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Risk Factors for Recurrence in Esophageal Squamous Cell Carcinoma Without Pathological Complete Response After Trimodal Therapy

TOMOAKI KUROKAWA, YOICHI HAMAI, MANABU EMI, YUTA IBUKI, TORU YOSHIKAWA, MANATO OHSAWA, RYOSUKE HIROHATA and MORIHITO OKADA

Department of Surgical Oncology, Hiroshima University, Hiroshima, Japan

Abstract. *Background/Aim: Intensive trimodal therapy is needed for locally advanced esophageal squamous cell carcinoma (ESCC). The prediction of recurrence is especially required for patients with pathological residual tumors in the resected primary sites and/or lymph nodes [non-pathological complete response (pCR)] who have a high possibility of recurrence after trimodal therapy. We aimed to determine the risk factors for cancer recurrence in ESCC patients diagnosed with non-pCR after trimodal therapy. Patients and Methods: We evaluated the risk factors for recurrence-free survival (RFS) using the multivariate Cox proportional hazards analysis, based on data from 105 ESCC patients diagnosed with non-pCR after neoadjuvant chemoradiotherapy followed by esophagectomy. Results: Univariate analysis revealed that RFS was significantly associated with postoperative complications, pathological T, N, M stage after therapy (ypT, ypN, ypM), tumor differentiation, lymphovascular invasion (LVI), and pathological response of the primary tumor. Subsequent multivariate analysis revealed postoperative complications ypN, tumor differentiation, and LVI as independent variables for RFS. The RFSs significantly differed between patients with and without these risk factors. Conclusion: Severe postoperative complications, ypN 2/3, poor tumor differentiation, and LVI were significantly associated with poor RFS. These factors may be used as prognostic factors in patients with non-pCR after trimodal therapy.*

An intensive trimodal approach comprising neoadjuvant chemoradiotherapy (NCRT) followed by surgery is frequently administered to locally control and improve the survival of patients with locally advanced esophageal cancers (1, 2). The prognosis after trimodal therapy is closely associated with tumor responses to NCRT, and the prognoses of patients with pathological complete responses (pCR) after trimodal therapy are significantly better than those of patients with pathological residual tumors at the resected primary sites and/or lymph nodes (LNs) (non-pCR) (3-8). The clinical factors associated with prognosis of esophageal squamous cell carcinoma (ESCC) with pCR after trimodal therapy, such as total chemotherapy dose, presence and absence of induction chemotherapy before NCRT and number of dissected LNs, have been indicated by few previous reports (9-11).

Cancer recurrence still occurs at a significant frequency in many patients with non-pCR, and the 5-year survival rates of such patients have been reported to be 20%-45% even after intensive and curative trimodal therapy (3-8). The necessity for postoperative therapy is actually considered for esophageal cancer patients with pathological non-response, pathological LN metastasis, or non-pCR even after highly invasive trimodal therapy (12-14). Therefore, prediction and prevention of recurrence is much more required for patients with non-pCR who have a higher possibility of recurrence and poorer prognosis after trimodal therapy, compared to patients with pCR.

Taking into account this consideration, as well as the fact that prognostic factors, including various pathological factors after trimodal therapy, can be evaluated only in patients with non-pCR, we aimed to assess the risk factors for cancer recurrence in ESCC patients diagnosed with non-pCR after trimodal therapy.

Patients and Methods

Patients. ESCC patients with a performance status of 0 or 1 according to the Eastern Cooperative Oncology Group criteria (15) underwent NCRT and surgery. Moreover, patients with resectable cancer in the thoracic esophagus or gastroesophageal junction, where tumors are more invasive than in the muscularis propria (clinical T2-T3), LN metastasis (clinical N+), or resectable

Correspondence to: Yoichi Hamai, Department of Surgical Oncology, Hiroshima University, 1-2-3 Kasumi, Minami-Ku, Hiroshima 734-8551, Japan. Tel: +81 822575866, Fax: +81 822567109, e-mail: yyhamai@hotmail.com

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supraclavicular (clinical M1 LYM) were treated with NCRT and surgery. Some patients with clinical T4 primary tumors that had been reduced and thus rendered potentially resectable after NCRT underwent esophagectomy. All histological tumor types were diagnosed as ESCC from biopsy samples obtained before treatment. The clinicopathological profiles of the tumors, as well as the definition of R0 resection as neither microscopic nor macroscopic residual tumors after surgery were based on the TNM Classification of Malignant Tumors, 7th edition (16).

