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Pathological tumor regression grade of metastatic tumors in lymph node predicts prognosis in esophageal cancer patients

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Tumor regression grade of the primary tumor (TRG-PT) and residual lymph node metastasis have been pathologically determined in esophageal squamous cell carcinoma (ESCC) patients who had received neoadjuvant chemotherapy (nCT) followed by surgery; however, TRG of the metastatic tumor involving lymph nodes (LN) has not yet been determined. The aim of the present study was to clarify the impact of TRG on the prognosis of ESCC patients. ESCC patients (n = 110) who had received nCT followed by surgery were enrolled. Dissected LN were classified into 2 categories: plausible positive metastatic LN (pp-MLN) where viable and/or degenerated ESCC cells and/or tissue modifications were observed, and non-metastatic LN (non-MLN) where neither of them was observed. We defined nCT-effective rate (CER) as the ratio of the number of pp-MLN that showed tumor regression to the total number of pp-MLN, and divided CER into low-CER (LCER; ≥0% and <50%) and high-CER (HCER; ≥50% and ≤100%). Relationships between CER and clinicopathological factors including prognosis were then examined. Multivariate analyses of 110 patients indicated that ypT3-4 (P = .023, HR; 2.551), positive venous infiltration (P = .006, HR; 3.526), and LCER (P = .033, HR; 1.922) were independently associated with shorter recurrence-free survival (RFS). Multivariate analyses of 43 patients with grade 0 TRG-PT showed that ypT3-4 (P = .033, HR; 3.397) and LCER (P = .008, HR; 3.543) were independently associated with shorter RFS. This study showed that CER was one of the prognostic factors for ESCC patients who had received nCT followed by surgery.

KEYWORDS
chemotherapy-effective rate, esophageal squamous cell carcinoma, neoadjuvant chemotherapy, tumor regression grade of lymph node, tumor regression grade of primary tumor

1 | INTRODUCTION

Neoadjuvant chemoradiotherapy followed by surgery has been one of the standard treatments for locally advanced thoracic ESCC, and nCT followed by surgery is the standard in Japan, based on the results of many clinical trials.[1-3] These studies have shown that nCT or nCRT improves the prognosis of patients with ESCC. We have reported that higher TRG-PT is a positive

prognostic factor, whereas residual LNM is a negative prognostic factor.[4]

Neoadjuvant chemotherapy followed by surgery has been the standard therapy for breast cancer patients, with the aim of preserving breast organ.[5] Therefore, lymph node tissue modified by nCT undergoes pathological examination. Not only TRG-PT but also TRG-LN involved in the metastatic tumor has been routinely subjected to pathological examination, because TRG of primary and metastatic tumors has been implicated in predicting prognosis.[6-8] No residual tumor in ALN after nCT is well known to be a better prognostic factor, even in breast cancer patients who still have residual tumor at the primary site.[7]

In contrast, regarding patients with ESCC who underwent nCRT or nCT using an anti-cancer effective regimen, residual LNM remains one of the poor prognostic factors. It suggests that it may be necessary for pathologists to determine the TRG of both primary and metastatic tumors involving LN in ESCC patients as well as in breast cancer patients who underwent nCT. It remains unknown whether TRG-PT or TRG-LN is associated with prognosis in ESCC patients. The aim of the present study was to clarify the significance of TRG-LN as a prognostic factor in ESCC patients who had undergone nCT followed by surgery.

2 | PATIENTS AND METHODS

2.1 | Patients

Patients with locally advanced esophageal cancer who had undergone a combination therapy of nCT followed by surgery at the National Cancer Center Hospital East between January 2008 and March 2013 were enrolled. Eligibility criteria were as follows: (i) patients pathologically diagnosed using biopsy specimens, with squamous cell carcinoma prior to receiving any nCT; (ii) patients who underwent total or subtotal thoracic esophagectomy with regional lymph node dissection after nCT; (iii) patients whose performance status according to ECOG was 0-1; and (iv) patients whose dissected LN included at least 1 pp-MLN where viable and/or degenerated ESCC cells and/or tissue modifications. Patients who received macroscopically incomplete resection after nCT or died in hospital post-surgery were excluded from this study. However, patients who were not able to receive a scheduled complete course of nCT were included. Consequently, 110 ESCC patients were enrolled in the study. Clinical staging before nCT was determined according to UICC-TNM classification (7th edition),[9] based on endoscopic findings and CECT. This study protocol was approved by the institutional review board of the National Cancer Center (2014-357).

2.2 | Neoadjuvant chemotherapy

The regimen of nCT was either 2 courses of CF,[3] or 3 courses of DCF. Each course was given every 3 weeks. All patients were scheduled to receive endoscopic examination and CECT after each course of the above chemotherapy for evaluating the therapeutic effect.

The patients underwent surgery after interrupting the course of nCT. Patients who did not respond to nCT or who presented with severe toxicity attributable to the nCT were included in this study.

