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Prognostic Factors for Patients With Esophageal Squamous Cell Carcinoma After Neoadjuvant Chemotherapy Followed by Surgery

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Abstract. *Background/Aim: Neoadjuvant chemotherapy (NAC) followed by surgery is a standard treatment for patients with locally advanced esophageal cancer. This study aimed to identify patients who might be eligible for postoperative adjuvant therapy. Patients and Methods: We reviewed the surgical outcomes of 84 patients who received NAC followed by esophagectomy to treat esophageal squamous cell carcinoma (ESCC) and revealed prognostic factors associated with locally advanced ESCC. Results: Univariate and multivariate analyses revealed the pretreatment level of squamous cell carcinoma-related antigen [SCC-A; hazard ratio (HR)=1.50, p=0.01], ypT ≥3 (HR=2.51; p=0.04), ypN ≥1 (HR=5.87; p=0.01), ypM1 (HR=2.38; p=0.049), and lymphovascular invasion (HR=3.12, p=0.049) as significant independent covariates for recurrence-free survival (RFS). The 5-year RFS rates for patients with 0-1, 2-3, or 4-5 of these indicators of poor prognosis were 97.1%, 51.2%, and 6.7% (p≤0.001 for all). Recurrence rates among these groups also significantly differed at 2.9%, 50.0%, and 93.3% (p<0.0001). Conclusion: Pretreatment SCC-A, ypT, ypN, ypM, and lymphovascular invasion were significantly associated with RFS in patients with ESCC who received NAC followed by surgery. The status of these prognostic factors in ESCC might indicate a need for postoperative adjuvant therapy after NAC followed by surgery.*

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Neoadjuvant therapy followed by surgery is widely accepted as a standard treatment for locally advanced esophageal cancer (1, 2). In Japan, neoadjuvant chemotherapy (NAC) is a standard recommended treatment for locally advanced esophageal squamous cell carcinoma (ESCC) based on the results of clinical trials (2-4). However, the 5-year survival rate of patients with locally advanced esophageal cancer can reach 60% (1-5), indicating a need for further improvement. The results of a randomized prospective trial associated postoperative adjuvant therapy using nivolumab with significantly longer disease-free survival compared with a placebo in patients with pathological residual tumors after neoadjuvant chemoradiotherapy (NACRT) followed by surgery (6). However, postoperative adjuvant therapy specifically for patients with ESCC after NAC followed by surgery has not been established. One study of adjuvant nivolumab therapy after NACRT followed by surgery found a higher hazard ratio (HR) for ESCC than for esophageal adenocarcinoma (6). Therefore, the possibility of adjuvant therapy should also be considered for ESCC when risk of recurrence remains high after NAC followed by surgery.

We retrospectively evaluated the prognostic factors and survival of patients with locally advanced ESCC who had received NAC followed by surgery at our Institution. This study investigated the clinicopathological indicators that might determine the prognoses of such patients to identify patients who might be eligible for postoperative adjuvant therapy.

Patients and Methods

Patients. Patients underwent a physical examination, basic laboratory tests, chest X-ray, esophagography, upper esophagogastroduodenoscopy and biopsy, and computed tomography (CT) imaging of the neck, chest, and abdomen before starting any kind of treatment and after NAC. Patients were also evaluated using systematic ^{18}F-fluorodeoxyglucose positron-emission tomography/CT imaging before and after NAC. The histological tumor type of all patients was diagnosed as ESCC from biopsy specimens obtained before NAC. The clinicopathological profiles of the tumors were determined based on the eighth edition of the TNM Classification of Malignant Tumors (7).

Patients with performance status 0 or 1 according to the Eastern Cooperative Oncology Group criteria received NAC followed by surgery when the esophageal or gastroesophageal junction cancer were resectable, tumor invasion was worse than cT2, lymph node metastasis was evident (cN+ LNM), or supraclavicular LNM was resectable (cM1 LYM). The present study included patients who had been diagnosed with cStage I (cT1N1M0) to IVB (M1 LYM) before treatment. We reviewed 84 consecutive patients with ESCC who had undergone NAC followed by transthoracic esophagectomy with R0 resection at Hiroshima University Hospital between January 2009 and April 2020. This study was approved by the Institutional Review Board of Hiroshima University (Approval no. E-2225).

