ANTICANCER RESEARCH *39*: 1433-1440 (2019)
doi:10.21873/anticanres.13259

Early Recurrence and Cancer Death After Trimodal Therapy for Esophageal Squamous Cell Carcinoma

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Abstract. *Background/Aim: Although locally advanced esophageal squamous cell carcinoma (ESCC) can be controlled and survival can be prolonged by neoadjuvant chemoradiotherapy (NCRT) followed by surgery (trimodal therapy), some patients still develop early recurrence and die of cancer even after such intensive therapy. The present study aimed to determine the factors associated with early recurrence and cancer death for patients with ESCC treated by trimodal therapy. Patients and Methods: We evaluated risk factors for recurrence within 6 months, as well as cancer death within 1 year based on data from 141 patients with ESCC who underwent NCRT followed by curative esophagectomy. Results: The carcinoembryonic antigen level before treatment, postoperative complications, pathology after neo-adjuvant therapy (ypT, ypN), lymphatic invasion, venous invasion and pathological response of the primary tumor were significant factors in a comparison of patients with and without early recurrence. Multivariate analysis subsequently selected ypN [ypN, 0/1 vs. 2/3; hazard ratio (HR)=4.13, 95% confidence interval (CI)=1.25-13.66; p=0.02] as an independent covariate for early recurrence. Postoperative complications, ypT, ypN, poorer tumor differentiation, lymphatic invasion and venous invasion were significant factors in a comparison of patients with and without early cancer death. Multivariate analysis subsequently selected postoperative complications of grade ≥3b (vs. <3b) defined according to the Clavien–Dindo classification (HR=5.9, 95% CI=1.53-23.47; p=0.01) and venous invasion (vs. without: HR=4.80, 95% CI=1.21-19.14; p=0.03) as independent covariates for early cancer death. Conclusion: Further reduction of postoperative complications are needed after NCRT for patients with ESCC. Meticulous surveillance and postoperative adjuvant therapy should be considered for patients with risk factors for early recurrence and cancer death.*

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Key Words: Chemoradiation, complication, esophagus, lymph node, vascular invasion.

Neoadjuvant therapy is currently the standard of care in locally advanced esophageal cancer because randomized studies have shown a significant survival benefit. Trimodal therapy comprising neoadjuvant chemotherapy, radiotherapy and surgery is frequently needed for local control and to improve the survival of patients with locally advanced esophageal cancer (1-3). Although the survival of patients with esophageal cancer has been improved, some still develop recurrence and die of cancer even after curative-intent procedures and intensive treatment. Therefore, the reported range of the 5-year survival rates of patients with locally advanced esophageal cancer after trimodal therapy is 30-50% (2-6).

Some studies have found that patients with esophageal cancer develop early recurrence or die of cancer ever after curative esophagectomy (7-14). However, to our knowledge, risk factors for early recurrence and early cancer death after trimodal therapy for locally advanced esophageal squamous cell carcinoma (ESCC) have never been investigated. The present study aimed to determine risk factors that influence early recurrence as well as early cancer death after neoadjuvant chemoradiotherapy (NCRT) followed by curative-intent esophagectomy in patients with locally advanced ESCC.

Patients and Methods

Patients. Patients defined as having performance status 0 or 1 according to the Eastern Cooperative Oncology Group criteria (15) received NCRT and underwent surgery if the cancer in the

esophagus or gastroesophageal junction was resectable, or if a tumor was more deeply invasive than cT2, positive for lymph node (LN) metastasis (cN+) or resectable supraclavicular LN metastasis (cM1 LYM). Five patients with cT4 primary tumors that had been reduced and thus rendered potentially resectable after NCRT underwent esophagectomy.

We reviewed 155 consecutive patients with ESCC who underwent NCRT followed by esophagectomy at our Institution between September 2003 and July 2016. Two patients with tumors in the cervical esophagus, 10 with incomplete resection (R2) and two with unrelated death within 1 year of esophagectomy were excluded. Therefore, we assessed data from 141 patients with locally advanced ESCC included in our surgical database who underwent NCRT followed by curative esophagectomy.

Table I shows the characteristics of the patients. The clinicopathological profiles of the tumors were based on the seventh edition of the TNM Classification of Malignant Tumors (16). Postoperative morbidity was graded from 0 to 5 based on the Clavien–Dindo classification of surgical complications (17, 18). The Institutional Review Board at Hiroshima University approved this study (Approval number: E-1501).

