PET-N positive	Post-PET-N negative	*p* value
No. of patients		21	30	
Sex	Male/female	3/18	7/23	0.423
Age (year)	Mean	61.9	63.2	0.552
	(range)	(42–76)	(51–75)	
Location	Ut/Mt/Lt	1/8/12	3/20/7	0.048
Histological type	G1/G2/G3	7/5/9	4/22/4	0.002
Pretreatment clinical factors				
cT factor	T1/2/3	1/3/17	3/7/20	0.523
cN factor	N0/N1	0/21	3/27	0.135
cM factor	M0/M1a/M1b	11/2/8	16/3/11	0.994
cStage	IIB	3	3	0.963
	III	8	13	
	IVA	2	3	
	IVB	8	11	
SUVmax of tumors	Mean	12.5	12.5	0.991
	(range)	(4.1–17.8)	(4.8–20.6)	
No. of PET positive LNs	0/1/≥2	0/12/9	0/14/16	0.881
Location of each PET-positive LN				
Periesophageal LNs				
Neck		0	4	
Mediastinum (Upper/middle/lower)		9/3/4	16/5/2	
Perigastric and celiac LNs		21	22	
Supraclavicular LNs		6	9	
Posttreatment clinical factors				
cStage	0	0	3	0.001
	I	1	11	
	IIA	0	6	
	IIB	4	4	
	III	9	2	
	IVA	0	1	
	IVB	7	3	
Clinical response of tumor	CR/PR/SD/PD	1/5/14/1	3/14/13/0	0.027
Clinical response of LNs	CR/PR/SD/PD	0/7/14/0	2/16/11/1	0.141
Total clinical response	CR/PR/SD/PD	0/8/12/1	2/18/9/1	0.136
SUVmax of tumors	Mean	9.1	6.1	0.124
	(range)	(1.9–18.3)	(1.4–22.1)	
Post-PET-T status	Negative/positive	6/15	19/11	0.015
No. of PET-positive LNs	0/1/≥2	0/15/6	30/0/0	<0.0001
Surgery				
Subtotal esophagectomy		21	30	
Lymphadenectomy	2F/3F	9/12	7/23	0.140
Resectability	R0/R1/R2	20/0/1	30/0/0	0.227
Pathological factors				
No. of harvested LNs	Mean	65.2	79.9	0.050
	(range)	(29–112)	(29–160)	
No. of metastatic LNs	Mean	5.7	1.9	0.0004
	(range)	(1–14)	(0–18)	

TABLE 1 continued

		Post-PET-N positive	Post-PET-N negative	*p* value
pStage	0	0	2	0.172
	I	0	4	
	IIA	1	6	
	IIB	4	3	
	III	7	7	
	IVA	1	2	
	IVB	8	6	
Pathological response of tumor	Grade			
	0/1a/1b/2/3	2/13/6/0/0	2/11/10/3/4	0.147

Ut upper thoracic esophagus, *Mt* middle thoracic esophagus; *Lt* lower thoracic esophagus; *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *2F* two-field lymphadenectomy, *3F* three-field lymphadenectomy, *R0*: no residual tumor cell, *R1* microscopic residual tumor cells, *R2* macroscopic residual tumor cells

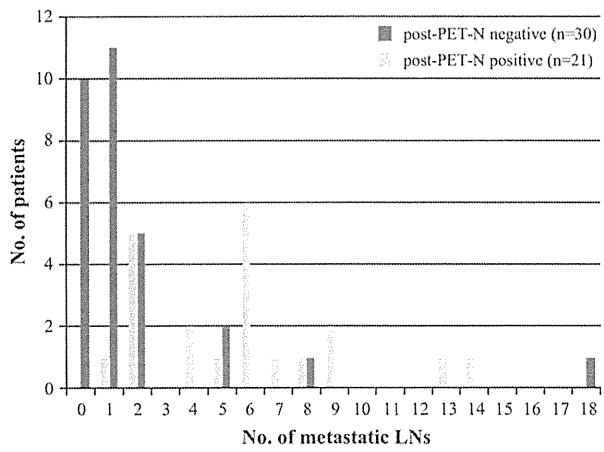

FIG. 1 Distribution of the number of pathological metastatic LNs according to posttreatment PET-N response. The blue and yellow bars show the results of posttreatment PET-N negative and positive groups, respectively. The *horizontal lines* show the number of metastatic lymph nodes and the *vertical lines* represent the number of patients

PET-N status (negative or positive) as the only independent risk factor impacting postoperative recurrence ($p = 0.015$).

DISCUSSION

We examined the significance of FDG uptake in LNs after NAC as a clinical response evaluation index and prognostic indicator for PET-N positive patients with resectable TESCC. Patients with ≥3 pLNMs showed extremely poor survival compared with those with ≤2 pLNMs. On the other hand, post-PET-N negative patients, 86.7 % of whom had ≤2 pLNMs, had a significantly lower average number of pLNMs than post-PET-N positive patients, so we defined post-PET-N negative and positive patients as NAC responders and nonresponders, respectively. Post-PET-N negative patients showed significantly higher 5-year RFS and OS rates and a lower recurrence rate than post-PET-N positive patients, and post-PET-N status was identified as the only significant preoperative risk factor for postoperative recurrence in multivariate analysis. Furthermore, in comprehensive response evaluation combining both post-PET-N and -T responses, the post-PET-N negative group showed higher 5-year RFS and OS irrespective of the post-PET-T response. Consequently, post-PET-N negative status is a critical determinant of postoperative survival and a key response marker for NAC in PET-N positive patients.

Current treatment response criteria (RECIST 1.1 or WHO) focus on changes in tumor size.[8–10] However, because the RECIST criteria were developed as a primary endpoint for trials assessing tumor response to new cancer therapies, only lesions accurately measurable by CT can be evaluated. However, TESCC often is associated with many small LNMs <15 mm in short axis length; thus, few TESCC lesions meet RECIST 1.1 criteria.[26]

FDG-PET evaluates only viable tumor cells. In addition, SUVmax shows a strong correlation with tumor size.[21] Therefore, response can be evaluated objectively even for primary tumors of the digestive tract and small LNMs. However, tumors smaller than approximately 5 mm in diameter still cannot be detected, limiting the accuracy of metastatic diagnosis in individual LNs compared with CT or endoscopic ultrasonography.[6,21] Conversely, such a moderate diagnostic accuracy is likely an advantage of FDG-PET in tumor staging and response evaluation. We reported in our previous study that PET-N positive patients had LNM with metastatic foci >5 mm in size.[6] The probabilities of ≤2 pLNMs were 92.0 and 15.4 % in the PET-N