NAC and clinical response assessment. NAC consisted of two courses of cisplatin (80 mg/m^2; day 1) and 5-fluorouracil (800 mg/m^2; days 1-5), three courses of docetaxel (70 mg/m^2; day 1), cisplatin (70 mg/m^2; day 1), and 5-fluorouracil (700 mg/m^2; days 1-5), and two courses of nedaplatin (80 mg/m^2; day 1) and 5-fluorouracil (800 mg/m^2; days 1-5) starting every 3 weeks after the previous course (8). Clinical tumor responses before NAC and at preoperative restaging were compared according to the Response Evaluation Criteria in Solid Tumors (9).

Surgery. Esophagectomy was scheduled for all patients at 3-6 weeks after completing NAC. All patients underwent thoracoscopic or open transthoracic esophagectomy with at least thoracic and abdominal (two-field) lymphadenectomy. Esophageal cancer in the upper and middle third of the thoracic esophagus and LNM in the superior mediastinum were essentially treated by cervical, thoracic, and abdominal (three-field) lymphadenectomy. Esophagi were reconstructed using a gastric tube or jejunum. Postoperative complications were determined according to the Clavien-Dindo classification (10).

Pathological assessment. Resected esophageal and LN specimens were promptly fixed in formalin fluid after esophagectomy. All areas that appeared to be primary tumors before treatment were cut into 5-mm sections, embedded in paraffin, and stained by hematoxylin and eosin. The degree of residual tumor and tumor depth were pathologically assessed. Lymphovascular invasion (LVI) was diagnosed from images of lymphatic and venous walls in specimens stained by hematoxylin and eosin, D2-40, and elastica van Gieson.

The pathological responses to NAC were graded from 0-3 according to the Japanese classification of esophageal cancer (11) as: no cytological or histological response (0), viable cancer cells account for ≥66% (1a), ≥33% but <66% (1b), and <33% (2) of tumor tissues, and no viable cancer cells (3).

Follow-up protocol and recurrence. All patients underwent physical examination, laboratory tests and CT imaging every 3-4 months for at least 2 years after NAC followed by surgery and every 6 months from 3 years thereafter and annual esophagogastroduodenoscopy. Almost all survivors attended an outpatient clinic for annual health checks after 5 years.

Tumor recurrence was determined at the first apparent site of metastasis. Locoregional recurrence was defined as tumor occurring at the site of initial esophagectomy or LN dissection (including LNs in the neck, mediastinum, or upper abdomen). Distant recurrence was defined as hematogenous metastasis within solid organs, pleural dissemination, or LNM at the abdominal para-aorta or other distant sites. Synchronous locoregional and distant recurrence was defined as "combined".

Table I. *Patient characteristics (n=84).*

Clinical parameter		Value
Age, years	Mean±SD	65.2±9.5
Sex, n (%)	Male	62 (73.8)
	Female	22 (26.2)
ECOG PS, n (%)	0	74 (88.1)
	1	10 (11.9)
Primary tumor location, n (%)	Upper third	10 (11.9)
	Middle third	47 (56.0)
	Lower third and esophagogastric junction	27 (32.1)
Pre-treatment CEA, ng/ml	Mean±SD	2.8±1.7
Pre-treatment SCC-A, ng/ml	Mean±SD	1.4±0.9
Pre-therapeutic cT, n (%)*	1	19 (22.6)
	2	25 (29.8)
	3	38 (45.2)
	4	2 (2.4)
Pre-therapeutic cN, n (%)*	0	28 (33.3)
	1	44 (52.4)
	2	12 (14.3)
	3	0 (0)
Pre-therapeutic cM (supraclavicular LNM), n (%)*	0	76 (90.5)
	1	8 (9.5)
Pre-therapeutic cStage, n (%)*	I	18 (21.4)
	II	33 (39.3)
	III	25 (29.8)
	IV	8 (9.5)

CEA: Carcinoembryonic antigen; ECOG PS: Eastern Cooperative Oncology Group performance score; LNM: lymph node metastasis; SCC-A: squamous cell carcinoma-related antigen; SD, standard deviation. *According to the TNM classification, 8th edition (7).