NCRT and surgery. NCRT and surgery comprised concurrent radiotherapy (40 Gy in 20 fractions) and chemotherapy with 5-fluorouracil and either docetaxel or cisplatin or a combination of both, as described elsewhere (4, 5, 19-23). The chemotherapy regimen between 2003 and 2007 consisted of docetaxel combined with 5-fluorouracil and that since 2008 has consisted of standard doses of cisplatin and 5-fluorouracil. Patients with elevated serum creatinine were treated with nedaplatin instead of cisplatin. Some patients were treated with docetaxel combined with cisplatin and 5-fluorouracil starting from 2009. The chemotherapy regimens were docetaxel/5-fluorouracil, cisplatin/5-fluorouracil, docetaxel/cisplatin/5-fluorouracil, or nedaplatin/5-fluorouracil in 34 (24.1%), 85 (60.3%), 18 (12.8%) and four (2.8%) patients, respectively.

Surgery was scheduled for all patients at 4 to 8 weeks after completing NCRT. All patients underwent open transthoracic or thoracoscopic esophagectomy and at least two-field (thoracic and abdominal fields) LN dissection. Esophageal cancer in the upper and middle third of the thoracic esophagus, and LN metastasis in the superior mediastinum were essentially treated by cervical lymphadenectomy. A gastric tube or colonic conduit was subsequently lifted via the posterior mediastinal or retrosternal route for cervical anastomosis with the esophagus.

Pathological assessment. 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-eosin. The residual tumor and tumor depth were pathologically examined. A pathological complete response (pCR) of a primary tumor was defined as no evidence of viable cancer cells. Specific immunostaining (D2-40) and elastica van Gieson stain were routinely applied, along with standard hematoxylin and eosin staining, to evaluate lymphatic and venous invasion, respectively. All LNs were cut along the longest axis and stained with hematoxylin-eosin, then examined for metastases.

Follow-up protocol and definition of early recurrence and death. All patients underwent postoperative medical and blood examinations and computed tomography imaging every 3-4 months for at least 2 years after surgery and every 6 months from 3 years thereafter and annual endoscopy. More detailed examinations proceeded if any symptoms were reported. After 5 years, almost all survivors attended an

Table I. *Patient characteristics*.

Parameter	n=141
Age, years	
Mean±SD	62.9±8.1
Gender, n (%)	
Male	122 (86.5)
Female	19 (13.5)
ECOG PS, n (%)	
0	129 (91.5)
1	12 (8.5)
Primary tumor location, n (%)	
Upper third	27 (19.1)
Middle third	71 (50.4)
Lower third and esophagogastric junction	43 (30.5)
cT, n (%)*	
1	2 (1.4)
2	19 (13.5)
3	115 (81.6)
4	5 (3.5)
cN, n (%)*	
0	32 (22.7)
1	78 (55.3)
2	29 (20.6)
3	2 (1.4)
cM, n (%)*#	
0	123 (87.2)
1	18 (12.8)
cStage, n (%)*	
IB	6 (4.3)
II	30 (21.3)
III	87 (61.7)
IV	18 (12.8)
ypT, n (%)**	
0	54 (38.3)
1	17 (12.1)
2	26 (18.4)
3	40 (28.4)
4	4 (2.8)
ypN, n (%)**	
0	80 (56.7)
1	41 (29.1)
2	16 (11.3)
3	4 (2.8)
ypM, n (%)**#	
0	135 (95.7)
1	6 (4.3)
ypStage, n (%)**	
0	41 (29.1)
I	19 (13.5)
II	46 (32.6)
III	29 (20.6)
IV	6 (4.3)

SD, Standard deviation; ECOG PS: Eastern Cooperative Oncology Group performance status. *Pretherapeutic/**pathological staging according to TNM Classification, seventh edition (16). #Supraclavicular lymph node metastasis.

outpatient clinic for annual health checks. Recurrence was diagnosed by radiology and, when possible, by cytology or histology. Early recurrence was defined as arising within 6 months after surgery (7), and early cancer death as occurring within 1 year after surgery as described elsewhere (8-12).