We reviewed 149 consecutive ESCC patients who underwent NCRT followed by esophagectomy with R0 resection at Hiroshima University Hospital between October 2003 and October 2017. A pCR was defined as the complete pathological disappearance in both primary tumors and all dissected LNs [ypT0N0M (LYM) 0 ypStage 0], and non-pCR was defined as the pathological residual tumor in the resected primary site and/or dissected LNs. Forty-three patients had pCR and 106 had non-pCR. All patients with pCR (n=43) as well as one patient with non-pCR, who died of non-occlusive mesenteric ischemia as a postoperative complication one month after surgery because this patient could not be evaluated for recurrence, were excluded from the present study. Therefore, the remaining 105 patients with non-pCR were included in the present study. The Institutional Review Board at Hiroshima University approved this study.

Neoadjuvant chemoradiotherapy and surgery. NCRT comprised concurrent radiotherapy (40 Gy) and chemotherapy with 5-fluorouracil plus either docetaxel, cisplatin, or both, as described (6-8, 17-22). Thirty-two (30.5%), 58 (55.2%), 10 (9.5%), and 5 (4.8%) patients were treated with docetaxel/5-fluorouracil, cisplatin/5-fluorouracil, docetaxel/cisplatin/5-fluorouracil, and nedaplatin/5-fluorouracil, respectively.

Five fractions per week of external beam radiotherapy with 10-MV X-rays were applied for 4 weeks (total dose of 40 Gy). Three-dimensional treatment was planned using a computed tomography (CT) simulator. The radiation field for upper thoracic tumors included the region from the supraclavicular and mediastinal LN to the carina. The field for mid-thoracic or lower thoracic tumors included the mediastinal and perigastric LN, and the supraclavicular fossa was included if the upper mediastinal nodes were positive. The field for esophagogastric junction tumors included the mediastinal (below the subcarinal), perigastric, and celiac LN. The primary tumor was included with a 2-cm craniocaudal margin (17-19).

All patients were surgically treated for 4-8 weeks after completing NCRT. All patients underwent open transthoracic or thoracoscopic esophagectomy and at least two–field LN dissection (thoracic and abdominal fields). Esophageal cancer in the upper and middle third of the thoracic esophagus or LN metastasis in the superior mediastinum was essentially treated by cervical lymphadenectomy (three-field LN dissection: cervical, thoracic, and abdominal fields). The gastric tube or colonic conduit was subsequently lifted via the posterior mediastinal or retrosternal route for cervical anastomosis with the esophagus. We graded postoperative morbidity based on the Clavien–Dindo classification of surgical complications (23).

Pathological examination. The resected esophageal and LN specimens were fixed in formalin immediately after surgery. All areas that were thought to be primary tumors before treatment were cut into 5-mm sections, embedded in paraffin, and stained with hematoxylin and eosin (H&E). Residual tumors and tumor depth were pathologically assessed. Specific immunostaining (D2-40) and Elastica van Gieson stain were routinely applied along with standard H&E staining to evaluate lymphovascular invasion (LVI). All LNs were cut along the longest axis and stained with H&E, and metastasis was evaluated.

The pathological response of primary tumors was graded according to the response evaluation criteria for the effects of radiation and/or chemotherapy published by the Japan Esophageal Society and were as follows: 0, no recognizable cytological or histological therapeutic effect; 1, slightly effective with apparently viable cancer cells accounting for at least one-third of the tumor tissue; 2, moderately effective with viable cancer cells accounting for less than one-third of the tumor tissue; and 3, markedly effective with no evidence of viable cancer cells (24).