2.3 | Histopathological examinations

Pathological diagnosis of surgically resected specimens was routinely carried out according to the Japanese Classification of Esophageal Cancer.[10] Microscopically incomplete resection was recorded as incomplete resection (R1), and complete resection was recorded as R0. TRG-PT was classified into 5 categories (grade 0, no therapeutic effect; grade 1a, viable cancer cells $\geq$2/3; grade 1b, 1/3 $\leq$ viable cancer cells <2/3; grade 2, viable cancer cells <1/3; and grade 3, no viable cancer cells) according to the ratio of viable cancer cells per tumor tissue.[4]
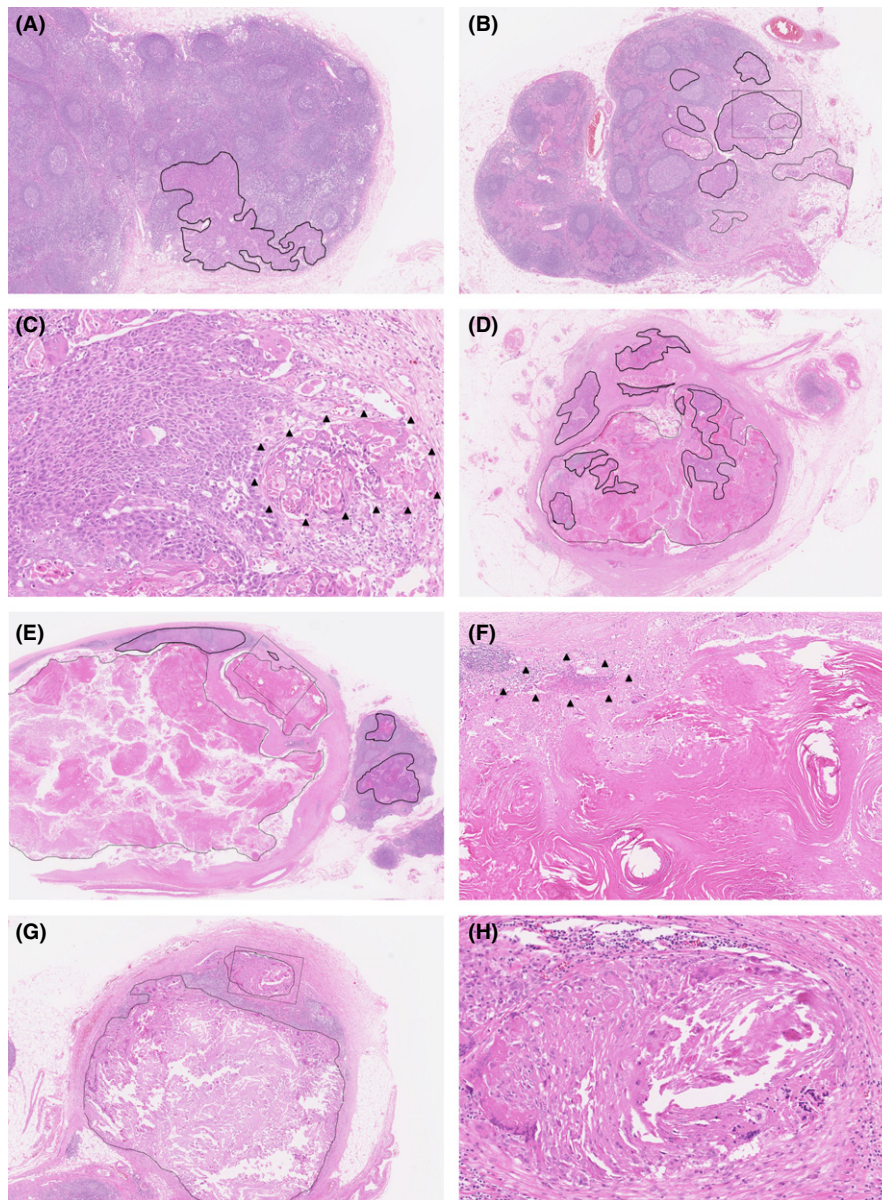
2.4 | TRG of metastatic lymph nodes

We newly determined TRG-LN in the present study as following 5 steps (Figure S1).