Statistical analysis. Categorical variables were analyzed using chi-square tests, and continuous variables were analyzed using unpaired *t*-tests. Covariates with $p<0.05$ in the univariate analysis were entered into logistic multivariate analyses to select independent factors for early recurrence and early cancer death. Survival data were analyzed using Kaplan–Meier curves and compared using log-rank tests. Recurrence-free survival (RFS) was defined as the time elapsed from the date of surgery until the first event (recurrence or death from any cause), or the most recent follow-up. Overall survival (OS) was defined as the time elapsed from the date of surgery until death from any cause or the most recent follow-up. All patients who remained alive were followed-up for at least 5 years after surgery. At the time of the outcome analysis, 49 patients remained alive and were followed-up for a median of 91.7 (range=30.1-165.3) months after surgery. All data were statistically analyzed using SPSS software version 20.0 (IBM Corporation, Armonk, NY, USA).

Results

Comparison of clinicopathological factors between patients with and without early recurrence and early cancer death. Table II shows a comparison of patients with and without early recurrence, as well as those with and without early cancer death. Disease recurred after trimodal therapy in 61 (43.3%) patients, among whom cancer recurred within 6 months after NCRT followed by esophagectomy in 29 (47.5%). Furthermore, 21 (34.4%) out of the 61 patients with recurrence died of esophageal cancer within 1 year after NCRT followed by esophagectomy.

Various clinicopathological factors were compared between patients with and without early recurrence. This comparison showed that increasing carcinoembryonic antigen levels before treatment ($p=0.02$), severe postoperative complications (Clavien–Dindo classification ≥3b, $p=0.03$), pathology after neo-adjuvant therapy ypT (2/3/4, $p=0.01$) and ypN (2/3, $p<0.0001$), lymphatic invasion ($p<0.0001$), venous invasion ($p=0.004$) and lack of pathological complete response (pCR) of the primary tumor ($p=0.03$) were significantly associated with early recurrence.

Furthermore, a comparison of clinicopathological parameters between patients who died early and those who did not found that severe postoperative complications (Clavien–Dindo classification ≥3b, $p=0.002$), ypT (2/3/4, $p=0.03$), ypN (2/3, $p=0.001$), tumor differentiation (poorly differentiated, $p=0.02$), lymphatic invasion ($p=0.01$) and venous invasion ($p=0.001$) were significant factors associated with early cancer death.

Multivariate analysis of clinicopathological factors associated with early recurrence and early cancer death. Table III shows the results of multivariate analyses of factors that were significant in univariate analyses for early recurrence and early cancer death. Multivariate analysis selected ypN 2/3 (hazard ratio (HR)=4.13, 95% confidence interval (CI)=1.25-13.66; $p=0.02$) as an independent covariate for early recurrence. Furthermore, multivariate analysis selected postoperative complications of grade ≥3b according to the Clavien–Dindo classification (HR=5.99; 95% CI=1.53-23.47; $p=0.01$) and venous invasion (HR=4.80; 95% CI=1.21-19.14; $p=0.03$) as independent covariates for early cancer death.

Rates of early recurrence and cancer death in patients with risk factors. Table IV shows the relationships between early recurrence and cancer death and their risk factors. Twelve (60.0%) and 17 (14.0%) patients with ypN2/3 (n=20) and with ypN0/1 (n=121), respectively, developed early recurrence ($p<0.0001$).

Six (42.9%) and 15 (11.8%) patients with (n=14) and without (n=127) postoperative complications grade ≥3b according to the Clavien–Dindo classification, respectively, succumbed to early cancer death ($p=0.002$). Seven (41.2%) and 14 (11.3%) patients with (n=17) and without (n=124) venous invasion, respectively, also succumbed to early cancer death ($p=0.001$). Furthermore, 12 (40.0%) and nine (8.1%) patients with (n=30) postoperative Clavien–Dindo classification ≥3b complications with/without venous invasion and without both risk factors (n=111) for early cancer death, respectively, succumbed to early cancer death ($p<0.0001$).

Survival according to risk factors for early recurrence and early cancer death. The 5-year RFS rates for patients with and without risk factors for early recurrence were 15.0% and 52.6% respectively (ypN2/3 *vs*. 0/1, $p<0.0001$; Figure 1A), and the corresponding 5-year OS rates were 15.0% and 56.9%, respectively ($p<0.0001$) (Figure 1A). Furthermore, the 5-year RFS rates for patients with and without risk factors for early cancer death were 23.3% and 53.7% respectively (with Clavien-Dindo grade ≥3b postoperative complications with/without venous invasion *vs*. without both: $p=0.0004$), and the corresponding 5-year OS rates were 29.1% and 56.7%, respectively ($p=0.001$) (Figure 1B).