Follow-up protocol. All patients underwent postoperative medical and blood examinations and CT imaging every 3-4 months for at least 2 years after surgery and every 6 months thereafter, and annual endoscopy. More detailed examinations were performed if any symptoms were reported. After 5 years, almost all survivors attended an outpatient clinic for annual health checks. Recurrence was diagnosed by radiology and, when possible, by cytology or histology.

Statistical analysis. Recurrence-free survival (RFS) was defined as the amount of elapsed time from the date of surgery until the first event (recurrence or death from any cause) or the most recent follow-up. The effects of various clinical and pathological parameters on survival were evaluated using the univariate analysis, and independent influences were assessed using the multivariate Cox proportional hazards analysis. Covariates with $p<0.05$ in the univariate analysis were entered into multivariate analyses. Survival data were also analyzed using the Kaplan–Meier method and compared using the log-rank test. All data were statistically analyzed using the SPSS software (version 20.0, IBM, Armonk, NY, USA).

Results

Clinical, surgical, and pathological findings in patients with non-pCR after trimodal therapy. The characteristics of the patients before treatment, surgical factors, and pathological findings after trimodal therapy are shown in Table I. The pretreatment clinical stages (cStage) of cancer were IB, II, III, and IV in 4 (3.8%), 23 (21.9%), 68 (64.8%), and 10 (9.5%) patients, respectively.

Open and thoracoscopic esophagectomy proceeded in 89 (84.8%) and 16 (15.2%) patients, respectively. The median surgical duration was 445 min (range=290-638). The median blood loss was 400 ml (range=136-2460). Postoperative complications according to the Clavien–Dindo classification (23) were identified in 42 (40.0), 2 (1.9), 21 (20.0), 26 (24.8), 8 (7.6), and 6 (5.7) patients in grades 0, 1 ,2, 3a, 3b, and 4, respectively.

The pathological stages of cancer were I, II, III, and IV in 20 (19.0%), 39 (37.1%), 27 (25.7%), and 5 (4.8%) patients, respectively. Although the primary tumor had completely disappeared as a result of NCRT, 14 (13.3%) patients had residual metastases in the dissected LN ($ypT0N^{+}$), and 41

Table I. *Characteristics of patients*.

	n=105
Age, years (mean±SD)	63.6±7.8
Gender	
Male	88 (83.8)
Female	17 (16.2)
Performance status[1]	
0	90 (85.7)
1	15 (14.3)
Primary tumor location	
Upper third	20 (19.0)
Middle third	52 (49.5)
Lower third and esophagogastric junction	33 (31.4)
cT[2]	
2	14 (13.3)
3	88 (83.8)
4	3 (2.9)
cN[2]	
0	22 (21.0)
1	60 (57.1)
2	21 (20.0)
3	2 (1.9)
cM[2] (supraclavicular lymph node metastasis)	
0	95 (90.5)
1	10 (9.5)
cStage[2]	
IB	4 (3.8)
II	23 (21.9)
III	68 (64.8)
IV	10 (9.5)
Operative procedure	
Open thoracotomy	89 (84.8)
Thoracoscopic surgery	16 (15.2)
Operative duration, min [median (range)]	445 (290-638)
Blood loss, ml [median (range)]	400 (136-2460)
Blood transfusion	
+	27 (25.7)
–	78 (74.3)
Postoperative complication[3]	
Grade 0	42 (40.0)
Grade 1	2 (1.9)
Grade 2	21 (20.0)
Grade 3a	26 (24.8)
Grade 3b	8 (7.6)
Grade 4	6 (5.7)
ypT[4]	
0	14 (13.3)
1	19 (18.1)
2	28 (26.7)
3	41 (39.0)
4	3 (2.9)
ypN[4]	
0	40 (38.1)
1	47 (44.8)
2	14 (13.3)
3	4 (3.8)
ypM[4] (Supraclavicular lymph node metastasis)	
0	100 (95.2)
1	5 (4.8)
ypStage[4]	
I	20 (19.0)
II	39 (37.1)
III	27 (25.7)
IV (M1 lymph node)	5 (4.8)
T0N+	14 (13.3)
Tumor differentiation by resected specimen	
Well-differentiated	9 (8.6)
Moderately-differentiated	36 (34.3)
Poorly-differentiated	33 (31.4)
pCR or not assessable	27 (25.7)
Lymphovascular invasion	
+	41 (39.0)
–	64 (61.0)
Pathological response of primary tumor[5]	
Grade 1	33 (31.4)
Grade 2	58 (55.2)
Grade 3	14 (13.3)