1. Each dissected LN was classified into 2 categories, including non-MLN and pp-MLN. The definition of both categories is as follows: non-MLN in which any viable ESCC cells, degenerated ESCC cells, or tissue modifications including necrosis and granulomatous reactions were not observed at all; and pp-MLN in which viable and/or degenerated ESCC cells and/or tissue modifications were observed in contrast to non-MLN.
2. TRG-LN grade (grades 0, 1a, 1b, 2, or 3) in the individual pp-MLN were pathologically determined according to the same criteria as that of the TRG-PT (Figure 1).
3. In each patient, the number of all pp-MLN and pp-MLN with grades 1a, 1b, 2, and 3 were counted.
4. The ratio of the number of pp-MLN that were categorized as grades 1a, 1b, 2, and 3 regarding TRG-LN to all pp-MLN (categorized as grades 0, 1a, 1b, 2, and 3 regarding TRG-LN) was calculated. We defined the ratio as the CER.
5. We classified CER into two categories: LCER (low rate, $\geq$0% and <50%) or HCER (high rate, $\geq$50% and $\leq$100%). We determined total TRG-LN evaluation for each patient based on the definition of CER (LCER or HCER), as described above. In addition, we determined the highest or the lowest TRG-LN grades of pp-MLN in each patient, and examined relationships between RFS, and the highest TRG-LN grade or the lowest TRG-LN grade.

2.5 | Statistical analysis

Recurrence-free survival curves were estimated using the Kaplan-Meier method and were compared using the log-rank test. RFS was defined as the period from the date of surgery until the date of death or recurrence which was clinically confirmed through endoscopy or CECT. OS period was defined as the time from the date of surgery until the last confirmed date of survival or death, regardless

FIGURE 1 Tumor regression grade of metastatic ESCC cells involving lymph nodes. A, Grade 0 tumor regression grade of lymph node (TRG-LN). Residual ESCC cells are observed (enclosed by the solid line), and no degenerated ESCC cells are seen. B, Grade 1a TRG-LN. Less than one-third of all ESCC cells were degenerated (enclosed by the dotted lines), and residual ESCC cells within the area enclosed by solid lines are observed. C, Residual ESCC cells are observed accompanied by degenerated ESCC cells within the area enclosed by black arrowheads. The micrograph is an enlarged image of the squared area of (B). D, Grade 1b TRG-LN. More than one-third and less than two-thirds of all ESCC cells were degenerated and tissue modification is observed (enclosed by the dotted line), replacing the space where necrotic ESCC cells existed before neoadjuvant therapy, and residual ESCC cells within the area enclosed by solid lines are observed. E, Grade 2 TRG-LN. More than two-thirds of all ESCC cells were degenerated (enclosed by the dotted line) and a few residual ESCC cells within the area enclosed by the solid line are observed. F, Small numbers of degenerated ESCC cells within the area enclosed by black arrowheads are observed accompanied by necrotic keratinizing materials originating from ESCC cells. The micrograph is an enlarged image of the squared area of (E). G, Grade 3 TRG-LN. No viable ESCC cells are observed although tissue modification is observed (enclosed by the dotted line). H, Tissue modification such as granulomatous reaction is shown. Only keratinizing materials accompanied by infiltration of foreign body types and multinucleated macrophages are observed. The micrograph is an enlarged image of the squared area of (G)

of the cause of death. Univariate Cox proportional hazards model was used to examine the association between all clinicopathological factors including CER and death or recurrence. Variables with a *P*-value <.10 were evaluated simultaneously using a multivariate analysis with the Cox proportional hazards model. We conducted

multivariate analyses including at least 8 outcome variables according to standard statistical methods. Next, clinicopathological factors were used to examine the difference between 2 subgroups (grade 0 TRG-PT vs grade 1a-3 TRG-PT), using univariate and multivariate analyses. All statistical analyses were done using the IBM SPSS

statistical software package (version 22.0 for Mac; IBM Japan Ltd, Tokyo, Japan). All *P*-values were reported as 2-sided, with a significance level of .05.

3 | RESULTS

3.1 | Patients and clinicopathological characteristics

Clinical characteristics of the 110 patients who were enrolled in this study are shown in Table 1. Male patients were predominant (82.7%), and the median age was 66 years (range, 42-77). Ten patients (9.1%) were diagnosed with non-regional lymph node metastasis clinically and regarded as cStage IV. Seventy patients (63.6%) underwent nCT with the CF regimen, and the remaining 40 patients (36.4%) underwent nCT with the DCF regimen prior to surgery. Of these, 44 (62.9%) and 23 (57.5%) patients underwent a full course of each regimen, respectively.

3.2 | TRG-PT, TRG-LN, and CER

Number of patients with grades 0, 1a, 1b, 2, and 3 TRG-PT were 43, 41, 13, 8, and 5, respectively. Number of patients with LCER and HCER were 47 (42.7%) and 63 (57.3%), respectively. Ratios of HCER in patients with grades 0, 1a, 1b, 2, and 3 TRG-PT were 39.5% (17/43), 58.5% (24/41), 84.6% (11/13), 75.0% (6/8), and 100.0% (5/5), respectively (Table S1).