Discussion

Patients with locally advanced esophageal cancer often undergo trimodal therapy, comprising NCRT followed by surgery (1-3). However, some patients develop early recurrence and succumb to cancer death even after such curative-intent and highly intensive treatment. The present study assessed factors associated with early recurrence and cancer death in a uniform cohort of patients with locally advanced ESCC who underwent NCRT and subsequent curative surgery with adequate lymph node dissection. Univariate and multivariate

Table II. *Comparison between patients with and without early recurrence or early cancer death.*

Factors		Early recurrence			Early cancer death		
		Yes (n=29)	No (n=112)	*p*-Value	Yes (n=21)	No (n=120)	*p*-Value
Pretherapeutic							
Age, years	Mean±SD	62.1±8.4	63.2±8.0	0.52	62.2±9.4	63.1±7.9	0.65
Gender	Male	24 (82.8)	98 (87.5)	0.51	17 (81.0)	105 (87.5)	0.42
	Female	5 (17.2)	14 (12.5)		4 (19.0)	15 (12.5)	
ECOG PS	0	27 (93.1)	102 (91.1)	0.73	19 (90.5)	110 (91.7)	0.86
	1	2 (6.9)	10 (8.9)		2 (9.5)	10 (8.3)	
Primary tumor location	Upper third	4 (13.8)	23 (20.5)	0.70	2 (9.5)	25 (20.8)	0.24
	Middle third	16 (55.2)	55 (49.1)		14 (66.7)	57 (47.5)	
	Lower third and esophagogastric junction	9 (31.0)	34 (30.4)		5 (23.8)	38 (31.7)	
Tumor differentiation (biopsy)	Poor	13 (44.8)	40 (35.7)	0.59	9 (42.9)	44 (36.7)	0.59
	Other	16 (55.2)	62 (55.4)		12 (57.1)	76 (63.3)	
Carcinoembryonic antigen, ng/ml	Mean±SD	4.5±4.6	3.1±2.0	0.02	3.7±2.9	3.3±2.8	0.52
SCC-related antigen, ng/mI	Mean±SD	2.0±2.2	2.0±2.3	0.99	1.9±2.3	2.1±2.3	0.80
cT*	1/2	2 (6.9)	19 (17.0)	0.17	1 (4.8)	20 (16.7)	0.16
	3/4	27 (93.1)	93 (83.0)		20 (95.2)	100 (83.3)	
cN*	0/1	20 (69.0)	90 (80.4)	0.19	17 (81.0)	93 (77.5)	0.72
	2/3	9 (31.0)	22 (19.6)		4 (19.0)	27 (22.5)	
cM*	0	24 (82.8)	99 (88.4)	0.42	18 (85.7)	105 (87.5)	0.82
	1	5 (17.2)	13 (11.6)		3 (14.3)	15 (12.5)	
Operative							
Thoracic surgical procedure	Open thoracotomy	24 (82.8)	99 (88.4)	0.42	17 (81.0)	106 (88.3)	0.35
	Thoracoscopic surgery	5 (17.2)	13 (11.6)		4 (19.0)	14 (11.7)	
Lymph node dissection	Two-field	9 (31.0)	37 (33.0)	0.84	8 (38.1)	38 (31.7)	0.56
	Three-field	20 (69.0)	75 (67.0)		13 (61.9)	82 (76.7)	
Surgical duration, min	Mean±SD	457±78	441±89	0.34	455±90	442±87	0.53
Blood loss, g	Mean±SD	600±480	578±505	0.83	619±507	576±499	0.71
Blood transfusion	Yes	8 (27.6)	28 (25.0)	0.78	8 (38.1)	28 (23.3)	0.15
	No	21 (72.4)	84 (75.0)		13 (61.9)	92 (76.7)	
Postoperative complications‡	≥Grade 3b	6 (20.7)	8 (7.1)	0.03	6 (28.6)	8 (6.7)	0.002
	<Grade 3b	23 (79.3)	104 (92.9)		15 (71.4)	112 (93.3)	
Postoperative infectious complications	Yes	11 (37.9)	38 (33.9)	0.95	9 (42.9)	40 (33.3)	0.40
	No	18 (62.1)	64 (57.1)		12 (57.1)	80 (66.7)	
Pathological							
ypT**	0/1	8 (27.6)	63 (56.3)	0.01	6 (28.6)	65 (54.2)	0.03
	2/3/4	21 (72.4)	49 (43.8)		15 (71.4)	55 (45.8)	
ypN**	0/1	17 (58.6)	104 (92.9)	<0.001	13 (61.9)	108 (90.0)	0.001
	2/3	12 (41.4)	8 (7.1)		8 (38.1)	12 (10.0)	
ypM**#	0	26 (89.7)	109 (97.3)	0.07	19 (90.5)	116 (96.7)	0.19
	1	3 (10.3)	3 (2.7)		2 (9.5)	4 (3.3)	
Tumor differentiation (resected specimen)	Poor	10 (34.5)	23 (20.5)	0.11	9 (42.9)	24 (20.0)	0.02
	Other	19 (65.5)	89 (79.5)		12 (57.1)	96 (80.0)	
Lymphatic invasion	With	16 (55.2)	20 (17.9)	<0.0001	10 (47.6)	26 (21.7)	0.01
	Without	13 (44.8)	92 (82.1)		11 (52.4)	94 (78.3)	
Venous invasion	With	8 (27.6)	9 (8.0)	0.004	7 (33.3)	10 (8.3)	0.001
	Without	21 (72.4)	103 (92.0)		14 (66.7)	110 (91.7)	
Pathological response of primary tumor	pCR	6 (20.7)	48 (42.9)	0.03	5 (23.8)	49 (40.8)	0.14
	Non-pCR	23 (79.3)	64 (57.1)		16 (76.2)	71 (59.2)	

