



# Prognostic Significance of Stratification Using Pathological Stage and Response to Neoadjuvant Chemotherapy for Esophageal Squamous Cell Carcinoma

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## ABSTRACT

**Purpose.** Risk stratification to select appropriate candidates for adjuvant therapy is required for esophageal cancer patients based on adjuvant therapy advancement including immunotherapy. The current study aims to develop a novel staging system using pathological stage (pStage) and response to neoadjuvant chemotherapy (NAC) for esophageal squamous cell carcinoma (ESCC).

**Methods.** ESCC patients who received NAC and underwent transthoracic esophagectomy at two Japanese high-volume esophageal centers were retrospectively reviewed. The prognostic value of NAC response was evaluated within the same pStage, and a novel risk stratification to predict cancer-specific survival (CSS) was developed.

**Results.** The HR (95% CI) of pathological responders in pStage 0–I, II, III, and IV was 0.29 (0.07–1.17), 0.37 (0.12–1.10), 0.37 (0.15–0.92), and 0.24 (0.06–0.98), respectively. Responders in pStage 0–II were classified to

be in the same class and those in pStage III/IV in another group, because the 5-year CSS (5y-CSS) rate of responders in pStage 0–I, II, III, and IV was 94%, 92%, 76%, and 71%, respectively. Combining nonresponders in pStage 0–II as the same group, all patients were subdivided into five groups. Intriguingly, the 5y-CSS in pStage III–IV responders was 75%, almost identical to that of nonresponders in pStage 0–II (78%).

**Conclusions.** The histological response influenced the long-term outcomes of patients who underwent esophagectomy after NAC, even within groups stratified by pathologic stage. The current risk stratification system will contribute to selecting appropriate candidates for adjuvant therapy.

Esophageal cancer is a devastating disease because of the wide range of lymph node (LN) metastasis, even at the early stage.<sup>1,2</sup> Multidisciplinary treatment combining surgery, chemotherapy, and radiotherapy has been standard to improve the outcome.<sup>3,4</sup> Neoadjuvant chemoradiotherapy (NACRT) and neoadjuvant chemotherapy (NAC) has been used in Western countries<sup>5</sup> and Japan, respectively, primarily for esophageal squamous cell carcinoma (ESCC).<sup>6–8</sup> Although postoperative treatment such as adjuvant chemotherapy was established as a standard treatment in gastric or colorectal cancer, proving the efficacy of adjuvant therapy for esophageal cancer has been challenging

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because of its high surgical invasiveness.<sup>9</sup> In fact, the percentage of patients who could receive adjuvant therapy was not high enough after esophagectomy.<sup>10,11</sup>

Recently, immune checkpoint inhibitors (ICI) were introduced for esophageal cancer and proved efficacious in the metastatic setting.<sup>12</sup> ICIs have less gastrointestinal toxicity compared with cytotoxic chemotherapy, potentially improving their tolerability in patients who undergo esophagectomy. More recently, the CheckMate-577 trial demonstrated that adjuvant nivolumab significantly improved the survival of patients who received NACRT followed by esophagectomy.<sup>13</sup> Therefore, while efficacy in patients who receive NAC remains unclear, adjuvant therapy including nivolumab could be the next standard treatment. On the other hand, immune-related adverse events (irAE) were reported to occur and required longer-lasting treatment in a certain number of patients.<sup>14,15</sup> Furthermore, the high cost of treatment would destroy public insurance systems worldwide. Therefore, risk stratification for appropriate selection of candidates for adjuvant therapy is desired.

TNM staging has been a standard to identify patients at high risk of postoperative recurrence.<sup>16</sup> In addition to the Japanese esophageal cancer classification,<sup>17,18</sup> the UICC/AJCC classification is a standard. Independent of the TNM staging system, the response to neoadjuvant treatment has been shown to predict postoperative survival, including in our recent report.<sup>19–22</sup> Therefore, this study hypothesized that the combination of pathological stage and histological response could be a simple and reliable risk stratification of cancer death. We developed a novel staging system combining pathological stage and histological response in ESCC patients who underwent esophagectomy after NAC, using the database from two Japanese esophageal centers.