3.3 | Recurrence-free survival and overall survival analysis

Median follow up was 25.5 months (range, 1.8-77.2 months). In the follow-up period, recurrence rate was 48.2% (53 of 110) and death occurred in 41 patients (37.3%). Kaplan-Meier curves for RFS according to TRG-PT are shown in Figure 2A,B. Patients with grades 1a-3 TRG-PT had significantly longer RFS rates than patients with grade 0 (*P* = .003). In addition, patients with LCER had significantly shorter RFS and OS rates than patients with HCER (*P* = .0014 and .0012), as shown in Figure 2C,D. In the analyses using the highest and the lowest TRG-LN grade, there were no clear correlations between RFS, and the highest TRG-LN grade or the lowest TRG-LN grade unless the lowest TRG-LN grade was 0 or 3 (Figure S2A,B), suggesting that overall evaluation of all pp-MLN in each patient may successfully predict prognosis rather than individual evaluation of pp-MLN such as the highest TRG-LN or the lowest TRG-LN regarding pp-MLN.

3.4 | Prognostic factors in univariate and multivariate analysis

Univariate analysis indicated that ypT3-4 (vs ypT0-2, HR; 4.553, *P* < .001), positive venous infiltration (vs negative, HR; 7.222, *P* < .001), grade 0 TRG-PT (vs grades 1a, 1b, 2, and 3 TRG-PT, HR; 2.228, *P* = .004), and LCER (vs HCER, HR; 2.367, *P* = .002) were

poor prognostic factors for RFS (Table 2). Consequently, of the variables with a *P*-value <.10, 6 factors (ypT stage, ypN stage, lymphatic infiltration, venous infiltration, TRG-PT, and CER) were selected for multivariable analyses. This showed that ypT3-4 (vs ypT0-2, HR; 2.551, *P* = .023), positive venous infiltration (vs negative, HR; 3.526, *P* = .006), and LCER (vs HCER, HR; 1.922, *P* = .033) were predictors of shorter RFS.

3.5 | Significance of combining TRG-PT and CER for prognostic factors

Next, we investigated whether a combination of CER and TRG-PT would allow classification of subgroups associated with patient prognosis. As an interaction between TRG-PT and CER in RFS in the Cox model was observed (*P* = .132), we examined whether CER was a prognostic factor in each subgroup (TRG-PT grade 0 group, and grades 1a, 1b, 2, and 3 group). RFS curves according to CER in patients according to grade 0 and grades 1a-3 TRG-PT groups is shown in Figure 3A,B. LCER was a significant poor prognostic factor for RFS among patients with grade 0 TRG-PT (*P* = .0028); however, LCER was not a significant poor prognostic factor for RFS among patients with grade 1a or 1b or 2 or 3 TRG-PT (*P* = .476). For OS, LCER was also a significant poor prognostic factor among patients with grade 0 TRG-PT (*P* = .015), not among patients with grades 1a-3 TRG-PT (*P* = .196), as shown in Figure 3C,D.

For patients with grade 0 TRG-PT, univariate analyses showed that the ypT factor (ypT3-4), venous infiltration, and LCER were predictors of a shorter RFS (Table 3). Multivariate analysis showed that ypT3-4 (vs ypT0-2, HR; 3.397, *P* = .033) and LCER (vs HCER, HR; 3.543, *P* = .008) were predictors of a shorter RFS. Patients with grade 0 TRG-PT and LCER had shorter RFS rates, and there was little difference between RFS rates of patients with grade 0 TRG-PT and HCER, and patients with grades 1a-3, regardless of the CER (Figure S3).

3.6 | Relationship between RFS, and TRG-PT or CER in patients with ypStage II or III

In cases of dividing the patients with ypStage III into 2 groups, including the patients with grade 0 TRG-PT and the patients with grades 1a-3 TRG-PT, the latter patients were shown to have significantly longer RFS compared with those of the former patients (*P* = .0015), implying that TRG-PT may have an impact on RFS (Figure S4A). In contrast, the same analysis in patients with ypStage II did not show any significant difference between the patients with grades 1a-3 TRG-PT and those with grade 0 TRG-PT (*P* = .91) (Figure S4A). This might be attributed to the small sample size of the patients with ypStage II (n = 25).

In cases of dividing the patients with ypStage III into 2 groups, including the patients with HCER and the patients with LCER, the former patients were shown to have significantly longer RFS compared with those of the latter patients (*P* = .020), implying that CER

TABLE 1 Clinical and pathological characteristics of patients in the present study

	N (%)
Gender	
Male	91 (82.7)
Female	19 (17.3)
Age (y)	
Median (range)	66 (42-77)
Tumor location	
Upper thoracic	14 (12.7)
Middle thoracic	59 (53.6)
Lower thoracic	34 (30.9)
Abdominal	3 (2.7)
cT stage	
1	8 (7.3)
2	14 (12.7)
3	88 (80.0)
cN stage	
0	24 (21.8)
1	53 (48.1)
2	30 (27.3)
3	3 (2.7)
cM stage	
0	100 (90.9)
1	10 (9.1)
cStage	
IB	6 (5.5)
IIA	17 (15.5)
IIB	11 (10.0)
IIIA	43 (39.1)
IIIB	21 (19.1)
IIIC	2 (1.8)
IV	10 (9.1)
Chemotherapy regimen	
CF	70 (63.6)
DCF	40 (36.4)
Planned chemotherapy course completed	
Yes	67 (60.9)
CF: 2 courses	44 (62.9)
DCF: 3 courses	23 (57.5)
No	43 (39.1)
ypT stage	
0	6 (5.5)
1	27 (24.5)
2	13 (11.8)
3	60 (54.5)
4	4 (3.6)