ECOG PS: Eastern Cooperative Oncology Group performance status; pCR, pathological complete response; SCC: squamous cell carcinoma; SD: standard deviation. *Pretherapeutic/**pathological according to TNM Classification, 7th edition (16). ‡According to Clavien–Dindo classification (17). #Supraclavicular lymph node metastasis.

analyses found ypN2/3 to be a risk factor for early recurrence, and that severe postoperative complications and pathological venous invasion were risk factors for early cancer death. Although a relatively small number of patients had these risk factors, such patients had extremely poor prognoses even after intensive multimodal therapy.

Various clinicopathological factors have been reported as risky for early recurrence or cancer death in patients with

Table III. *Multivariate analysis of factors associated with early recurrence and cancer death.*

Variable	Multivariate analysis		
	HR	95% CI	*p*-Value
Early recurrence			
Carcinoembryonic antigen			
Continuous	1.12	0.93-1.34	0.25
Postoperative complications‡			
<Grade 3b	1		
≥Grade 3b	2.78	0.68-11.41	0.16
ypT*			
0/1	1		
2/3/4	1.99	0.37-10.70	0.43
ypN*			
0/1	1		
2/3	4.13	1.25-13.66	0.02
Pathological response of primary tumor			
pCR	1		
Non-pCR	1.75	0.28-10.78	0.55
Lymphatic invasion			
Without	1		
With	2.34	0.71-7.77	0.17
Venous invasion			
Without	1		
With	2.42	0.65-8.99	0.19
Early cancer death			
Postoperative complications‡			
<Grade 3b	1		
≥Grade 3b	5.99	1.53-23.47	0.01
Tumor differentiation (resected specimen)			
Other	1		
Poor	2.05	0.65-6.51	0.22
ypT*			
0/1	1		
2/3/4	1.21	0.33-4.48	0.78
ypN*			
0/1	1		
2/3	3.44	0.94-12.66	0.06
Lymphatic invasion			
Without	1		
With	1.08	0.27-4.28	0.92
Venous invasion			
Without	1		
With	4.80	1.21-19.14	0.03

CI: Confidence interval; HR: hazard ratio; pCR: pathological complete response. ‡According to Clavien–Dindo classification (17). *Pathological staging according to TNM classification, 7th edition (16).