## METHODS

### *Patient Selection*

Patients with ESCC who underwent transthoracic subtotal esophagectomy at Keio University Hospital or the Cancer Institute Hospital of the Japanese Foundation for Cancer Research between 2004 and 2016 were retrospectively reviewed. Among these, patients with cStage I, II, III (excluding cT1N0 and cT4b), or IV ESCC due to supraclavicular LN metastasis who received NAC, and whose histological response was available, were included in the analysis. Patients with salvage esophagectomy after definitive chemoradiotherapy or R2 resection were excluded.

Patient characteristics, clinicopathological factors, and surgical procedures were reviewed. Clinical stage was

determined by esophagogastroduodenoscopy (EGD) and computed tomography (CT) in all patients. Postoperative complications were evaluated using the Clavien–Dindo classification.<sup>23</sup> This study was approved by the ethics committee of the Keio University School of Medicine and Cancer Institute Hospital of Japanese Foundation for Cancer Research. Extent of tumor spread was evaluated using the 8th edition of the TNM classification, which was established by the Union for International Cancer Control (Supplementary Table 1). pT1 was applied with the patient's pN following the TNM staging manual when patients encountered complete histological response in the primary tumor while having residual disease in the lymph node.

### *Treatment and Follow-Up*

Transthoracic esophagectomy with right thoracotomy and gastric tube reconstruction is performed as a standard curative surgical procedure. Mediastinal LNs with bilateral recurrent nerve and abdominal LNs, including paracardial LNs and LNs along the lesser curvature and the left gastric artery, were routinely dissected. The supraclavicular LNs were also dissected if the primary tumor was located between the upper- and mid-thoracic esophagus. Cisplatin and 5-FU (CF) therapy twice every 3 weeks was the standard preoperative treatment at the present study's institutions based on the JCOG9907 study.<sup>4</sup> A regimen of CF plus docetaxel (DCF) administered three times every 3 weeks was an alternative treatment option. DCF was considered for patients in this study with either borderline-resectable disease or multiple LN metastases at diagnosis. Regardless of response to NAC before esophagectomy, postoperative treatment was not given unless patients had apparent residual disease. All treatment strategies were discussed at a multidisciplinary oncology conference attended by surgical oncologists, medical oncologists, diagnostic radiologists, and radiation oncologists. Postoperative follow-up included EGD and CT every 6 months for 5 years after surgery. When a patient was diagnosed as having pN2 or higher, the CT follow-up interval was 3–4 months during the first year after surgery. Cancer-specific survival (CSS) was calculated from day of surgery to day of death due to primary disease or last follow-up. In CSS, noncancer deaths were dealt with as censored cases at date of death. Overall survival was calculated from day of surgery to day of death or last follow-up. Patients were followed up until death or until July 2019.

### *Histological Response Criteria and Patterns of Recurrence*

The primary tumors were examined according to the Japanese Classification of Esophageal Cancer to evaluate the histological response to preoperative treatment.<sup>17,18</sup> This classification scheme includes five grade (grade 0, no tumor response; grade 1a, necrotic or fibrotic change observed in less than one-third of the tumor; grade 1b, necrotic or fibrotic change observed in between one- and two-thirds of the tumor; grade 2, more than two-thirds of the tumor was necrotic or fibrotic; and grade 3, no viable tumor cells).

### *Statistical Analysis*

Student's *t*-test was conducted to identify the difference in mean age between the groups. The distribution of operative time, blood, and number of LN retrieved were described using median (range) and compared using Mann–Whitney *U* test. Differences between categories were identified using the chi-squared test or Fisher's exact test. Survival curves were estimated using the Kaplan–Meier method. All comparisons between the two groups were made using the log-rank test. The hazard ratio (HR) was calculated using the Cox proportional-hazards model in cases in which more than two groups were described in survival analysis or in multivariate survival analysis. Factors with significance level of  $p < 0.1$  on univariate analysis were included in the multivariate analysis. All statistical analyses were conducted using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA), and differences were considered statistically significant when associated for two-sided  $p$ -value  $< 0.05$ .