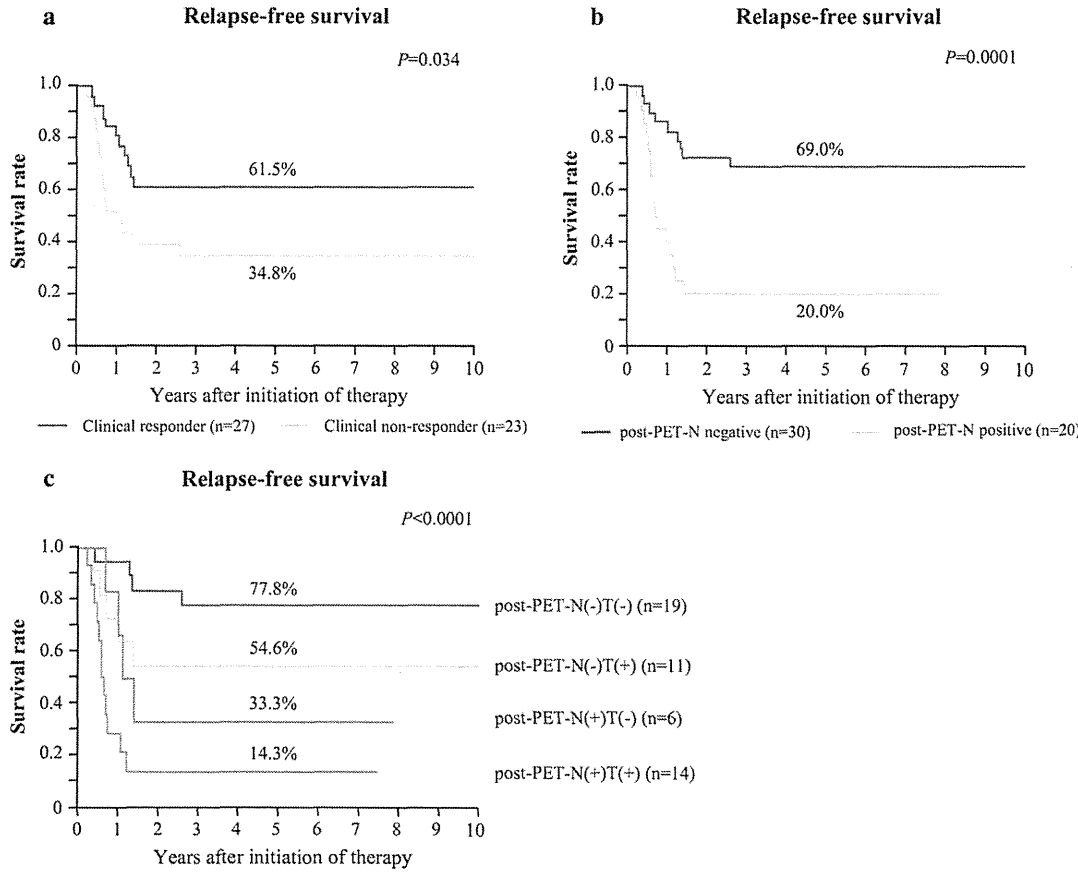

FIG. 2 **a** Relapse-free survival according to clinical response. **b** Relapse-free survival according to posttreatment PET-N response. **c** Relapse-free survival according to the response evaluation with a combination of posttreatment PET-N and T responses. Each *percent* value shows 5-year survival rate

TABLE 2 Posttreatment PET-N diagnosis and patterns of failure

Patterns of failure	Post-PET-N positive (n = 20)	Post-PET-N negative (n = 30)	p value
Local recurrence	1 (5.0%)	0 (0 %)	0.216
LN (N1)	1 (5.0 %)	3 (10.0 %)	0.523
Distant metastasis	14 (70.0 %)	7 (23.3 %)	0.001
LN (M1LYM)	7 (35.0 %)	5 (16.7 %)	0.137
Dissemination	3 (15.0 %)	0 (0 %)	0.029
Hematogenous metastasis	8 (40.0 %)	5 (16.7 %)	0.066
Lung	0	4	
Liver	4	1	
Bone	3	0	
Muscle	1	0	
Total recurrence	15/20 (75.0 %)	8/30 (26.6 %)	0.001

negative and positive groups, respectively, and these proportions were not substantially changed after NAC (86.7 and 28.6 %, respectively). The seventh edition of the tumor node metastasis classification of the AJCC/UICC classified N stage into four groups according to the number of pLNMs: N0; N1 (1–2); N2 (3–6); and N3 (≥7); N2/N3 patients had significantly lower survival.[4,5] In the present study, post-PET-N positive patients showed a threefold higher recurrence rate and less than one-third the RFS of post-PET-N negative patients. Thus, the PET-N evaluation is likely able to differentiate N2/N3 from N1/N0 with high probability preoperatively and thereby predict patients who will have a favorable prognosis because of good systemic control.

Most studies assessing the response by FDG-PET have used FDG uptake values of the primary tumor.[12–14] Indeed, we also reported that post-PET-T negativity reliably predicted better histological response and postoperative survival in locally advanced TESCC.[21] Few studies, however, have examined FDG uptake in LNs, such as that by Gillies et al.[27] To examine the optimal NAC response evaluation criteria for TESCC patients with pretreatment PET-positive LNs, we conducted multivariate analyses. Analyses revealed that post-PET-N status (negative or

TABLE 3 Univariate and multivariate Cox's proportional hazards regression analysis of preoperative risk factors for relapse-free survival

Risk factor	Univariate analysis			Multivariate analysis		
	HR	95 % CI	*p* value	HR	95 % CI	*p* value
Age (year)						
≥65 versus <65	1.252	0.555–2.753	0.580			
≥70 versus <70	0.968	0.352–2.292	0.944			
Sex						
Male versus female	1.052	0.350–2.601	0.920			
Tumor location						
Upper/middle versus lower	1.015	0.461–2.336	0.971			
Pretreatment factors						
Clinical stage						
III/IV versus IIB	1.008	0.238–2.910	0.990			
M1LYM						
Presence versus absence	0.844	0.379–1.862	0.672			
SUVmax of tumor						
≥6 versus <6	1.427	0.485–6.080	0.551			
≥8 versus <8	1.543	0.574–5.349	0.413			
≥10 versus <10	1.569	0.619–4.783	0.359			
≥12 versus <12	1.629	0.685–4.277	0.276			
No. of PET-positive LNs						
≥2 versus 1	1.964	0.883–4.651	0.099	1.417	0.607–3.473	0.424
≥3 versus ≤2	1.708	0.649–5.859	0.299			
Posttreatment factor						
Clinical stage						
III/IV versus 0/I/IIA/IIB	3.181	1.436–7.223	0.005	2.008	0.852–4.778	0.110
IIB/III/IV versus 0/I/IIA	2.983	1.255–8.216	0.012			
M1LYM						
Presence versus absence	1.485	0.577–3.412	0.390			
Clinical response of tumor						
CR/PR versus SD/PD	0.437	0.178–0.985	0.046			
Clinical response of LNs						
CR/PR versus SD/PD	0.488	0.206–1.089	0.079			
Total clinical response						
CR/PR versus SD/PD	0.430	0.187–0.950	0.037	0.886	0.347–2.179	0.793
Post-PET-T status[21]						
Negative versus positive	0.346	0.141–0.784	0.011	0.527	0.195–1.336	0.179
Post-PET-N status[6,27]						
Negative versus positive	0.222	0.093–0.501	0.0003	0.324	0.127–0.801	0.015
Surgical factor						
Lymphadenectomy						
3F versus 2F	0.792	0.357–1.873	0.581			
No. of harvested LNs						
≥50 versus <50	0.893	0.362–2.686	0.824			
≥60 versus <60	0.608	0.276–1.401	0.234			
≥70 versus <70	0.850	0.385–1.892	0.686			

HR hazard ratio, *CI* confidence interval, *Ut, Mt, and Lt* upper, middle, and lower thoracic esophagus, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *LNs* lymph nodes

positive), but not post-PET-T status, was the only independent risk factor impacting RFS. Indeed, in the response evaluation using both post-PET-N and -T responses, patients were clearly stratified into survival groups from highest (double negative) to lowest (double positive) according to the post-PET-N response.