pCR: Pathological complete response; SD: standard deviation. [1]Eastern Cooperative Oncology Group performance status. [2]Pretherapeutic staging according to the TNM Classification criteria, 7th edition. [3]According to Clavien–Dindo classification. [4]Pathological staging according to the TNM classification criteria, 7th edition. [5]Grade of pathological response of primary tumors according to the Japan Esophageal Society.

(39.0%) had LVI. The pathological responses of primary tumors to NCRT in 33 (31.4%), 58 (55.2%) and 14 (13.3%) patients were graded as 1, 2, and 3, respectively, according to the criteria of the Japan Esophageal Society (24). Since only patients with R0 resection were evaluated in the present study, treatment failure (grade 0) was not observed,

Univariate and multivariate analyses for recurrence-free survival. Factors affecting RFS of patients after trimodal therapy were investigated using the univariate and multivariate analyses (Table II). At univariate analysis, postoperative complications [grade <3b *vs*. ≥3b: Hazard ratio (HR)=2.04; 95% confidence interval (CI)=1.09-3.79; p=0.03], ypT (0/1/2 *vs*. 3/4: HR=1.67; 95% CI=1.06-2.62; p=0.03), ypN (0/1 *vs*. 2/3: HR=2.24; 95% CI=1.29-2.62; p=0.03), ypM (0 *vs*. 1: HR=4.44; 95% CI=1.72-3.91; p=0.004), tumor differentiation (others *vs*. poorly: HR=1.71; 95% CI=1.07-2.72; p=0.02), LVI (– *vs*. +: HR=2.06; 95% CI=1.31-3.23; p=0.002), and pathological response of primary tumor (Grade 1 *vs*. 2/3: HR=0.060; 95% CI=0.38-0.96; p=0.03) were significantly associated with RFS.

Subsequently, the factors identified as significant in univariate analysis, were further tested in multivariate analysis. The results revealed that postoperative complications (grade

Table II. *Univariate and multivariate analyses for recurrence-free survival after trimodal therapy.*

Variables	Recurrence-free survival					
	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Age (continuous)	1.01	0.98-1.04	0.87			
Gender						
Female	1					
Male	1.65	0.82-3.31	0.16			
Performance status[1]						
0	1					
1	1.30	0.71-2.38	0.39			
Primary tumor location						
Upper and middle third	1					
Lower third and esophagogastric junction	1.09	0.67-1.75	0.74			
Carcinoembryonic antigen (ng/ml)	1.07	0.99-1.14	0.10			
Squamous cell carcinoma-related antigen (ng/ml)	1.01	0.93-1.10	0.80			
Thoracic surgical procedure						
Open thoracotomy	1					
Thoracoscopic surgery	1.68	0.89-3.14	0.11			
Surgical duration (min)	1.00	0.99-1.00	0.31			
Blood loss (g)	1.00	1.00-1.00	0.13			
Blood transfusion						
–	1					
+	1.11	0.67-1.83	0.68			
Postoperative complications[2]						
<Grade 3b	1			1		
≥Grade 3b	2.04	1.09-3.79	**0.03**	2.02	1.04-3.94	**0.04**
ypT[3]						
0/1/2	1			1		
3/4	1.67	1.06-2.62	**0.03**	1.34	0.82-2.21	0.24
ypN[3]						
0/1	1			1		
2/3	2.24	1.29-3.91	**0.004**	1.98	1.06-3.68	**0.03**
ypM[3] (supraclavicular LN metastasis)						
0	1			1		
1	4.44	1.72-11.49	**0.002**	2.44	0.86-6.84	**0.09**
Tumor differentiation (resected specimen)						
Others	1			1		
Poorly	1.71	1.07-2.72	**0.02**	1.67	1.04-2.70	**0.03**
Lymphovascular invasion						
–	1			1		
+	2.06	1.31-3.23	**0.002**	1.74	1.02-2.96	**0.04**
Pathological response of primary tumor[4]						
Grade 1	1			1		
Grade 2/3	0.60	0.38-0.96	**0.03**	1.11	0.64-1.94	0.72