## **RESULTS**

### *Response to Neoadjuvant Chemotherapy and Clinicopathological Factors*

The distribution of patients across grade 0–3 is presented in Table 1. Of the 483 patients included in this study, 82% were male. Among all patients, 50% of the tumors were located in the mid-thoracic esophagus. The numbers of cStage I, II, III, and IV patients were 52 (11%), 199 (41%), 204 (42%), and 28 (6%), respectively. In terms of NAC, 453 patients (94%) received CF and 30 (6%) received DCF. Regarding histological responses, grade 0–1a, 1b, 2, and 3 response was observed in 339 (72%), 68 (14%), 56 (10%), and 20 (4%), respectively. There was a significant association between clinical stage and histological response (Table 1). The NAC regimen did not affect the response. Regarding pathological stage, the

numbers of pStage 0, I, II, III, and IV patients were 13 (3%), 81 (17%), 134 (28%), 180 (37%), and 75 (15%), respectively. Twelve (21%) and two (10%) patients in the grade 2 and 3 groups, respectively, showed pathological stage (pStage) III or higher. The response did not influence the short-term outcomes, including operative time, amount of blood loss, and postoperative complications.

### *Cancer-Specific Survival and Histological Response*

To evaluate the external validity of histological responses, the prognostic impact of histological response criteria was compared between institutions. Consequently, we found that the cancer-specific survival of responders and nonresponders was almost identical between institutions (Supplementary Fig. 1). The CSS among the groups stratified by pathologic grade is shown in Fig. 1a. The HR (95% CI) of CSS in grade 1b, 2, and 3 relative to that in grade 0–1a was 0.27 (0.14–0.53), 0.13 (0.05–0.36), and 0.09 (0.01–0.65), respectively. The differences in the CSS between grade 0–1a and the others were common among the pathologic stages (Fig. 1b–e). Therefore, grade 1b, 2, and 3 were defined as responders and grade 0–1a as nonresponders in subsequent analyses.

### *Prognostic Significance of Responders for Each Pathological Stage*

The survival of responders was favorable compared with nonresponders in pStage 0–I [HR (95% CI), 0.29 (0.07–1.17); Fig. 2a] and II [HR (95% CI), 0.37 (0.12–1.10); Fig. 2b], but not statistically significantly so. Meanwhile, the HR (95% CI) of responders was 0.37 (0.15–0.92) and 0.24 (0.06–0.98) in pStage III (Fig. 2c) and IV (Fig. 2d), respectively, when compared with nonresponders. As shown in Supplementary Figs. 2 and 3, responders had significantly longer CSS than nonresponders in all groups stratified by pN stages, and in those with pT1 and pT3.

### *Establishment of Classification and Risk Score Using pStage and Histological Response*

The 5-year CSS (5y-CSS) rates of responders in pStage 0–I, II, III, and IV were 94%, 92%, 76%, and 71%, respectively. Therefore, responders in pStage 0–II were classified into one group, and those in pStage III and IV into another (Fig. 3). The 5y-CSS rates of the nonresponders in pStage 0–I and II were 81% and 77%, thus we classified these patients into one group. Finally, the patients were subdivided into five groups. Intriguingly, the 5y-CSS in pStage III–IV responders was 75%, almost identical to that of nonresponders in pStage 0–II (78%). As shown in