The impact of lesion response on prognosis differs markedly between patients with marginally unresectable locally advanced tumor and patients with resectable primary tumor who have multiple LNMs. In the former case, response of the primary tumor has the greatest influence on prognosis, while in the latter, LNM response has the greater influence. Even in an analysis of 4,627 patients with esophageal and esophagogastric junction cancer (from the Worldwide Esophageal Cancer Collaboration) who underwent surgery alone, the number of pLNMs was a better predictor of poor prognosis than pT.[5] Therefore, the focus of resectable TESCC patient treatment should be on LNM number because patients with ≥3 pLNMs despite aggressive NAC showed very dismal prognosis, with a 5-year RFS of only approximately 10 %.

The individualization of multimodality therapy according to optimal response evaluation is the key to further improving clinical outcome. To this end, the post-PET-N response evaluation clearly differentiated NAC responders from nonresponders in patients with resectable TESCC and PET-positive LNs. Post-PET-N positive status is predictive of NAC treatment failure and thus may facilitate timely surgical intervention or a change in treatment regimen, such as a change from platinum-based to taxane-based chemotherapy or the conversion to chemoradiotherapy.

The major limitation of this study is the small sample size due to the strict eligibility criteria, which stipulated that patients had PET-positive LNs and resectable esophageal tumors. On the contrary, however, this selection strengthens our conclusions, because the subject population is a relatively homogenous group. All patients had confirmed pLNMs before NAC as shown in our previous report, and all except one underwent curative resection.[6] Nonetheless, the significance and usefulness of our response criteria must be validated in a future large-scale study.

CONCLUSIONS

PET-N negative status predicts ≤2 pLNMs, a low distant recurrence rate, and a favorable postoperative survival rate irrespective of treatment. Thus, in patients with resectable TESCC and PET-positive LNs, conversion from PET-N positive to negative should be the central response index for NAC, because it suggests adequate systemic control. Hereafter, response evaluation should be shifted from anatomic tumor responses to responses with demonstrated prognostic efficacy according to the patient's tumor stage. During individual therapy, response criteria should be reevaluated according to metabolic response on FDG-PET rather than anatomic response on CT.

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ORIGINAL ARTICLE

Systemic control and evaluation of the response to neoadjuvant chemotherapy in resectable thoracic esophageal squamous cell carcinoma with ^{18}F-fluorodeoxyglucose positron emission tomography-positive lymph nodes

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Abstract
Purpose ^{18}F-fluorodeoxyglucose positron emission tomography-positive lymph nodes (PET-N positive) in patients with resectable thoracic esophageal squamous cell carcinoma (TESCC) are associated with a high rate of postoperative distant recurrence. The purpose of this study was to evaluate the systemic control and survival benefit of neoadjuvant chemotherapy (NAC, cisplatin + doxorubicin + 5-fluorouracil) in these patients.
Methods Of 77 patients with resectable TESCC who were PET-N positive, we evaluated 51 treated with NAC + surgery in this study and 26 who had undergone surgery alone (SA) in a previous study. Historical comparisons of the groups were made, and the response to treatment was evaluated in the NAC group.
Results The NAC group had a higher rate of pN0-1 and a lower rate of postoperative recurrence ($p < 0.0001$ and $p < 0.024$, respectively) than the SA group; however, their relapse-free survival (RFS) rates were not significantly different. The NAC group had a significantly higher RFS in cT1/T2 cases, but showed similar survival in cT3 cases. On the other hand, post-treatment PET-N-negative patients had a higher RFS ($p = 0.008$) and a lower rate of distant recurrence ($p = 0.021$), even with cT3 disease. A multivariate analysis identified the post-treatment PET-N evaluation to be the only significant predictor of the RFS in cT3 cases.
Conclusions NAC significantly suppressed postoperative recurrence in TESCC PET-N-positive patients, but the survival benefit was unclear. However, post-treatment PET-N-negative patients were likely responders to NAC.

Keywords Neoadjuvant chemotherapy · Esophageal squamous cell carcinoma · Lymph node metastasis · Positron emission tomography · Response evaluation · Survival benefit

Introduction

Esophageal carcinoma is a high-grade tumor with a dismal prognosis, although it can be successfully resected. In particular, the presence of multiple pathological lymph node metastases (pLNMs) is associated with a high rate of postoperative recurrence [1–3], especially hematogenous recurrence [3]. Therefore, the survival benefit of neoadjuvant chemotherapy (NAC) has been examined in many randomized controlled trials (RCTs) [4–6]. However, even in the latest meta-analysis, the hazard ratio for all-cause mortality of NAC was 0.88 [95 % confidence interval (CI) = 0.80–0.96] in patients with esophageal adenocarcinoma and 0.92 (95 % CI = 0.81–1.04) in patients with esophageal squamous cell carcinoma (ESCC) [7], thus suggesting that a survival benefit is not observed in ESCC, which is common in Japan. Notably, in all of the RCTs included in this meta-analysis, the R0 resection rates were fairly low: in two of the largest trials included, the rates were 60.9 % (in the RTOG trial 8911; US intergroup 113)

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[8] and 56.5 % (in the OEO2 trial; UK MRC group) [5]. In addition, the percentage of patients with no resection included in those trials was 16.5 and 10.7 %, respectively. The aim for NAC, as described by Kelsen, is (1) to improve the resectability rate by decreasing the size of the primary tumor; (2) to reduce the risk of tumor cell spillage during surgery; and (3) to control subclinical metastases [9]. The first aim could be evaluated from the results of the meta-analyses. However, the second and third aims—the prevention of intraoperative tumor spread and postoperative recurrence necessitating NAC—need to be evaluated in patients with resectable ESCC and multiple LNMs who are likely to have a high rate of distant recurrence in spite of R0 resection, because non-curative resection or no resection greatly affects the outcome of the patients.

We previously reported that ESCC patients showing ^{18}F-fluorodeoxyglucose (FDG) uptake in lymph nodes (LNs) on positron emission tomography (PET), namely, those with PET-positive LNs, might be a high-risk population for postoperative recurrence in spite of curative resection [10]. Approximately 85 % of patients with PET-positive LNs exhibited at least three pathological LNMs, and they had a >2.5 times higher rate of distant recurrence and a <50 % 5-year overall survival (OS) rate compared with patients without PET-positive LNs. These findings suggest that PET-positive LNs are a significant preoperative indicator of systemic disease. The patients with resectable primary tumors and PET-positive LNs may be candidates for NAC, and it is appropriate to examine the usefulness of NAC in this population.

The goal of this study was to clarify the effects of NAC for preventing distant recurrence and improving the survival in ESCC patients. Therefore, we prospectively performed NAC for patients with resectable thoracic ESCC and PET-positive LNs, then evaluated the usefulness of NAC by comparing the outcomes with those of patients with PET-positive LNs in our previous study who underwent surgery without NAC [10].

Methods

Study design and patients

This was a prospective, non-randomized, single-institution clinical study. We performed NAC followed by surgery at Osaka University Hospital for patients who met the following eligibility criteria: cT3 or less, resectable, and histologically confirmed thoracic ESCC, with the presence of PET-positive LNs (FDG uptake on PET observed in LNs within a three-field region, including M1LYM of the supraclavicular, cervical paratracheal and celiac artery LNs) [10], no evidence of distant metastasis, age 20–79 years, Eastern Cooperative Oncology Group performance status 0–1 [11], adequate hematological and visceral function, no severe diabetes mellitus, no severe mental disorder, no prior treatment for the same disease and no active malignant disease. Enrollment was performed from January 2002 to June 2006. At first, patients with two or more PET-positive LNs were included, but since April 2004, all patients with at least one PET-positive LN were eligible, because the patients with PET-positive LNs showed a poor prognosis irrespective of the number of PET-positive LNs in our previous study [10]. The number of patients who were eligible and admitted to our hospital for surgery during the study period was 197, 68 of whom had PET-positive LNs. We excluded 10 patients with only one PET-positive LN during the first half of this study period as described above. We also excluded three patients who required salvage surgery, three who had synchronous or metachronous double cancer (one had prostate cancer and two had gastric cancer) and one who had interstitial pneumonia and was on steroids. Finally, 51 patients were enrolled in this study. Informed consent was obtained from all patients.