Statistical analysis. Categorical and continuous variables were compared using chi-square and unpaired *t*-tests, respectively. Overall survival (OS) was defined as time elapsed from the day of surgery until the day of death from any cause. Recurrence-free survival (RFS) was defined as time elapsed between the day of surgery and the day of cancer recurrence or death from any cause. Both OS and RFS were estimated from Kaplan-Meier curves, and survival differences between patient groups were determined using log-rank analysis. *p*-Values and hazard ratios with 95% confidence interval in multivariate analyses were calculated using the Cox regression model with forward stepwise selection. Statistical significance was taken at $p<0.05$. All data were statistically calculated using JMP statistical software package (version 15.0; JMP, Inc., Chicago, IL, USA).

Results

Patient characteristics. Table I, Table II and Table III show pre-treatment clinical factors, NAC data and the surgical factors, and pathological factors, respectively, of our cohort of 84 patients. The pre-treatment clinical cancer stages were I, II, III, and IV for 18 (21.4%), 33 (39.3%), 25 (29.8%), and 8 (9.5%) patients, respectively. The pathological stages were

Table II. *Neoadjuvant therapy and surgical characteristics of patients (n=84).*

Parameter	Subgroup	Value
Neoadjuvant chemotherapy, n (%)	CDDP/5-FU	64 (76.2)
	CDDP/DOC/5-FU	15 (17.9)
	NDP/5-FU	5 (6.0)
Clinical response (RECIST), n (%)	Complete response	6 (7.1)
	Partial response	54 (64.3)
	Stable disease	20 (23.8)
	Progressive disease	4 (4.8)
Type of surgery, n (%)	Open	40 (47.6)
	Thoracoscopic	44 (52.4)
Lymph node dissection, n (%)	Thoracic+abdominal	32 (38.1)
	Cervical, thoracic+abdominal	52 (61.9)
Operative duration, min	Median (range)	505 (280-1,003)
Blood loss, ml	Median (range)	292 (13-1,920)
Dissected lymph nodes, n	Median (range)	45 (11-98)
Postoperative complications, grade*	0	30 (35.7)
	1	8 (9.5)
	2	22 (26.2)
	3	21 (25.0)
	4	3 (3.6)
	5	0 (0)

CDDP: Cisplatin; DOC: docetaxel; 5-FU: 5-fluorouracil; NDP: nedaplatin; RECIST: Response Evaluation Criteria in Solid Tumors (9). *Clavien-Dindo classification.

Table III. *Pathological characteristics of patients (n=84).*

Pathological parameter	Subgroup	Frequency, n (%)
ypT[a]	0 (pCR of primary tumor)	11 (13.1)
	Tis	2 (2.4)
	1	28 (33.3)
	2	10 (11.9)
	3	30 (35.7)
	4	3 (3.6)
ypN[a]	0	34 (40.5)
	1	22 (26.2)
	2	23 (27.4)
	3	5 (6.0)
ypM (supraclavicular LNM)[a]	0	76 (90.5)
	1	8 (9.5)
ypStage[a]	0	9 (10.7)
	I	18 (21.4)
	II	15 (17.9)
	III	27 (32.1)
	IVA	3 (3.6)
	IVB	8 (9.5)
	T0N+	4 (4.8)
Tumor differentiation (resected specimen)	Well	9 (10.7)
	Moderate	34 (40.5)
	Poor	16 (19.0)
	pCR or SCC-A (not assessable)	25 (29.8)
Lymphovascular invasion	Yes	38 (45.2)
	No	46 (54.8)
Pathological response grade[b]	0	6 (7.1)
	1a	43 (51.2)
	1b	7 (8.3)
	2	17 (20.2)
	3	11 (13.1)

PCR: Pathological complete response; LNM: lymph node metastasis; SCC-A: squamous cell carcinoma. [a]TNM Classification, 8th edition (7). [b]Response evaluation criteria of Japan Esophageal Society (11).