CI: Confidence interval; EG: esophagogastric junction; L: lower third; HR: hazard ratio; M: middle third; U: upper third. Statistically significant *p*-values are shown in bold. [1]Eastern Cooperative Oncology Group performance status. [2]According to the Clavien–Dindo classification. [3]Pathological staging according to the TNM classification criteria, 7th edition. [4]Grade of pathological response of primary tumors according to the Japan Esophageal Society.

<3b *vs*. 3b: HR=2.02; 95% CI=1.04-3.94; *p*=0.01), ypN (0/1 *vs*. 2/3: HR=1.98; 95% CI=1.06-3.68; *p*=0.03), tumor differentiation (others *vs*. poorly: HR=1.67; 95% CI=1.04-2.70; *p*=0.03), and LVI (without *vs*. with HR=1.11; 95% CI=1.02-2.96; *p*=0.04) were independent significant factors associated with RFS.

Survival according to risk factors for recurrence. The RFS rates according to risk factors of recurrence in patients with non-pCR after trimodal therapy are shown in Figure 1. The 5-year RFS of patients with postoperative complications < and ≥grade 3b according to the Clavien–Dindo classifications were 42.6% and 14.3%, respectively, (Figure 1A, *p*=0.02). The 5-

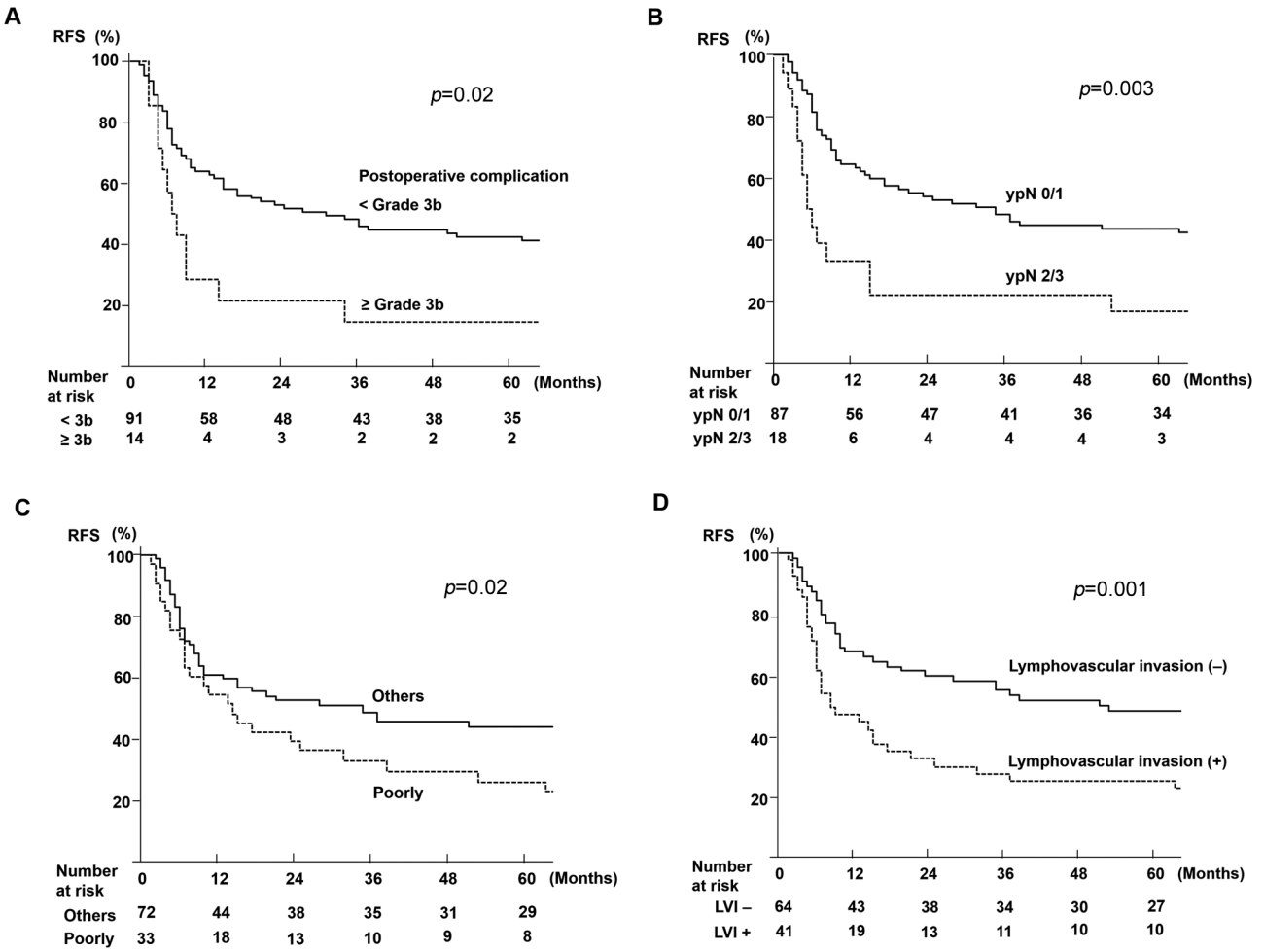

Figure 1. *Survival associated with prognostic factors in patients with non-pCR after trimodal therapy. Recurrence-free survival (RFS) rates of patients with postoperative complications < and ≥ grade 3b according to the Clavien–Dindo classifications (p=0.02) (A). RFS rates of patients with ypN 0/1 and 2/3 (p=0.003) (B). RFS rates of patients with the poorly-differentiated tumor and others (p=0.02) (C). RFS rates of patients with and without lymphovascular invasion (p=0.001) (D).*

year RFS rates of patients with ypN 0/1 and 2/3 were 43.4% and 16.7%, respectively, (Figure 1B, p=0.003). The 5-year RFS rates of patients with poorly-differentiated tumors and others were 44.4% and 26.4%, respectively, (Figure 1C, p=0.02). The 5-year RFS rates of patients with and without LVI were 48.0% and 24.4%, respectively (Figure 1D, p=0.001).

Discussion

ESCC is one of the most aggressive types of malignancy. Although NCRT followed by surgery can be effective against locally advanced ESCC, some patients, especially those with non-pCR, still frequently develop recurrence even after trimodal therapy. The early detection of recurrence, prompt treatment, and postoperative adjuvant therapy might further improve survival of some patients with non-pCR after trimodal therapy. Therefore, we evaluated the prognostic value of specific clinical, surgical and pathological factors, in patients with locally advanced ESCC who underwent NCRT followed by curative intent esophagectomy and had a pathological residual tumor in the resected specimens, even after such intensive treatment. We found that severe postoperative complications (≥grade 3b according to the Clavien–Dindo classification), ypN status, tumor differentiation, and LVI were independent prognostic factors for RFS in ESCC patients with non-pCR after trimodal therapy.