Initial and repeat conventional staging by barium esophagography, gastroesophageal endoscopy and neck, thoracic, and abdominal computed tomography (CT), followed by FDG-PET, were performed approximately 2 weeks before the administration and after the completion of NAC for tumor staging according to the 6th edition of the tumor node metastasis classification of the AJCC/UICC [12, 13]. Some patients also underwent magnetic resonance imaging, endoscopic ultrasonography, and/or bronchoscopy to obtain further information. Surgical resection was conducted within 2 weeks of the second FDG-PET examination.

The historical control group included 26 patients with PET-positive LNs from a previous study who met the same eligibility criteria as in this study and underwent surgery alone without NAC (SA group) [10]. The follow-up data for all patients were newly revised. When we compared the 51 patients in this study (NAC group) with the SA group, we analyzed the number of pLNMs, relapse-free survival (RFS), OS and patterns of failure.

This study was approved by the High-Degree Advanced Medical Committee of Osaka University Hospital.

PET imaging and the diagnosis of PET-positive LNs

PET was performed using a dedicated PET scanner (HEADTOME/SET 2400W, Shimadzu Co., Kyoto, Japan) as reported previously [14, 15]. Each patient fasted for at least 4 h before the intravenous administration of approximately 370 MBq of FDG. The blood sugar levels of all patients were <150 mg/dL at the time of the PET scan. Whole body image acquisition was initiated 1 h after the injection. Images of a total of four sections, spanning from

the head to the thigh, were captured for a total of 10 min per section. The images were reconstructed with an iterative median root prior to the reconstruction algorithm (mask size 3 × 3, β 0.3, subsets 24, iteration 1). The acquired PET images were combined with the CT images to yield fusion images by utilizing a commercially available digital software program (T-B Fusion; Shimadzu) [14]. A maximum standardized uptake value (SUV_{max}) of ≥2.5 was defined as positive, because FDG uptake at SUV_{max} <2.5 cannot be seen. A PET-positive LN was defined as the presence of FDG uptake of SUV_{max} ≥2.5 in the region which coincided with the LNs in the CT image, as well as with the primary tumor. All assessments were performed by one radiologist and two surgeons specializing in esophageal cancer.

Neoadjuvant chemotherapy and evaluations

Chemotherapy was administered for two cycles preoperatively. The regimen, FAP, consisted of 5-fluorouracil (700 mg/m^2/day) administered daily for 7 days by continuous intravenous infusion, doxorubicin (35 mg/m^2) administered by intravenous bolus on day 1 and cisplatin (70 mg/m^2) administered intravenously with hydration on day 1 [16]. The courses were repeated twice every 28 days according to the hematological, digestive and renal tolerance of the patients.

The clinical tumor responses were evaluated by CT 2 weeks after the completion of chemotherapy according to the World Health Organization criteria [17, 18]. The tumor metabolic responses were evaluated with FDG-PET and CT in the same period. Patients with a complete metabolic response in the T factor (i.e., SUV_{max} <2.5 after NAC in the primary tumor) were regarded as post-treatment PET-T negative, and those with a complete metabolic response in the N factor (i.e., SUV_{max} <2.5 after NAC in all PET-positive LNs) were regarded as post-treatment PET-N negative. These groups were defined as responders in the T and N factors, respectively.

Surgical treatment

All patients underwent transthoracic subtotal esophagectomy with esophageal reconstruction with a gastric tube (45 patients) or a pedicled jejunum (six patients). A three-field lymphadenectomy was performed for patients with supraclavicular or recurrent laryngeal nerve LNMs in preoperative staging [19] or intraoperative rapid diagnosis [20], or with a primary tumor located in the upper third of the thoracic esophagus. In the lymphadenectomy treatment strategies reported in previous studies, no significant survival differences were observed between patients with two- and three-field lymphadenectomy [19, 20].

Histopathological examination

All nodal materials were dissected separately from the specimen and classified. Conventional histological examinations were performed in all cases and for all harvested LNs. The pathological responses were classified into four main categories as follows: Grade 3, complete disappearance of cancer cells; Grade 2, more than 2/3 disappearance; Grade 1b, <2/3 to >1/3 disappearance; Grade 1a, <1/3 disappearance; Grade 0, no disappearance. All classifications were performed according to the guidelines for clinical and pathological studies on carcinoma of the esophagus by the Japan Esophageal Society [21].

Follow-up studies

All patients who underwent curative R0 resection, excluding one patient with an R2 resection, were followed up without postoperative adjuvant treatment until recurrence was detected. The surviving patients were followed up as outpatients every 3–6 months for the first 5 years, and then on an annual basis. CT scans of the neck, chest and abdomen were performed twice a year, and endoscopy was performed once a year. Recurrent disease was classified as either locoregional (occurring in the mediastinum and upper abdomen) or distant (other areas than locoregional).

Statistical analysis

Differences in the non-continuous data between the two groups were evaluated by χ^2 and Mann–Whitney U tests, and continuous data were compared by Student's t test. The RFS and OS were calculated in all patients, and in all except the one patient who had undergone R2 resection, respectively, by the Kaplan–Meier method, and were calculated from the date therapy was initiated (day 1 of the first NAC in the NAC group and the date of surgery in the SA group) to the date of the first evidence of a relapse and the date of death, respectively, and were compared by the log-rank test. The risk factors were analyzed by Cox's proportional hazards regression model. Differences were considered to be statistically significant for p values <0.05.

Results

Patient characteristics

Table 1 shows the patients' preoperative characteristics at the initial staging in each group and after chemotherapy in the NAC group. At initial staging, the NAC group included a higher number of young patients with a tumor in the

Table 1 The preoperative patient characteristics

Characteristic		Initial staging			Post-treatment staging	
		NAC	SA	*p* value	NAC	*p* value*
No. of patients		51	26			
Sex	Male/female	41/10	25/1	0.062		
Age	Mean (range)	62.7 (42–76)	67.2 (57–80)	0.017		
Tumor location	Upper/middle/lower	4/28/19	7/8/11	0.036		
Histological grade	G1/G2/G3	11/27/13	5/14/7	0.970		
Tumor stage						
T factor	T0/T1/T2/T3/T4	0/4/10/37/0	0/2/10/14/0	0.195	3/18/9/19/2	<0.001
N factor	N0/N1	3/48	1/25	0.703	23/28	<0.001
M factor	M0/M1LYM	27/24	24/2	0.002	44/7	0.087
Stage	0/I/IIA/IIB/III/IV	0/0/0/6/21/24	0/0/0/12/12/2	<0.001	3/12/6/10/13/7	<0.001
SUV_{max} of primary tumor	Mean (range)	12.5 (4.1–20.6)	13.2 (3.1–44)	0.701	7.25 (1.4–22.1)	<0.001
	Positive/negative	0/51			27/24	<0.001
No. of PET-positive LNs	≥0/1/2	0/26/25	0/12/14	0.689	30/15/6	<0.001
Cycles of chemotherapy	0/1/2				0/3/48	
Clinical response	CR/PR/SD/PD				2/26/21/2	

NAC neoadjuvant chemotherapy group, *SA* surgery alone group, *upper/middle/lower* upper, middle and lower third thoracic esophagus, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