0, I, II, III, IVA and IVB for 9 (10.7%), 18 (21.4%), 15 (17.9%), 27 (32.1%), 3 (3.6%), and 8 (9.5%) patients, respectively. Pathological residual tumors in LNs only (T0N+) were discovered in four (4.8%) patients.

Survival after NAC with surgery. Fifty-nine of the patients remained alive at the time of this outcome analysis, 23 died of esophageal cancer and two died of other causes. The median follow-up of survivors was 62.1 (range=24-159) months after surgery. The 5-year RFS and OS rates for patients overall were 62.2% and 69.7% respectively (Figure 1A and B).

Prognostic factors after NAC followed by surgery. We extracted significantly independent prognostic factors from the clinicopathological features of RFS using Cox proportional hazards analysis (Table IV). The results of univariate analyses showed that male sex, and values for carcinoembryonic antigen, squamous cell carcinoma-related antigen (SCC-A), cT, clinical response, ypT, ypN, ypM, LVI, and pathological response were significant prognostic factors associated with RFS. Furthermore, multivariate analysis subsequently identified increasing SCC (HR=1.50, p=0.01), ypT ≥3 (HR=2.51, p=0.04), ypN ≥1 (HR=5.87, p=0.01), ypM1 (HR=2.38, p=0.049), and LVI (HR=3.12, p=0.049) as significant independent covariates for poor RFS.

Rates of RFS according to prognostic factors. The RFS rates according to the significant prognostic factors in the above analyses were estimated from Kaplan-Meier curves. The 5-year RFS rates for patients with SCC-A ≤1.5 ng/ml (normal) and >1.5 ng/ml were 70.8% and 48.2%, respectively (p=0.04; Figure 2A). The 5-year RFS rates for patients with ypT stages 0-2 and 3-4 were 81.7% and 31.3 %, respectively (p<0.001; Figure 2B). The 5-year RFS rates for patients with ypN stage 0 and those with stage 1/2/3 were 97.1% and 37.4%, respectively (p<0.001; Figure 2C). The 5-year RFS rates were 68.9% and 0.0% for patients with ypM stage 0 and 1 (p<0.001; Figure 2D), respectively, and 91.3% and 28.5% for those without and with LVI, respectively (p<0.001; Figure 2E).

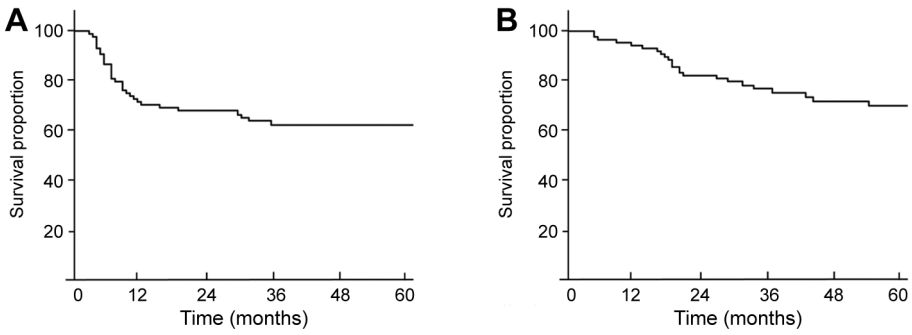

Figure 1. *Survival after neoadjuvant chemotherapy followed by surgery for esophageal squamous cell carcinoma. Recurrence-free (A) and overall (B) survival rates considering all patients (n=84).*

Survival and recurrence according to the number of prognostic factors. We evaluated survival rates and recurrence according to three groups based on the number of poor prognosis indicators, 0-1, 2-3, and 4-5 (Figure 3 and Table V). The corresponding 5-year RFS rates were 97.1%, 51.2%, and 6.7% (0-1 *vs*. 2-3: $p<0.001$; 0-1 *vs*. 4-5: $p<0.001$; 2-3 *vs*. 4-5: $p=0.001$; Figure 3A), respectively, and the 5-year OS rates for these groups were 96.8%, 60.0%, and 26.7%, respectively (0-1 *vs*. 2-3: $p<0.001$; 0-1 *vs*. 4-5: $p<0.001$; 2-3 *vs*. 4-5: $p=0.001$; Figure 3B).