**TABLE 1** Comparison of pathological grade and patients

	All patients <i>n</i> = 483	Grades 0–1a <i>n</i> = 339	Grade 1b <i>n</i> = 68	Grade 2 <i>n</i> = 56	Grade 3 <i>n</i> = 20	<i>p</i> value
Age (mean ± SD)	63.1 ± 8.1	63.1 ± 7.9	64.1 ± 8.0	63.1 ± 8.0	59.7 ± 10.3	0.203
Sex						0.093
Male	395 (82%)	286 (84%)	54 (79%)	40 (75%)	15 (82%)	
Female	88 (18%)	53 (16%)	14 (21%)	16 (25%)	5 (18%)	
Location						0.495
Ce	3 (0.6%)	3 (1%)	0 (0%)	0 (0%)	0 (0%)	
Ut	63 (13%)	41 (12%)	14 (%)	7 (%)	1 (%)	
Mt	245 (50.4%)	171 (50%)	30 (%)	30 (%)	14 (%)	
Lt	172 (36%)	124 (%)	24 (%)	19 (%)	5 (%)	
NAC						0.386
CF	453 (94%)	320 (94%)	65 (96%)	50 (89%)	18 (90%)	
DCF	30 (6%)	19 (6%)	3 (4%)	6 (11%)	2 (10%)	
Depth of invasion						0.006
cT1	58 (12%)	32 (10%)	9 (13%)	13 (23%)	4 (20%)	
cT2	146 (30%)	98 (29%)	28 (42%)	13 (23%)	7 (35%)	
cT3	275 (57.8%)	207 (61%)	29 (43%)	30 (54%)	9 (45%)	
cT4a	1 (0.2%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	
LN metastasis						0.285
cN0	143 (30%)	99 (29%)	25 (37%)	13 (23%)	6 (20%)	
cN1	257 (53.2%)	176 (52%)	35 (51%)	35 (63%)	11 (55%)	
cN2	79 (16%)	62 (18%)	6 (9%)	8 (14%)	3 (15%)	
cN3	4 (0.8%)	2 (1%)	2 (3%)	0 (0%)	0 (0%)	
Distant metastasis						0.33
cM0	461 (95%)	320 (94%)	67 (98%)	54 (96%)	20 (100%)	
cM1 (supraclavicular LN positive)	22 (5%)	19 (6%)	1 (2%)	2 (4%)	0 (0%)	
Clinical stage						0.034
cStage I	52 (11%)	29 (8%)	7 (10%)	12 (21%)	4 (20%)	
cStage II	199 (41%)	135 (40%)	37 (54%)	19 (34%)	8 (40%)	
cStage III	204 (42%)	152 (45%)	20 (30%)	23 (41%)	8 (40%)	
cStage IV	28 (6%)	22 (7%)	4 (6%)	2 (4%)	0 (0%)	
Pathological depth of invasion						< 0.001
pT0	20 (4%)	0 (0%)	0 (0%)	00 (0%)	20 (100%)	
pTis	1 (0.2%)	0 (0%)	0 (0%)	11 (2%)	0 (0%)	
pT1a	31 (6%)	14 (4%)	3 (4%)	14 (25%)	0 (0%)	
pT1b	123 (26%)	72 (21%)	29 (43%)	22 (39%)	0 (0%)	
pT2	82 (17%)	54 (16%)	14 (21%)	14 (25%)	0 (0%)	
pT3	215 (45%)	189 (56%)	21 (31%)	55 (9%)	0 (0%)	
pT4	11 (2.8%)	10 (3%)	1 (1%)	0 (0%)	0 (0%)	
Pathological LN metastasis						< 0.001
pN0	179 (37%)	96 (28%)	35 (52%)	36 (64%)	12 (60%)	
pN1	157 (33%)	115 (34%)	21 (31%)	15 (27%)	6 (30%)	
pN2	104 (21%)	90 (27%)	9 (13%)	3 (5%)	2 (10%)	
pN3	43 (9%)	38 (11%)	3 (4%)	2 (4%)	0 (0%)	
Pathological distant metastasis						0.012
pM0	433 (90%)	294 (87%)	66 (97%)	53 (95%)	20 (100%)	
pM1 (supraclavicular LN positive)	50 (10%)	45 (13%)	2 (3%)	3 (5%)	0 (0%)	
Pathological stage						< 0.001
pStage 0	13 (3%)	0 (0%)	0 (0%)	1 (2%)	12 (60%)	

TABLE 1 continued

	All patients <i>n</i> = 483	Grades 0–1a <i>n</i> = 339	Grade 1b <i>n</i> = 68	Grade 2 <i>n</i> = 56	Grade 3 <i>n</i> = 20	<i>p</i> value
pStage I	81 (17%)	38 (11%)	19 (28%)	24 (43%)	0 (0%)	
pStage II	134 (28%)	81 (24%)	28 (41%)	19 (34%)	6 (30%)	
pStage III	180 (37%)	153 (45%)	16 (24%)	9 (16%)	2 (10%)	
pStage IV	75 (15%)	67 (20%)	5 (7%)	3 (5%)	0 (0%)	
Operative time (min, median, IQR)	548, 495–615	544, 499–615	548, 481–619	572, 517–628	551, 490–572	0.527
Blood (g, median, IQR)	270, 150–450	280, 160–450	261, 130–443	240, 115–489	230, 100–430	0.441
Postoperative complication						
Pneumonia ( $\geq$ CDII)	81 (17%)	52 (15%)	13 (19%)	10 (18%)	6 (30%)	0.345
Anastomotic leakage ( $\geq$ CDIII)	26 (5%)	22 (7%)	3 (4%)	0 (0%)	1 (5%)	0.247
Mortality within 30 days	None	None	None	None	None	
Number of LN retrieved (median, IQR)	59, 47–72	60, 47–75	57, 44–69	58, 49–70	61, 49–69	0.453