* Comparison between the initial and the post-treatment clinical stages in the NAC group

Table 2 The surgical and pathological findings

Characteristic		NAC	SA	*p* value
Lymphadenectomy	2F/3F	16/35	14/12	0.056
Residual tumor	R0/R1/R2	50/0/1	26/0/0	0.472
Tumor stage				
pT factor	T0/T1/T2/T3/T4	4/7/10/26/4	0/2/7/17/0	0.225
pN factor	N0/N1	11/40	0/26	0.011
pM factor	M0/M1LYM	34/17	17/9	0.910
pStage	0/I/IIA/IIB/III/IV	2/4/7/7/14/17	0/0/5/12/9	0.119
No. of harvested LNs	Mean (range)	73.9 (29–160)	58.9 (21–128)	0.023
No. of metastatic LNs	Mean (range)	3.5 (0–18)	5.4 (1–11)	0.032
Pathological response	Grade 0/1a/1b/2/3	4/24/16/3/4		

NAC neoadjuvant chemotherapy group, *SA* surgery alone group, *2F* two-field lymphadenectomy, *3F* three-field lymphadenectomy, *R0* no residual tumor cell, *R1* microscopic residual tumor cells, *R2* macroscopic residual tumor cells, *LN* lymph node

middle or lower thoracic esophagus and a more advanced stage with regard to the cM and cStage factors. Two courses of NAC were completed in 48 patients (94.1 %); the remaining three patients had progressive disease, a decrease in performance status or withdrew from the study. There were no chemotherapy-related deaths and no delays in surgery due to adverse events. Subtotal esophagectomy through a right thoracotomy was performed in all patients (Table 2). R0 resection was performed in all but one patient (R2 resection due to invasion of the left and right pulmonary veins). The number of harvested LNs was greater in the NAC group than in the SA group, reflecting the different ratios of two-field and three-field lymphadenectomy.

The clinical and pathological responses, and the number of LNMs

The overall clinical response rate to NAC was 54.9 % (Table 1), and the pathological responses were grade 0, 1a, 1b, 2 and 3 in four, 24, 16, three and four patients, respectively (Table 2). After NAC, 20 patients converted from cN1 to cN0, and the cStage was downstaged in 30 patients (58.8 %). The average SUV_{max} of the primary tumors decreased significantly after NAC ($p < 0.001$), and the FDG uptake in LNs disappeared in 30 patients (Table 1).

The average number of pLNMs was lower in the NAC group ($p = 0.032$), and no pLNMs were observed in 10

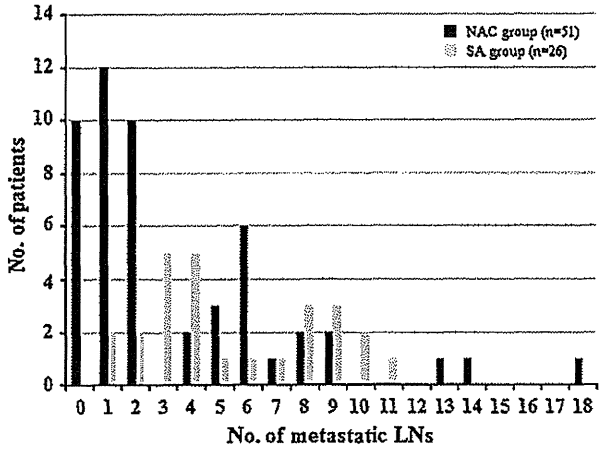

Fig. 1 The distribution according to the number of pathological metastatic lymph nodes and the presence or absence of neoadjuvant chemotherapy (NAC). The *black* and *gray bars* show the results of the NAC and the surgery alone (SA) groups, respectively. The *horizontal line* shows the number of metastatic lymph nodes and the *vertical line* shows the number of patients

patients, compared with no patients in the SA group (Table 2). The ratio of patients with ≤2 pLNMs was 62.7 % in the NAC group compared to 15.4 % in the SA group ($p < 0.0001$) (Fig. 1).

Relapse-free survival and overall survival

There were no postoperative deaths within 30 days and no significant differences between the two groups in the incidence of short-term surgical complications. The median follow-up of censored patients was 81.5 months (range 48.2–120.9 months). During this period, three patients died, one each due to cardiac infarction, septicemia and primary lung cancer. Tumor recurrence was identified in 35 patients, all but three of whom had died by the end of the follow-up period (two with a solitary left supraclavicular LNM and one with a left adrenal metastasis, who are all still alive and recurrence-free following chemoradiation or surgical resection).

Both the RFS and OS in all patients demonstrated a tendency to be about 20 % higher in the NAC group than in the SA group; however, there were no significant differences between the two groups (Fig. 2a, b). Meanwhile, the subgroup analyses performed according to the initial tumor depth revealed that the cT1/T2 cases showed a significantly better RFS and OS ($p = 0.022$ and $p = 0.012$) in the NAC group than those in the SA group (Fig. 3a, b). However, in the cT3 cases, both the RFS and OS were similar between the NAC and SA groups (Fig. 3c, d).

Table 3 shows a comparison of the patient characteristics in the NAC and SA groups for the cT1/T2 and cT3 cases. The cT3 cases had more young patients in the NAC group than in the SA group, and both the cT1/T2 and cT3 cases showed the NAC group to have a higher number of patients with a more advanced pretreatment stage than the SA group. On the other hand, the average number of pLNMs was slightly lower in the NAC group than in the SA group in both the cT1/T2 ($n = 3.29$) and cT3 ($n = 3.59$) cases.

Failure patterns

The patterns of failure were compared in the NAC and SA groups, excluding the one patient with R2 resection (Table 4). The rate of tumor recurrence was significantly lower in the NAC group than in the SA group ($p = 0.024$). In particular, the locoregional recurrence rate was significantly reduced in the NAC group ($p = 0.023$); however, no significant difference was observed in the distant recurrence rate between the two groups. On the other hand, the cT1/T2 cases in the NAC group showed no locoregional recurrence. In addition, they had nearly one-sixth the rate of hematogenous recurrence compared to the values of the SA group

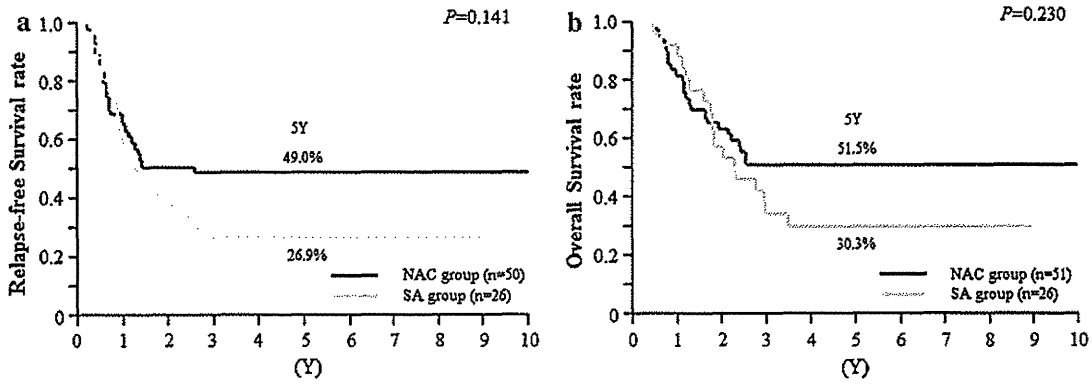

Fig. 2 The relapse-free survival rate (a) and overall survival rate (b) in all patients. The *black* and *gray bars* show the survival curves of the NAC and the SA groups, respectively. *NAC* neoadjuvant chemotherapy, *SA* surgery alone