(Continues)

TABLE 1 (Continued)

	N (%)
ypN stage	
0	17 (15.5)
1	50 (45.5)
2	30 (27.3)
3	13 (11.8)
ypM stage	
0	101 (91.8)
1	9 (8.2)
ypStage	
0	5 (4.5)
IA	5 (4.5)
IB	3 (2.7)
IIA	5 (4.5)
IIB	20 (18.2)
IIIA	33 (30.0)
IIIB	18 (16.4)
IIIC	12 (10.9)
IV	9 (8.2)
Histological differentiation	
Well differentiated	18 (16.4)
Moderately differentiated	68 (61.8)
Poorly differentiated	24 (21.8)
TRG-PT	
Grade 0	43 (39.1)
Grade 1a	41 (37.2)
Grade 1b	13 (11.8)
Grade 2	8 (7.3)
Grade 3	5 (4.5)
Lymphatic infiltration	
0	62 (56.4)
1	33 (30.0)
2	9 (8.2)
3	6 (5.5)
Venous infiltration	
0	47 (42.7)
1	45 (40.9)
2	16 (14.5)
3	2 (1.8)
Residual tumor	
R0 (complete resection)	102 (92.7)
R1 (incomplete resection)	8 (7.3)
CER	
LCER	47 (42.7)
HCER	63 (57.3)

CER, chemotherapy-effective rate; CF, cisplatin + 5-FU; DCF, docetaxel + cisplatin + 5-fluorouracil; HCER, high chemotherapy-effective rate; LCER, low chemotherapy-effective rate; TRG-PT, tumor regression grade of primary tumor.
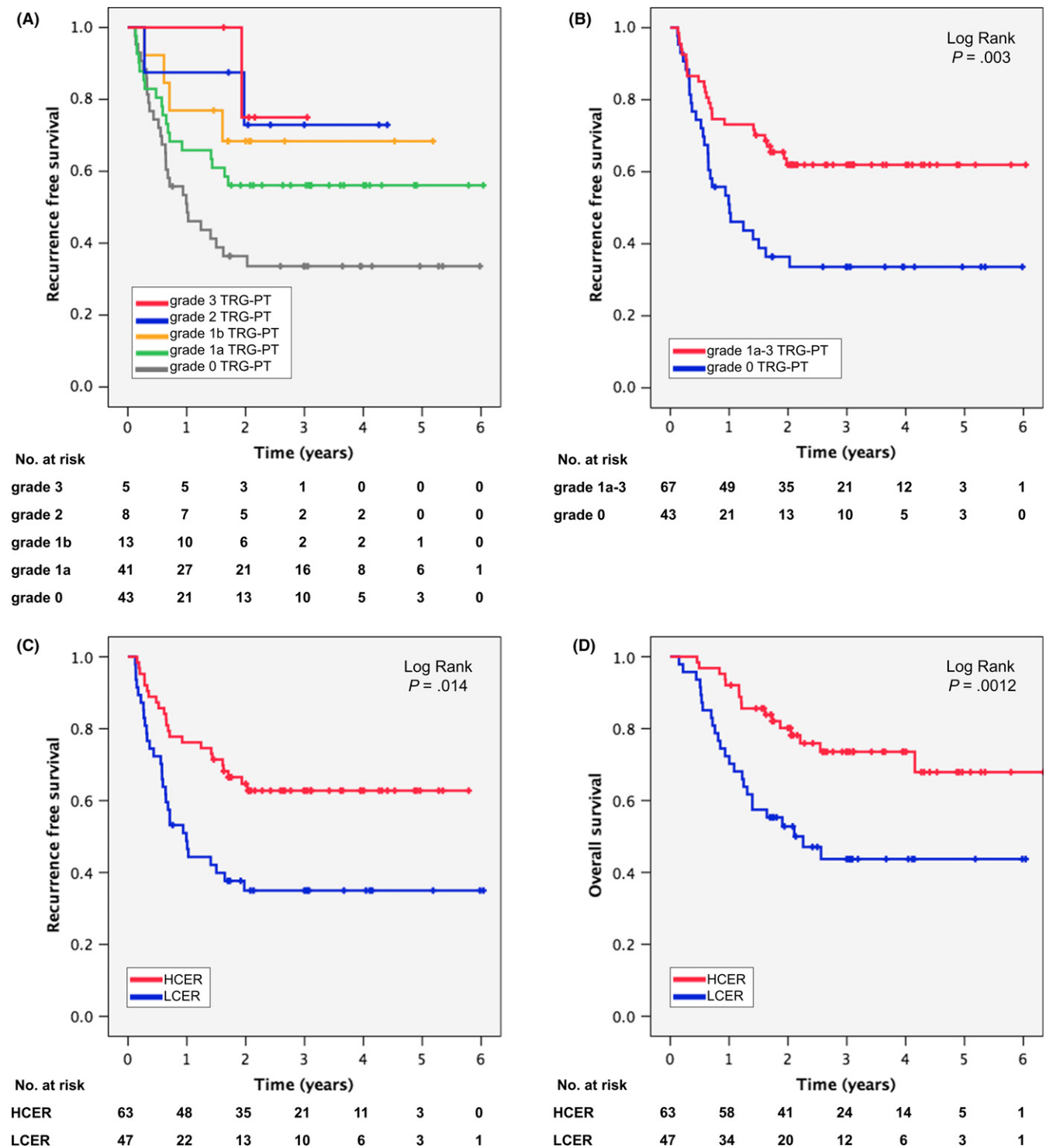
FIGURE 2 Recurrence-free survival (RFS) and overall survival (OS) curves according to tumor regression grade of primary tumor (TRG-PT) or chemotherapy-effective rate (CER). A, RFS curves according to TRG-PT including grades 0, 1a, 1b, 2, and 3. B, RFS curves of the 2 groups of grade 0 TRG-PT and grades 1a, 1b, 2, and 3. There was a significant difference between the grade 0 group and the grades 1a, 1b, 2, and 3 group (P = .003). C, RFS curves of low CER (LCER) and high CER (HCER). There was a significant difference in RFS between LCER and HCER groups (P = .0014). D, OS curves of LCER and HCER. There was a significant difference in OS between LCER and HCER groups (P = .0012)