Disease recurred after NAC and surgery in 32 (38.1%) out of 84 patients and at locoregional, distant, and combined sites in 9 (28.1%), 14 (43.8%) and 9 (28.1%) patients, respectively. Recurrence rates significantly differed among patients with 0-1, 2-3, and 4-5 indicators of poor prognosis (2.9%, 50.0%, and 93.3%, respectively, $p<0.0001$). Sites of recurrence sites did not significantly differ among the prognostic groups ($p=0.50$).

Discussion

Although NAC followed by surgery can be effective against locally advanced ESCC, some patients still develop recurrence (1-5). Postoperative adjuvant therapy as well as early detection of recurrence followed by prompt treatment might further improve the survival of patients with ESCC who undergo NAC followed by surgery. Therefore, we evaluated prognostic indicators in patients with locally advanced ESCC who underwent NAC and curative-intent esophagectomy. We found that pretreatment SCC-A value, ypT, ypN, and ypM status, and LVI were independently and significantly associated with RFS. Therefore, survival rates were significantly stratified according to these factors.

Staging cancer based on T, N, and M status is prognostically significant for ESCC (7). Our findings of RFS indicated that ypTNM, rather than cTNM status before treatment can serve as a prognostic predictor for ESCC after NAC followed by surgery. Clinical staging of cT, cN, and cM status was less prognostically relevant (12, 13), and thus the important objectives of initial staging would be to identify the resectability of locally advanced ESCC for patients who receive neoadjuvant therapy. The tumor response to chemotherapy substantially differs among individuals and influences subsequent tumor staging. Pathological TNM status after NAC not only reflects the inherent extent of tumors but also the degree of tumor responses to NAC. Therefore, ypT, ypN, and ypM were all naturally independent prognostic factors for patients with ESCC after NAC followed by surgery, as shown herein.

Neoadjuvant chemotherapy can reduce the number of LNMs and improve the outcomes of patients with ESCC after esophagectomy (14). Several studies have found that ypN status is an extremely important prognostic factor for patients with ESCC who are treated by NAC followed by surgery (15, 16). The findings of residual tumor tissues in LNs after NAC might be a clear benchmark of malignant potential such as tumor metastatic ability and resistance to chemotherapy. The degree of aggressive tumor behavior in ESCC might be closely associated with residual LNM after NAC. Therefore, postoperative adjuvant therapy should be considered necessary for patients with pathological LNM not only after upfront surgery, but also after NAC followed by surgery.

Supraclavicular LNM is diagnosed as M1 LYM (stage IVB) in the TNM classification (7). Pathological supraclavicular LNM was also an independent prognostic factor, and the prognosis of patients with supraclavicular LNM was very poor in the present study. However, others have suggested that supraclavicular LNM in patients with ESCC who were treated with NAC then surgery reflects the total number of LNMs (17), and such metastasis is regarded as regional LNM (18-20). The prognostic value of supraclavicular LNM can change according to the location of primary tumors (21). Furthermore, few prospective trials have compared two- and three-field LN dissections, and the effects and safety of supraclavicular LN dissection await elucidation (22). Large prospective studies should evaluate the effects of supraclavicular LN dissection to

Table IV. *Univariate and multivariate analyses of preoperative factors for recurrence-free survival.*