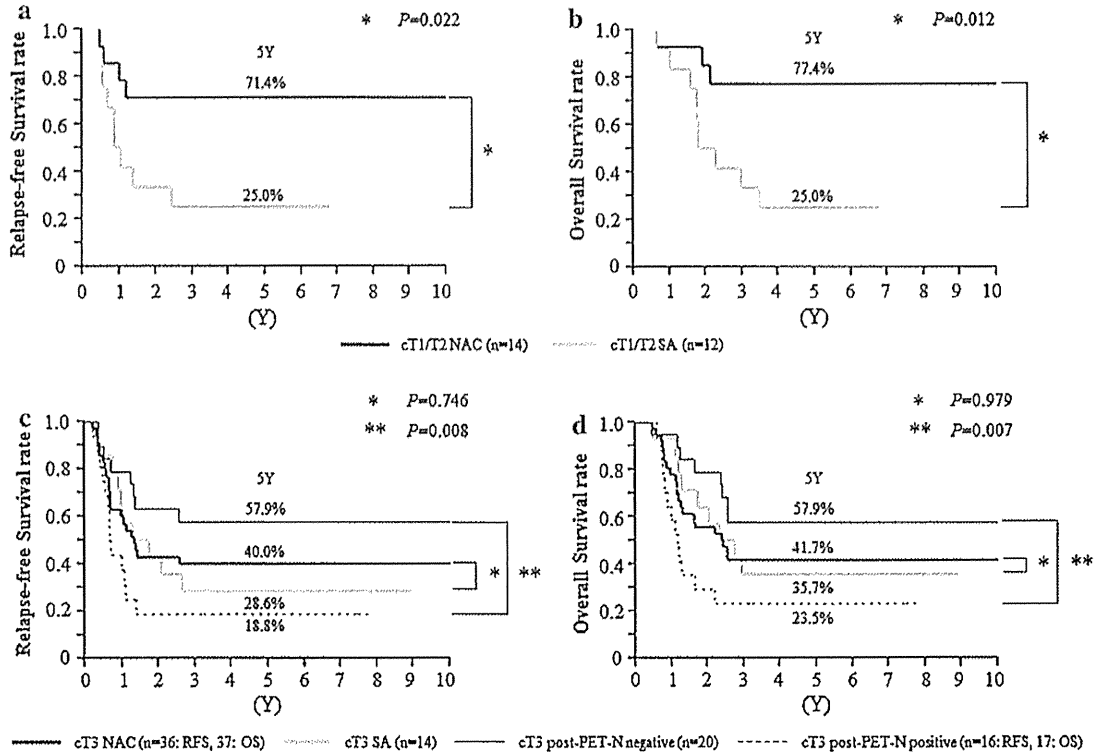

Fig. 3 The relapse-free survival (RFS) and overall survival (OS) rates in patients with cT1/T2 tumors (**a**, **b**) and patients with cT3 tumors (**c**, **d**), respectively. The *bold black* and *gray bars* show the survival curves of the NAC and SA groups, respectively. The *thin* and *dotted black bars* show the survival curves of the post-positron emission tomography-negative and positive lymph nodes in the NAC group, respectively. *NAC* neoadjuvant chemotherapy, *SA* surgery alone

Table 3 The patient characteristics in the NAC and SA groups according to the initial tumor depth

	cT1/T2 cases			cT3 cases		
	NAC	SA	*p* value	NAC	SA	*p* value
Sex: male/female	2/12	0/12	0.173	8/29	1/13	0.226
Age	62.6	63.3	0.811	62.7	70.5	0.002
Location: upper/middle/lower	3/7/4	3/6/3	0.967	1/21/15	2/5/7	0.182
Initial stage						
cN0/N1	0/14	0/12		3/34	0/14	0.272
cM0/M1	7/7	12/0	0.004	19/18	12/2	0.025
cStage IIB/III/IV	6/1/7	12/0/0	0.007	0/20/17	0/12/2	0.037
SUV_{max} of primary tumor, mean	10.5	12.3	0.619	13.3	13.9	0.696
No. of PET-positive LNs: 0/1/≥ 2	0/5/9	0/6/6	0.463	0/21/16	0/6/8	0.375
Pathological stage						
pT0/T1/T2/T3	2/4/4/4	0/2/3/7	0.322	2/3/6/22/4	0/0/4/10/0	0.351
pN0/N1	3/11	0/12	0.089	8/29	0/14	0.058
pM0/M1	9/5	9/3	0.551	25/12	8/6	0.487
pStage0/I/IIA/IIB/III/IV	0/2/1/3/3/5	0/0/0/3/6/3	0.358	2/2/6/4/11/12	0/0/0/2/6/6	0.450
No. of metastatic LNs, mean	3.29	5.17	0.253	3.54	5.64	0.067

NAC neoadjuvant chemotherapy group, *SA* surgery alone group, *upper, middle and lower* location within the thoracic esophagus, *LN* lymph node

Table 4 The patterns of failure

Group	Pattern of failure	NAC	SA	*p* value
All	Locoregional recurrence	5 (10.0 %)	8 (30.8 %)	0.023
	Distant recurrence	21 (42.0 %)	15 (57.6 %)	0.194
	LN (M1LYM)	12 (24.0 %)	6 (23.1 %)	0.928
	Dissemination	3 (6.0 %)	2 (7.7 %)	0.778
	Hematogenous recurrence	13 (26.0 %)	10 (38.5 %)	0.262
	Total recurrence	23/50 (46.0 %)	19/26 (73.1 %)	0.024
cT1/T2	Locoregional recurrence	0 (0.0 %)	4 (33.3 %)	0.019
	Distant recurrence	4 (28.6 %)	7 (58.3 %)	0.126
	LN (M1LYM)	2 (14.3 %)	2 (16.7 %)	0.867
	Dissemination	1 (7.1 %)	1 (8.3 %)	0.910
	Hematogenous recurrence	1 (7.1 %)	5 (41.7 %)	0.037
	Total recurrence	4/14 (28.6 %)	9/12 (75.0 %)	0.018
cT3	Locoregional recurrence	5 (13.9 %)	4 (28.6 %)	0.225
	Distant recurrence	17 (47.2 %)	8 (57.1 %)	0.529
	LN (M1LYM)	10 (27.8 %)	4 (28.6 %)	0.955
	Dissemination	2 (5.6 %)	1 (7.1 %)	0.832
	Hematogenous recurrence	12 (33.3 %)	5 (35.7 %)	0.873
	Total recurrence	19/36 (52.8 %)	10/14 (71.4 %)	0.230

NAC neoadjuvant chemotherapy group, *SA* surgery alone group, *LN* lymph node

($p = 0.037$). On the other hand, in the cT3 cases, both the locoregional and distant recurrence rates were lower in the NAC group, and were less than half of the value of the SA group for locoregional recurrence, although the difference was not significant. When we compared the clinical and PET metabolic responses of the T and/or N factors between the cT1/T2 and cT3 cases, as well as the pathological responses, no significant differences in the response rates were observed, even when they were assessed according to various response categories (Table 5).

The efficacy of NAC in cT3 cases

The preoperative factors impacting the RFS in patients with cT3 tumors, including the pre- and post-treatment factors, are shown in Table 6. The univariate analysis revealed that a metabolic response for the N factor and the number of post-treatment cN-positive cases were significantly associated with the RFS rate; however, as these factors are mutually confounding, we used a lower *p* value to evaluate the post-treatment PET-N as a covariate in a multivariate analysis. When the multivariate analysis was performed after adding the risk factors with a p value <0.1 (i.e., clinical response), a post-treatment PET-N negative status was identified as the only significant factor associated with the postoperative recurrence ($p = 0.025$).