may have an impact on RFS (Figure S4B). In contrast, the same analysis in patients with ypStage II did not show any significant difference between the patients with HCER and those with LCER (P = 0.17) (Figure S4B). This might be attributed to the small sample size of the patients with ypStage II (n = 25). However, the number of patients with ypStage I or IV was so small that it was impossible to conduct the same statistical analyses as described above (Table S2).

4 | DISCUSSION

Lymph node metastasis is a critical negative prognostic factor in ESCC patients. Some previous investigators attempted to classify ESCC patients who received neoadjuvant therapy including nCT and nCRT followed by surgery, according to a combination of TRG-PT and residual LNM; however, these classifiers could not be used to divide patients with completely different prognoses.[11-16] It is

TABLE 2 Univariate and multivariate logistic regression model of the pathological predictors of RFS

	N (%)		Univariate analysis			Multivariate analysis		
			HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age (y)								
<65	59	(53.6)	Ref		Ref			
≥65	51	(46.4)	0.98	0.571-1.684	.943			
Gender								
Male	91	(82.7)	Ref		Ref			
Female	19	(17.3)	1.022	0.499-2.094	.953			
Chemotherapy regimen								
CF	70	(63.6)	Ref		Ref			
DCF	40	(36.4)	0.663	0.364-1.205	.177			
Planned chemotherapy course completed								
Yes	67	(60.9)	Ref		Ref			
No	43	(39.1)	0.926	0.533-1.606	.783			
ypT stage								
0-2	22	(20.0)	Ref		Ref	Ref		Ref
3-4	88	(80.0)	4.553	2.281-9.089	<.001	2.551	1.135-5.730	.023
ypN stage								
0	17	(15.5)	Ref		Ref	Ref		Ref
1-3	93	(84.5)	2.736	0.986-7.590	.053	0.961	0.311-2.969	.945
ypM stage								
0	101	(91.8)	Ref		Ref			
1	9	(8.2)	2.242	0.957-5.253	.063			
Residual tumor								
Residual tumor					Ref			
R1 (incomplete resection)	8	(7.3)	2.337	0.928-5.888	.072			
Histological differentiation								
Well, Moderately differentiated	86	(78.2)	Ref		Ref			
Poorly differentiated	24	(21.8)	0.55	0.259-1.167	.12			
Lymphatic infiltration								
Negative	62	(56.4)	Ref		Ref	Ref		Ref
Positive	48	(44.6)	1.618	0.943-2.776	.081	0.966	0.551-1.693	.904
Venous infiltration								
Negative	47	(42.7)	Ref		Ref	Ref		Ref
Positive	63	(57.3)	7.222	3.382-15.422	<.001	3.526	1.429-8.704	.006
TRG-PT								
Grade 0	43	(39.1)	2.228	1.295-3.832	.004	1.531	0.847-2.767	.159
Grade 1a, 1b, 2, and 3	67	(60.9)	Ref		Ref	Ref		Ref
CER								
LCER	47	(42.7)	2.367	1.371-4.085	.002	1.922	1.056-3.500	.033
HCER	63	(57.3)	Ref		Ref	Ref		Ref