		Univariate			Multivariate		
Variable	Subgroup	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Age, years	Continuous	0.98	0.95-1.02	0.33	–	–	–
Sex	Female	1			–	–	–
	Male	3.23	1.15-9.09	**0.03**	–	–	–
ECOG PS	0	1			–	–	–
	1	1.13	0.40-3.23	0.81	–	–	–
Pretreatment CEA, ng/ml	Continuous	1.25	1.08-1.44	**0.003**	–	–	–
SCC-A, ng/ml	Continuous	1.60	1.23-2.09	**<0.001**	1.50	1.12-2.00	**0.01**
Main tumor location	U/M	1			–	–	–
	L/EGJ	0.65	0.29-1.45	0.29	–	–	–
cT[a]	0/1/2	1			–	–	–
	3/4	2.56	1.26-5.22	**0.01**	-	-	
cN[a]	0	1			–	–	–
	1/2	1.37	0.80-2.36	0.25	-	-	
cM[a]	0	1			–	–	–
(supraclavicular LNM)	1	2.20	0.84-5.75	0.11	–	–	–
Chemotherapy	Other	1			–	–	–
	DCF	1.16	0.48-2.82	0.74	–	–	–
Clinical response	CR/PR	1			–	–	–
(RECIST)	SD/PD	3.65	1.84-7.24	**<0.001**	–	–	–
Surgical procedure	Open	1			–	–	–
	Thoracoscopic	0.78	0.39-1.55	0.78	–	–	–
Lymph node dissection	Thoracic+abdominal	1			–	–	–
	Cervical, thoracic+abdominal	1.46	0.70-3.08	0.32	–	–	–
Median operative duration, min	Continuous	1.00	0.996-1.002	0.66	–	–	–
Median blood loss, ml	Continuous	1.00	0.999-1.001	0.54	–	–	–
Dissected lymph nodes, n	Continuous	1.02	0.996-1.04	0.12	–	–	–
Postoperative	0/1	1			–	–	–
complications[b]	2/3/4	1.32	0.66-2.66	0.44	–	–	–
ypT[a]	0/1/2	1			1		
	3/4	5.87	2.76-12.50	**<0.001**	2.51	1.05-6.00	**0.04**
ypN[a]	0	1			1		
	1/2/3	12.08	3.63-40.27	**<0.001**	5.87	1.55-22.23	**0.01**
ypM[a]	0	1			1		
(supraclavicular LNM)	1	5.93	2.59-13.57	**<0.001**	2.38	1.004-5.64	**0.049**
Tumor differentiation	Other	1			–	–	–
	Poor	1.25	0.54-2.88	0.61	–	–	–
Lymphovascular invasion	Yes	1			1		
	No	11.42	4.35-30.01	**<0.001**	3.12	1.004-9.67	**0.049**
Pathological response grade[c]	0/1a	1			–	–	–
	1b/2/3	0.13	0.04-0.36	**<0.001**	–	–	–

CEA: Carcinoembryonic antigen; CI: confidence interval; CR: complete response; DCF: docetaxel, cisplatin, and 5-fluorouracil; ECOG PS: Eastern Cooperative Oncology Group performance score; EGJ: esophagogastric junction; HR: hazard ratio; L: lower third; LNM: lymph node metastasis; M: middle third; PD: progressive disease; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumors: SCC-A: squamous cell carcinoma-related antigen; SD: stable disease; U: upper third. [a]TNM classification, 8th edition (7). [b]Clavien-Dindo classification. [c]Response evaluation criteria of Japan Esophageal Society (11). Statistically significant *p*-values are shown in bold.

treat regional LNM in patients with ESCC after neoadjuvant therapy followed by surgery.

The invasion of lymphatic ducts and vessels by tumor cells also indicates aggressive malignant behavior. The presence of LVI is clearly associated with LNM in patients with superficial esophageal cancer (23). Therefore, additional treatment such as surgery and chemoradiotherapy should be considered when LVI is diagnosed after endoscopic resection in such patients (24). Furthermore, lymphatic invasion and venous invasion are independent prognostic factors for