Table 5 The response rates for the cT1/T2 and cT3 cases

Response	cT1/T2	cT3	*p* value
Clinical response in T and N factors	7 (50.0 %)	16 (43.2 %)	0.665
in T factor	8 (57.1 %)	19 (51.4 %)	0.712
in N factor	8 (57.1 %)	18 (48.7 %)	0.588
Post-treatment PET-T negative status	8 (57.1 %)	17 (46.0 %)	0.475
Post-treatment PET-N negative status	10 (71.4 %)	20 (54.1 %)	0.261
Pathological response, Grade 0/Ia/Ib/II/III	0/9/2/1/2	4/15/14/2/2	0.231

PET-T positron emission tomography-response evaluation in primary tumor, *PET-N* PET-response evaluation in lymph nodes

Failure patterns and survival in cT3 cases according to the PET-N response to NAC

The failure patterns were compared between the patients who were post-treatment PET-N positive and those who were PET-N negative (Table 7). The distant recurrence rate was significantly lower in the patients who were post-treatment PET-N negative ($p = 0.021$), although the locoregional recurrence rates were similar. Both the RFS and OS rates were significantly higher in the patients who were post-treatment PET-N negative than in those who were post-treatment PET-N positive ($p = 0.008$ and $p = 0.007$, respectively) (Fig. 3c, d).

Discussion

We performed the present study to clarify the significance of NAC for systemic control of subclinical micrometastases. Therefore, NAC was carried out on the patients with resectable thoracic ESCC who had PET-positive LNs, which were closely related to multiple pLNMs and a high rate of postoperative recurrence, and who were likely to have a poor prognosis [10]. NAC decreased the number of pLNMs, and the ratio of patients with ≤ 2 pLNMs was four times higher in the NAC group than in the SA group. Recurrence was not significantly suppressed at distant sites and no survival benefit was observed. However, a subgroup analysis according to the initial tumor depth showed significant survival benefits in terms of both the RFS and OS

Table 6 The results of the univariate and multivariate proportional hazards regression analyses of the pre- and post-treatment factors affecting the relapse-free survival in patients with cT3 tumors in the NAC group

Risk factor	Univariate analyses			Multivariate analyses		
	HR	95 % CI	*p* value	HR	95 % CI	*p* value
Sex: male vs. female	0.827	0.323–2.531	0.715			
Age ≥70 vs. <70 years	1.013	0.361–2.500	0.978			
Tumor location						
Upper/middle vs. lower	1.105	0.545–2.280	0.781			
Pretreatment factors						
Clinical stage, IV vs. III	1.342	0.629–2.672	0.457			
No. of cN positive, 3≤ vs. ≤2	1.116	0.441–2.654	0.808			
SUV_{max} of the primary tumor						
≥6 vs. <6	1.366	0.215–4.862	0.692			
≥8 vs. <8	1.235	0.285–3.762	0.745			
≥10 vs. <10	1.212	0.398–5.245	0.757			
No. of PET-positive LNs						
≥2 vs. 1	1.205	0.507–1.972	0.677			
≥3 vs. ≤2	1.681	0.568–7.183	0.377			
Post-treatment factors						
Clinical stage IIB/III/IV vs. I/IIA	2.175	0.848–6.672	0.109			
No. of cN positive ≥ 3 vs. ≤ 2	3.769	1.030–11.344	0.046			
Clinical response SD/PD vs. CR/PR	2.234	0.942–5.492	0.068	1.787	0.737–4.487	0.198
Tumor SD/PD vs. CR/PR	1.779	0.747–4.504	0.194			
LN SD/PD vs. CR/PR	2.064	0.867–5.232	0.102			
Post-treatment PET-T positive vs. negative	1.769	0.742–4.484	0.199			
Post-treatment PET-N positive vs. negative	3.200	1.326–8.215	0.010	2.804	1.137–7.339	0.025

HR hazard ratio, *CI* confidence interval, SUV_{max} maximum standardized uptake value, *upper, middle and lower* location within the thoracic esophagus, *LN* lymph node, *NAC* neoadjuvant chemotherapy, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

Table 7 The failure patterns of the cT3 tumors in the patients in the NAC group

Failure pattern	Post-treatment PET-N negative	Post-treatment PET-N positive	*p* value
Locoregional recurrence	3 (15.0 %)	2 (12.5 %)	0.829
Distant recurrence	6 (30.0 %)	11 (68.8 %)	0.021
LN (M1LYM)	4 (20.0 %)	6 (37.5 %)	0.244
Dissemination	0 (0 %)	2 (12.5 %)	0.104
Hematogenous recurrence	5 (25.0 %)	7 (43.8 %)	0.236
Total recurrence	7/20 (35.0 %)	12/16 (75.0 %)	0.017

for cT1/T2 cases in the NAC group due to suppression of both locoregional and hematogenous recurrences. Meanwhile, for cT3 cases, no significant survival benefit was observed in the NAC group, whereas the responders whose FDG uptake in LNs disappeared after NAC treatment showed a lower distant recurrence rate and better RFS and OS rates than non-responders with a PET-N positive status, even after NAC. A multivariate analysis identified a post-treatment PET-N negative status as being a significant independent predictor of postoperative recurrence in patients with cT3 tumors.

Of all malignant diseases, esophageal cancer is remarkable for its progressive nature and poor prognosis. The success or failure of systemic control by neoadjuvant therapy, as well as the quality of local control by surgery, affect the postoperative survival of patients with resectable tumors. This study showed that both hematogenous recurrence and locoregional recurrence were significantly suppressed by NAC in cT1/T2 cases, showing higher RFS and OS rates in the NAC group. However, some may consider the survival rates in the SA group to be poor. To have ≥1 PET-positive LNs, as reported previously, means that there will be ≥3 pLNMs about 85 % of the time [10]. Therefore, even in cT1/T2 cases, the average number of pLNMs was 5.17 in the SA group but still ≥3 in the NAC group, which had a higher number of patients with more advanced initial stage disease than the SA group. According to the analyses conducted by the Worldwide Esophageal Cancer Collaboration, the 50th percentile for the 5-year risk-adjusted survival of ESCC patients with three to six and seven or more pLNMs were about 35 and 20 % in those with pT1 tumors and about 25 and 20 % in those with pT2 tumors, respectively [22]. These results were similar to the 5-year

OS rate of the SA group, which was not inferior to that of the NAC group. Therefore, the improvement of survival observed in the NAC group appears to reflect mainly the response to NAC. Consequently, NAC appears to have an advantage in the systemic control of subclinical micrometastases in cT1/T2 cases.

Our FAP regimen did not significantly suppress distant recurrence in cases with cT3 tumors. Compared with the cT1/T2 and cT3 cases in the NAC group, no significant differences were noted in the clinical and pathological response rates, pathological stage, the number of pLNMs or the patient characteristics (Table 3, p values not shown). Furthermore, all but one patient underwent R0 resection. However, the hematogenous recurrence rate in the NAC group was about fivefold higher in the cT3 cases than in the cT1/T2 cases, whereas that of the SA group was almost equal between the two groups. It is therefore clear that the systemic control by NAC was incomplete in the cT3 cases. In terms of preventing postoperative recurrence, complete eradication, not just a relative reduction of subclinical micrometastases outside the surgical site, is required in NAC. As tumors invade more deeply, the number and volume of subclinical micrometastases is expected to increase. Therefore, NAC with two cycles of the FAP regimen could be sufficient for cT1/T2 tumors, while it is likely insufficient for cT3 tumors, although patients with an advanced initial cStage of III or higher comprised the majority of the cT3 cases in the NAC group.