CER, chemotherapy-effective rate; CF, cisplatin + 5-FU; DCF, docetaxel + cisplatin + 5-fluorouracil; HCER, high chemotherapy-effective rate; LCER, low chemotherapy-effective rate; RFS, recurrence-free survival; TRG-PT, tumor regression grade of primary tumor.

possible that TRG-PT reflects the neoadjuvant therapeutic effect on the primary tumor, whereas ypN stage reflects only the residual tumor in LN after neoadjuvant therapy. In other words, ypN stage cannot reflect the degree of the therapeutic effect on tumor cells in metastatic LN, according to nCT. This suggests that it might be necessary to evaluate the degree of tumor regression in metastatic LN; therefore, we created a new category, CER, which could reflect the degree of the neoadjuvant therapeutic effect. In the present study,
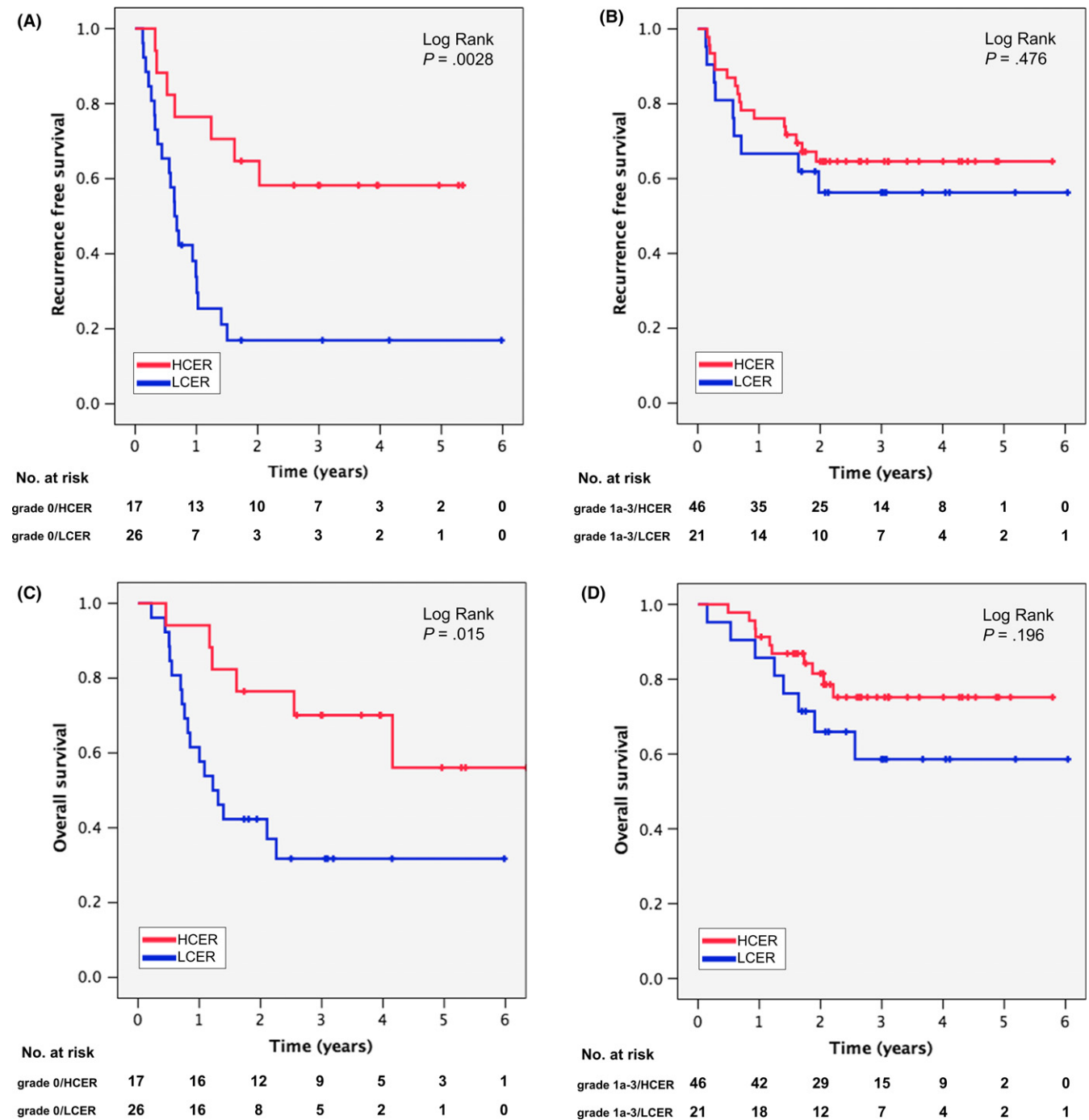
FIGURE 3 Recurrence-free survival (RFS) and overall survival (OS) curves of low chemotherapy-effective rate (LCER) and high chemotherapy-effective rate (HCER) groups in the grade 0 tumor regression grade of primary tumor (TRG-PT) group and in the grades 1a, 1b, 2, and 3 TRG-PT group. A, RFS curves of LCER and HCER groups in patients with grade 0 TRG-PT. There was a significant difference between LCER and HCER groups (*P* = .0028). B, RFS curves of LCER and HCER groups in patients with grades 1a, 1b, 2, and 3 TRG-PT. There was not a significant difference between LCER and HCER groups (*P* = .476). C, OS curves of LCER and HCER groups in patients with grade 0 TRG-PT. There was a significant difference between the LCER and HCER groups (*P* = .015). D, OS curves of LCER and HCER groups in patients with grades 1a, 1b, 2, and 3 TRG-PT. There was not a significant difference between the LCER and HCER groups (*P* = .196)