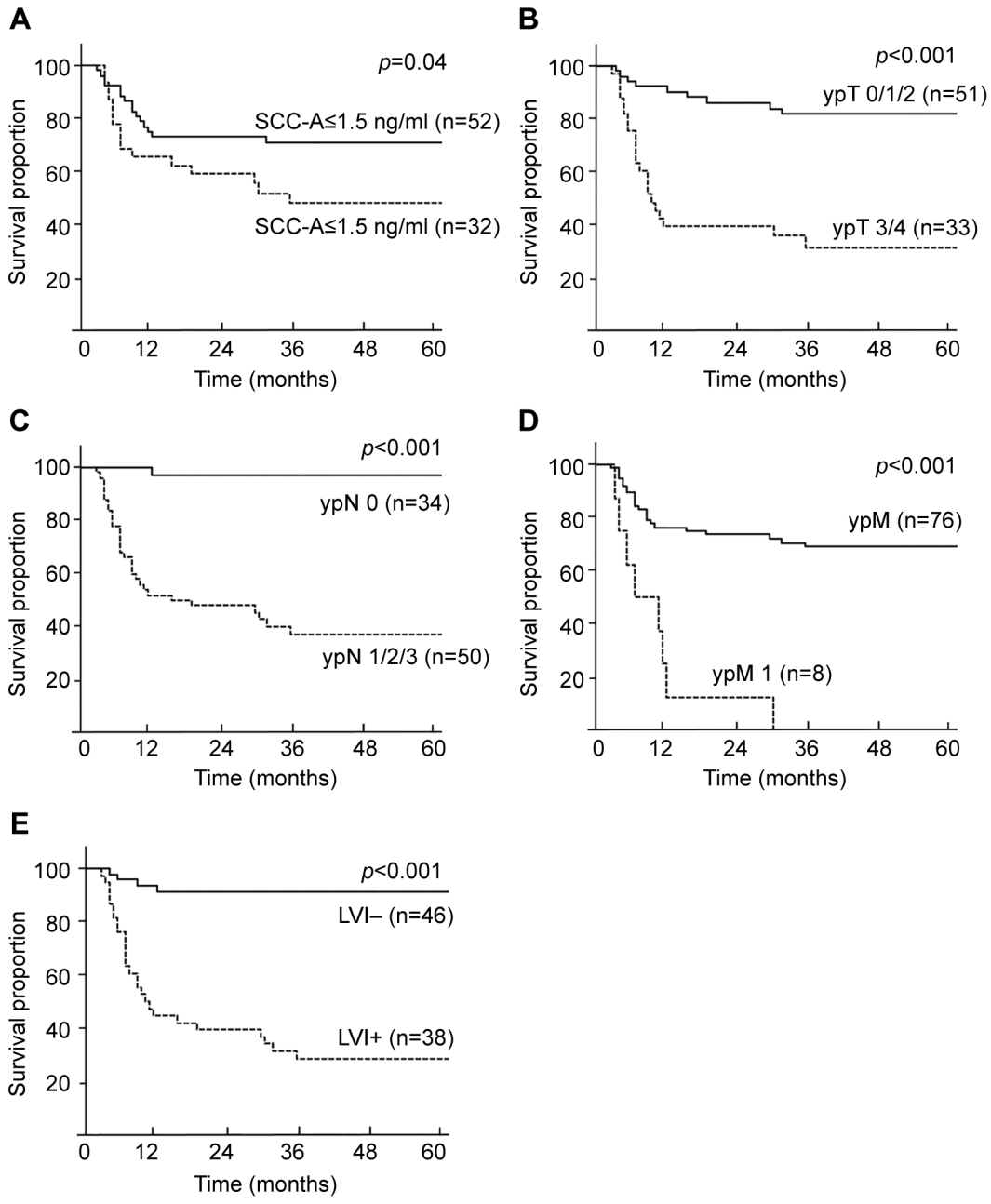

Figure 2. *Recurrence-free survival associated with prognostic factors after neoadjuvant chemotherapy followed by surgery for esophageal squamous cell carcinoma. Recurrence-free survival rates of patients according to squamous cell carcinoma-related antigen (SCC-A) level (p=0.04) (A), ypT stage (p<0.001) (B), ypN stage (p<0.001) (C), ypM stage (p<0.001) (D), and lymphovascular invasion (LVI) (p<0.001) (E).*

survival not only after initial surgical ESCC resection (25, 26), but also after NAC followed by surgery (27). If LVI was included as a criterion for conventional TNM staging of patients with locally advanced ESCC undergoing NAC followed by surgery, the RFS curves of each novel stage would show the stratification of each stage more clearly than the current staging system (20). The present study similarly found that LVI is an independent prognostic factor along with ypT, ypN, and ypM.