However, the pretreatment cStage was not a significant risk factor for postoperative recurrence in the cT3 cases. A notable difference in the post-treatment PET-N negative rate was observed between the cT1/T2 and cT3 cases. Because the value of FDG uptake correlates with the tumor size [23], PET-positive LNs indicate not only the presence of LNMs, but also that of LNMs with large metastatic foci (>5 mm) in diameter [10]. They also indicate a poor prognosis, with a 5-year survival rate of about 20 % [24]. In other words, although the mean number of pLNMs was roughly equal between the cT1/T2 and cT3 cases in the NAC group (3.29 vs. 3.54, respectively), large metastatic foci in the LNs was more common in patients with cT3 tumors. Despite this, NAC was not totally ineffective for cT3 tumors. Patients with a post-treatment PET-N negative status (i.e., NAC responders) showed a tendency to have a lower rate of hematogenous recurrence. Consequently, they demonstrated a significantly lower distant recurrence rate and a threefold higher RFS rate than those with a post-treatment PET-N positive status (i.e., non-responders). An increased response rate holds the key for improved survival in patients with cT3 tumors. As a result, conversion of NAC to a more aggressive regimen may provide an advantage for patients with cT3 tumors.

Cunningham et al. [25] reported that a perioperative regimen of ECF (epirubicin + cisplatin + 5-fluorouracil) administered for three cycles preoperatively and three cycles postoperatively significantly improved the progression-free and overall survival in patients with operable gastric or lower esophageal adenocarcinoma. The tumor cell type was different, but considering that >60 % of the enrolled patients had T3 or deeper tumors, this result suggests the usefulness of such aggressive chemotherapy before and after surgery for more advanced tumors. Alternatively, more powerful regimens including taxane agents, such as DCF (docetaxel + cisplatin + 5-fluorouracil), which was reported to show a better overall response rate than ECF for patients with advanced gastric cancer [26] and a high response rate for patients with advanced or recurrent ESCC [27], might be promising.

Accurately evaluating the response to NAC, especially predicting the extent of systemic control, which reflects the postoperative survival, is very important for deciding on the subsequent treatments on an individual basis. However, assessing the effects of treatment on subclinical micrometastases, which differs from assessing the objective response, has been difficult. The present post-treatment PET-N evaluation method is likely the only predictor of postoperative recurrence in patients with cT3 tumors. Even in cases with cT1/T2 tumors, patients with a post-treatment PET-N negative status showed a lower distant recurrence rate of 10 % (1 of 10) compared with 75 % (three of four) in patients with PET-N positive status (data not shown). Because the goal of NAC in resectable tumors is to prevent postoperative recurrence by eradicating systemic micrometastases, evaluating the response in metastatic sites, rather than in primary tumors, is likely a better indicator for systemic control. FDG-PET can be used to accurately and objectively predict the treatment response of LNMs whose evaluation has conventionally been considered difficult. Therefore, post-treatment PET-N evaluation has good potential for use as one of the treatment evaluation criteria for NAC.

The main limitation of our study is the comparison of the NAC group, which was prospectively examined, with the SA group, which was a historical control. As described previously, the SA group had a smaller number of patients with advanced tumors in the initial cStage than the NAC group. Therefore, the patient background was initially different between the groups. However, without NAC, the NAC group would have had a poorer prognosis than the SA group. It is thus unlikely that the efficacy of NAC was overestimated. The potential false-positive evaluation of LNMs by FDG-PET was another limitation. However, the impact on the results was not notable, because PET has a high positive-predictive value of >80 % [28], and PET-positive LNs were evaluated on the basis of the same diagnostic criteria in both the NAC and SA groups, excluding the hilar LNs, which are likely to be responsible

for the false positives [29]. At any rate, this was a non-randomized small-scale study, and therefore, the present results should be confirmed in the near future.

In our series, NAC with the FAP regimen in patients with resectable thoracic ESCC, PET-positive LNs and a poor prognosis revealed no survival benefit, but significantly reduced the number of pLNMs and postoperative recurrences. In patients with cT1/T2 tumors, hematogenous recurrence was significantly suppressed, and a significant survival benefit was obtained. On the other hand, the effect of NAC appeared to be minimal for cT3 tumors. However, patients with a post-treatment PET-N negative status showed a lower hematogenous recurrence rate and higher RFS rate than those with a post-treatment PET-N positive status. Taken together, these findings suggest that an improved response rate to NAC is important. The effectiveness of a more aggressive chemotherapeutic regimen using taxanes, and the usefulness of the post-treatment PET-N evaluation as an indicator for systemic control need to be clarified by a prospective, large-scale, randomized study.

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ORIGINAL ARTICLE

Decreased preoperative plasma substance P concentration is likely associated with postoperative silent aspiration after esophagectomy

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Abstract
Background Postoperative pneumonia is the most common complication after esophagectomy and is closely associated with swallowing dysfunction and silent aspiration. Silent aspiration in the elderly is associated with decreased secretion of substance P (SP), which controls the swallowing and cough reflexes. The majority of patients with esophageal cancer are elderly. We hypothesized that surgical stress would decrease SP secretion, thereby increasing the risk of postoperative aspiration after esophagectomy, and prospectively investigated.
Methods Thirty patients with esophageal cancer scheduled to undergo esophagectomy were enrolled in the study. Plasma and salivary SP concentrations and cough reflex sensitivity were measured before surgery and on postoperative days 2 and 7 to examine the association with postoperative aspiration.
Results Postoperative silent aspiration was observed in 6 patients, 4 of whom developed pneumonia. Plasma SP concentration did not change significantly during the perioperative period. Salivary SP concentration and cough reflex sensitivity could not be measured in nearly one-third of patients because of postoperative dry mouth and unwillingness of patients to undergo measurement, respectively; thus, these perioperative changes could not be assessed. Preoperative plasma and salivary SP concentrations had a significant association with postoperative aspiration on univariate analysis and multivariate logistic regression analysis using variables selected by stepwise forward selection identified preoperative plasma SP concentration as the only significant risk factor for postoperative aspiration ($p = 0.023$).
Conclusion Definitive results supporting our hypothesis could not be obtained. However, multivariate analysis suggested that decreased preoperative plasma SP concentration is likely associated with postoperative silent aspiration after esophagectomy.

Keywords Esophagectomy · Aspiration pneumonia · Substance P · Postoperative complication · Elderly patient

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Introduction

Postoperative pneumonia is one of the life-threatening complications after esophageal cancer surgery [1–3] and its development is associated with many factors, including malnutrition and immunodeficiency due to dysphagia and preoperative therapy, oral flora, unilateral ventilation, prolonged intubation, excess surgical stress due to a long thoracoabdominal surgery, postoperative recurrent laryngeal nerve palsy, and respiratory depression due to postoperative wound pain. With the aim of reducing the risk of postoperative pneumonia, various interventions have been introduced; for example, perioperative enteral nutrition, oral care and respiratory rehabilitation, minimally invasive surgery [4], early extubation and early postoperative ambulation, intense bronchial hygiene with a mini-tracheostomy tube, and epidural analgesia. While these interventions likely improve the patient's pulmonary toilet and contribute to reducing postoperative esophagectomy morbidities, including pneumonia [5], postoperative pneumonia remains the most common complication and the main cause of death after esophagectomy [1–3].