TABLE 3 Univariate and multivariate logistic regression model of the pathological predictors of RFS for patients with grade 0 TRG-PT

	N (%)		Univariate analysis			Multivariate analysis		
			HR	95% CI	P-value	HR	95% CI	P-value
Age (y)								
<65	22	(51.2)	Ref		Ref			
≥65	21	(48.8)	0.956	0.455-2.008	.906			
Gender								
Male	37	(86.0)	Ref		Ref			
Female	6	(14.0)	2.135	0.850-5.361	.106			
Chemotherapy regimen								
CF	37	(86.0)	Ref		Ref			
DCF	6	(14.0)	1.271	0.438-3.69	.659			
Planned chemotherapy course completed								
Yes	24	(55.8)	Ref		Ref			
No	19	(44.2)	0.708	0.331-1.515	.374			
ypT stage								
0-2	16	(37.2)	Ref		Ref	Ref		Ref
3-4	27	(62.8)	4.823	1.812-12.838	.002	3.397	1.104-10.453	.033
ypN stage								
0	1	(2.3)	Ref		Ref			
1-3	42	(97.7)	21.463	0.004-118 603	.486			
ypM stage								
0	40	(93.0)	Ref		Ref			
1	3	(7.0)	0.415	0.056-3.068	.389			
Residual tumor								
R0 (complete resection)	38	(88.4)	Ref		Ref			
R1 (incomplete resection)	5	(11.6)	0.994	0.299-3.302	.992			
Histological differentiation								
Well, Moderately differentiated	35	(81.4)	Ref		Ref			
Poorly differentiated	8	(18.6)	0.643	0.223-1.857	.415			
Lymphatic infiltration								
Negative	19	(44.2)	Ref		Ref			
Positive	24	(55.8)	1.287	0.603-2.751	.514			
Venous infiltration								
Negative	10	(23.2)	Ref		Ref	Ref		Ref
Positive	33	(76.8)	8.432	1.973-36.036	.004	3.098	0.585-16.406	.184
CER								
LCER	26	(60.4)	3.534	1.473-8.479	.005	3.543	1.401-8.963	.008
HCER	17	(39.6)	Ref		Ref	Ref		Ref

CER, chemotherapy-effective rate; CF, cisplatin + 5-FU; DCF, docetaxel + cisplatin + 5-fluorouracil; HCER, high chemotherapy-effective rate; LCER, low chemotherapy-effective rate; RFS, recurrence-free survival; TRG-PT, tumor regression grade of primary tumor.

CER was shown to be an independent predictor for a poor prognosis, especially in patients with grade 0 TRG-PT. This suggested that the chemotherapeutic effect in LN might be a better prognostic factor, even with residual tumor at the primary site as well as in breast cancer.[7]

In the present study, CER could be used to identify the patient group with the worst prognosis that was not selected by only TRG-PT as one of the classifiers. That is, patients with grade 0 TRG-PT

and residual LNM with an LCER had a worse prognosis. Currently, nCT or nCRT followed by surgery is one of the standard treatments in Japan based on results from some clinical trials comparing the therapeutic effect of only surgery with that of surgery followed by adjuvant CT or CRT. However, trial results showed that the 5-year overall survival and progression-free survival was not so high (55% and 44%).[3] Therefore, a new therapeutic strategy needs to be established for patients who do not respond to neoadjuvant therapy. As a

first step, candidate patients requiring a new therapeutic strategy should be narrowed down by using our new categories, for example, CER.

In the present study, we examined all LN dissected together with the primary resected tumor, according to the same classification as that of TRG-PT, and could set the CER for LN as an independent prognostic factor. Because our study was retrospective in nature, and enrolled patients from one institution only, it will be necessary to carry out a validation study in another cohort.

In conclusion, our study showed that accurate evaluation of TRG-LN under the microscope, in addition to TRG-PT, allowed us to predict the prognosis of patients who had received nCT followed by surgery.

CONFLICTS OF INTEREST

Authors declare no conflicts of interest for this article.

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SUPPORTING INFORMATION

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