Table IV. *Relationships between early recurrence or cancer death and their risk factors.*

Parameter	Frequency, n (%)		*p*-Value
	Yes	No	
Early recurrence	(n=29)	(n=112)	
ypN*			
0/1	17 (14.0)	104 (86.0)	<0.0001
2/3	12 (60.0)	8 (40.0)	
Early cancer death	(n=21)	(n=120)	
Postoperative complications‡			
<Grade 3b	15 (11.8)	112 (88.2)	0.002
≥Grade 3b	6 (42.9)	8 (57.1)	
VI			
Without	14 (11.3)	110 (88.7)	0.001
With	7 (41.2)	10 (58.8)	
Postoperative complications‡ and VI			
<Grade 3b, no VI	9 (8.1)	102 (91.9)	<0.0001
≥Grade 3b and/or with VI	12 (40.0)	18 (60.0)	

VI: Venous invasion. *Pathological staging according to TNM classification, 7th edition (16). ‡According to Clavien–Dindo classification (17).

esophageal cancer. Preoperative smoking, increased C-reactive protein levels before treatment, postoperative complications, poor tumor differentiation, increased tumor depth of invasion, pathological venous invasion, microscopically incomplete resection (R1), increased positive-to-resected lymph node ratio and extracapsular lymph node involvement are associated with early recurrence after esophagectomy (7, 13, 14). Furthermore, poor performance status (1 or 2), lack of response to neoadjuvant therapy, intramural metastasis, microscopically and macroscopically incomplete resection (R1 or 2), increased tumor depth of invasion, increased lymph node metastases, and poor tumor differentiation are associated with early cancer death (8-12). These reports describe patients with several histological types of esophageal cancer (ESCC or adenocarcinoma), various surgical strategies (transthoracic, trans-hiatal or left thoracotomy) and treatment modalities (surgery alone or neoadjuvant therapy followed by surgery). Therefore, the risk factors for early recurrence and death might somewhat differ among studies.

Pathological LN metastasis is an important prognostic factor for esophageal cancer treated with NCRT followed by surgery (5, 24, 25). The present multivariate analysis selected ypN2/3 as the only significant independent risk factor for early recurrence and showed that it also tended to be a risk factor for early cancer death (p=0.06). Disease in patients with multiple pathological LN metastases even after NCRT might be considered resistant to chemotherapy and radiotherapy. Furthermore, they have a very high probability of unrecognized occult metastases during treatment. Therefore, postoperative therapy, preferably with anticancer drugs that differ from those used in NCRT, should be carefully considered for patients with multiple pathological LN metastases in order to delay and reduce recurrence after trimodal therapy. Such patients also require meticulous surveillance to detect early recurrence.

Lymphatic and venous invasion are independent prognostic factors for survival after initial surgical resection of ESCC (26-