The outcome of a prospective randomized trial of nivolumab as adjuvant therapy was positive for patients with pathological residual tumors (ypT+ and/or ypN+) after NACRT followed by R0 resection (6). However, the optimal candidates for postoperative adjuvant therapy are supposed

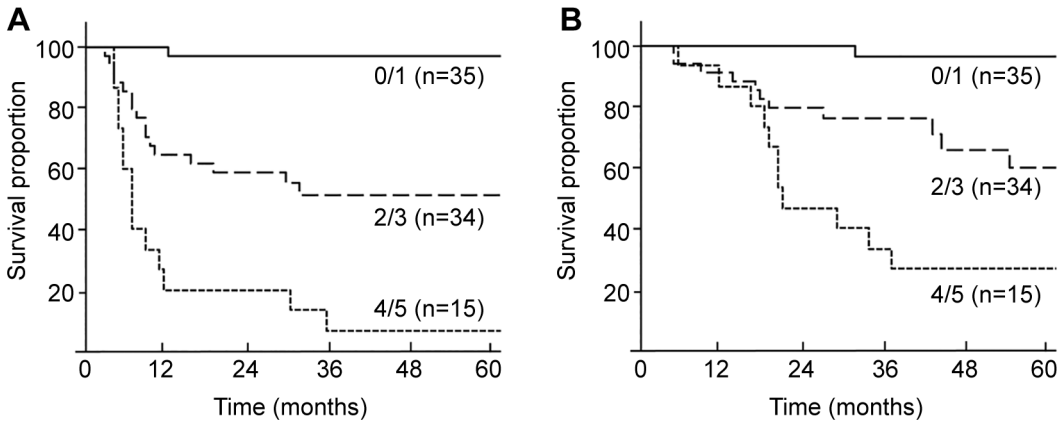

Figure 3. *Survival associated with the number of factors of poor prognosis determined after neoadjuvant chemotherapy followed by surgery. Recurrence-free (A) and overall (B) survival rates for patients with 0-1, 2-3, and 4-5 factors of poor prognosis (0-1 vs. 2-3, 0-1 vs. 4-5, 2-3 vs. 4-5: p≤0.001 for all).*

Table V. *Site of recurrence according to prognostic factors.*

Number of prognostic factors	Recurrence, n (%)			Recurrence site, n (%)			
	No (n=52)	Yes (n=32)	*p*-Value	Locoregional (n=9)	Distant (n=14)	Combined (n=9)	*p*-Value
0, 1 (n=35)	34 (97.1)	1 (2.9)	**<0.0001**	1 (100)	0 (0)	0 (0)	0.50
2, 3 (n=34)	17 (50.0)	17 (50.0)		4 (23.5)	7 (41.2)	6 (35.3)	
4, 5 (n=15)	1 (6.7)	14 (93.3)		4 (28.6)	7 (50.0)	3 (21.4)	

to differ between patients with ESCC after NAC and NACRT due to different rates of tumor and pathological complete responses to these therapies. The present study found significantly different recurrence rates, and that survival rates were significantly stratified according to the number of prognostic factors. Recurrence should be predicted among patients with ESCC who received NAC followed by surgery based on a combination of several criteria rather than a prognostic factor to select candidates for adjuvant therapy.

The present study is limited by having a single-center, retrospective design, variations in chemotherapy regimens at different times throughout the investigation, and the inclusion of patients treated until April 2020. The 2-year follow-up period might be somewhat insufficient to assess long-term postoperative prognoses or recurrence. However, it should be noted that >80% of cancers recur within 2 years, even after curative esophagectomy (28, 29).

In conclusion, pretreatment SCC-A value, ypT, ypN and ypM, as well as LVI, were significant prognostic factors associated with RFS for patients with ESCC who received NAC followed by surgery. Additional postoperative adjuvant treatment including novel modalities should be implemented to improve the therapeutic outcomes of patients with ESCC and the above indicators of poor prognosis.

Conflicts of Interest

The Authors have no commercial support or conflicts of interest to disclose.

Authors' Contributions

NK and YH drafted the article. NK, YH, ME, TK, TY, RH, and MOh contributed to patient care. NK, YH, and MOk performed the literature search. ME, TK, TY, RH, MOh, and MOk participated in the critical revision of the article. All Authors read and approved the final article.

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