Esophageal surgery is highly invasive, and various postoperative complications after esophageactomy have been reported to be significantly associated with overall, recurrence-free, and disease-specific survival (25-28). The implications of postoperative complications with respect to the prognosis

of esophageal cancer patients are associated with various issues such as poor general status before treatment, inherent immunological capacity and immunocompromised status, poor nutrition. Moreover, they are associated with insufficient therapy after recurrence according to an overall decline in general status induced by severe postoperative complications (22). Furthermore, we have previously reported that the postoperative CRP levels could predict the prognosis of esophageal cancer patients (29). The elevated postoperative CRP levels are thought to indicate persistent inflammation, and systemic inflammation due to postoperative complications may cause the cancer development (29). The relationship between severe postoperative complications and cancer recurrence might be attributable to complex interactions and the effects of these factors. Therefore, minimally invasive surgery should focus on reducing postoperative complications to improve survival outcomes.

Pathological LN metastasis is an important prognostic factor for esophageal cancer treated with NCRT followed by surgery (8, 9, 22). The present multivariate analysis also selected ypN2/3 as a significant independent risk factor for RFS. Patients with multiple pathological LN metastases even after NCRT might be considered resistant to chemotherapy and radiotherapy (8). Moreover, they have a very high probability of unrecognized occult metastases during treatment (8). Consequently, postoperative therapy, preferably with anticancer drugs that differ from those used in NCRT, should be carefully considered for patients with multiple pathological LN metastases to delay and decrease recurrence after trimodal therapy.

Lymphatic and/or venous invasion is an independent prognostic factor for poor survival after the initial ESCC surgical resection (30, 31) as well as after neoadjuvant therapy followed by surgery (32). Specifically, LVI had prognostic value in ESCC patients treated with NCRT followed by surgery, which have the same histological type and treatment modality as in the present study (32). Additionally, LVI has been shown as a significant prognostic factor for survival in node-negative ESCC patients who underwent esophagectomy (33). In the present study, LVI was also an independent predictive factor for recurrence in ESCC with non-pCR after trimodal therapy. Thus, LVI is an indicator of highly aggressive behavior, even in various situations for ESCC.

Tumor differentiation was also a significant independent predictive factor for RFS in the present study and has been identified as important for prognostic grouping in the AJCC staging system (16). It has been shown that to distinguish well-differentiated from moderately-differentiated and poorly-differentiated types is important for classifying the prognosis of stage I and II ESCC (16). Furthermore, some previous reports on esophageal cancer have shown that poorly-differentiated ESCC is associated with early recurrence and death after esophagectomy (34), as well as with a higher risk for developing distant metastasis after multimodal therapy (35). Postoperative adjuvant therapy as well as strict surveillance might be needed for further improvement of survival for poorly-differentiated ESCC.

The retrospective design and the chemotherapy regimens that varied at different times during the study period are the main limitations of the present study. Nonetheless, the present study also included a relatively large cohort of uniform patients with locally advanced ESCC who underwent NCRT with 40 Gy of radiation followed by surgery with adequate LN dissection. To our knowledge, this is the first report to evaluate the risk factors for recurrence in patients with non-pCR after trimodal therapy.

In conclusion, severe postoperative complications (≥ grade 3b according to the Clavien–Dindo classification), ypN 2/3, poor tumor differentiation, and LVI were shown to be independent prognostic factors for RFS in patients with non-pCR after trimodal therapy. The prognosis of patients with these factors was especially poor even after trimodal therapy. Therefore, further prevention of postoperative complications is needed to improve the postoperative general condition as well as the prognosis for esophageal cancer patients, and meticulous surveillance is required for early detection of recurrence, especially in patients with recurrence risk factors. Postoperative adjuvant therapy should be considered for such patients, taking into account their general condition after trimodal therapy.

Conflicts of Interest

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

Authors' Contributions

TK and YH drafted the article. TK, YH, ME, YI, TY, MO, and RH contributed to patient care. TK and YH performed the literature search. ME, YI, TY, MO, RH, and MO participated in the critical revision of the article. All the authors read and approved the final article.

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