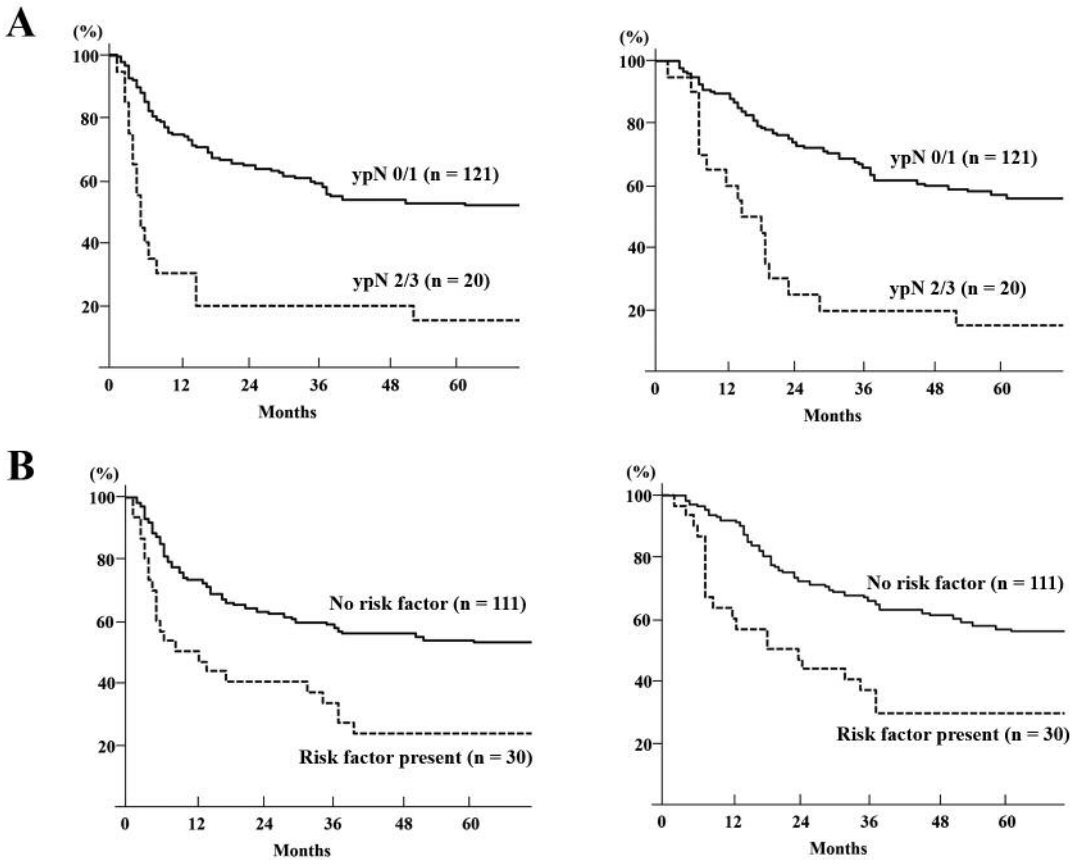

Figure 1. *Recurrence-free (RFS; left panel) and overall (OS; right panel) survival of patients with esophageal squamous cell carcinoma after trimodal therapy according to the presence of risk factors [pathological nodal staging (ypN), postoperative complications, and venous invasion] associated with early recurrence and early cancer death. A: Survival rates of patients according to ypN as a risk factor for early recurrence ($p<0.0001$). B: Survival rates of patients with Clavien–Dindo grade ≥3b postoperative complications with/without venous invasion compared with those with neither of them as risk factors for early cancer death (RFS: $p=0.0004$; OS: $p=0.001$).*

28) and after neoadjuvant therapy followed by surgery (29-31). Among these reports, lymphovascular invasion had prognostic value in patients with ESCC treated by NCRT followed by surgery, which are the same histological type and treatment modality as the present study (30, 31). Therefore, lymphatic/vascular invasion is very important for the prognosis of esophageal cancer, not only after surgery, but also after neoadjuvant therapy followed by surgery. However, the present findings indicated that venous invasion might be more important than lymphatic invasion, especially in terms of early cancer death among patients with ESCC after trimodal therapy.

Esophageal surgery is highly invasive, and postoperative complications reportedly have an important prognostic impact on patients with esophageal cancer (14, 32-34). The implications of postoperative complications with respect to prognosis of patients with esophageal cancer are associated with various issues such as poor general status before treatment, inherent immunological capacity and immunocompromised status, poor nutrition and insufficient therapy after recurrence according to an overall decline in general status induced by severe postoperative complications. The relationship between severe postoperative complications and early cancer death might be attributable to complex interactions and effects of these factors. Therefore, minimally invasive surgery should focus on reducing postoperative complications.

Risk factors for early recurrence and early cancer death have not previously been concurrently evaluated as far as we are aware. We assessed both these factors in a single patient cohort and found that multivariate analyses selected significant factors that differed between early recurrence and death. This finding indicates that important prognostic factors might somewhat change before and after recurrence. These factors might be closely associated with complex combined causes of malignant tumor potential, occult cancer after macroscopically curative surgery, being refractory to

chemo- or radiation therapy, and being difficult to treat after recurrence. Taken together, the prognosis of patients with ypN2/3, venous invasion and severe postoperative complications after trimodal therapy for ESCC was significantly poor.

The retrospective design is a limitation of the present study and another is that the chemotherapy regimens varied at different times during the study period. Nonetheless, the present study included a relatively large cohort of uniform patients with locally advanced ESCC who all underwent NCRT with 40 Gy of radiation followed by surgery with adequate LN dissection.

We conclude that ypN2/3 is a risk factor for early recurrence, whereas severe postoperative complications and venous invasion are risk factors for early cancer death after trimodal therapy for ESCC. Further prevention of postoperative complications is needed for patients with esophageal cancer, and meticulous surveillance is needed especially for those with risk factors for early recurrence and cancer death. Postoperative adjuvant therapy should be considered for such patients, in consideration of their general condition after trimodal therapy.

Conflicts of Interest

The Authors have no commercial support or conflicts of interest to disclose in regard to this study.

Authors' Contributions

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Received January 28, 2019
Revised February 16, 2019
Accepted February 21, 2019