CF cisplatin plus 5-FU, DCF docetaxel, cisplatin, and 5-FU, LN lymph node, IQR interquartile range, CD Clavien–Dindo classification

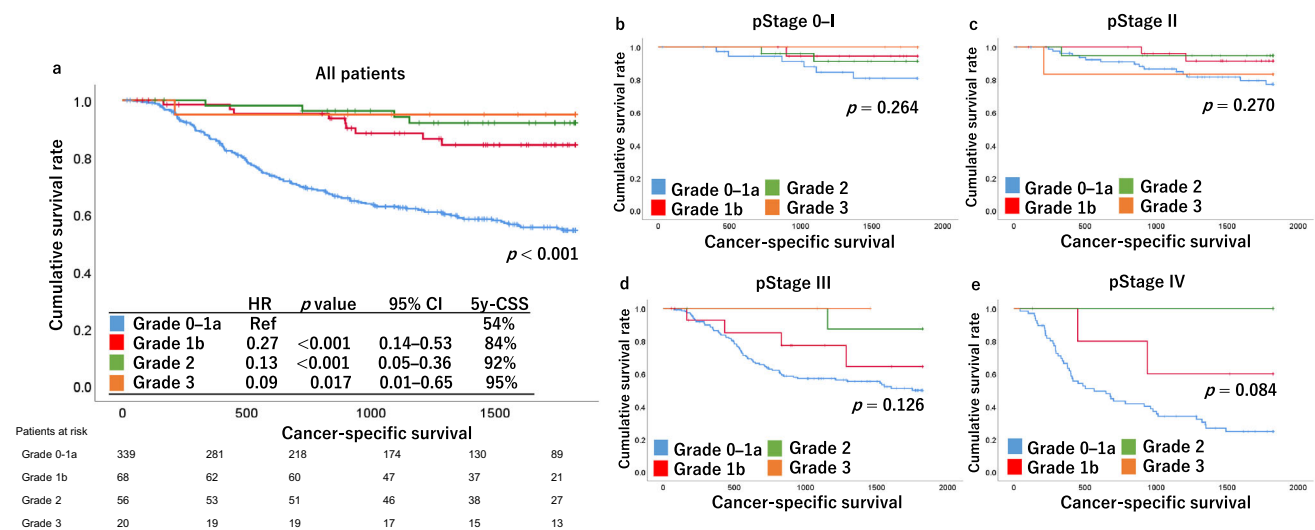


FIG. 1 Histological response and cancer-specific survival. (a) Histological response of primary tumor to NAC and cancer-specific survival (CSS). (b–d) Pathological histological response and CSS under stratification using the pathological stage

Supplementary Fig. 4, the previously reported stratifications using pN and histological response<sup>21,24</sup> were not as notable as our classification. When overall survival was evaluated, prognostic value was almost identical to CSS, as shown in Supplementary Fig. 5.

To develop a risk score, we conducted multivariate analysis using pStage and histological response, which were found to be significant prognostic factors on univariate analysis (Table 2). The results showed that these variables were independent prognostic factors of CSS (pStage II/III/IV, HR 1.25/3.71/7.59,  $p = 0.579/<0.001/<0.001$ ; nonresponders 3.07,  $p < 0.001$ ). Based on the

multiplication of hazard ratio from each group in which the reference group was set as 1.0 and all HR were rounded to integers, a scoring system was developed. As shown in Fig. 4, the scoring system successfully stratified the patient's prognosis significantly.

## DISCUSSION

The efficacy of NAC has been a well-known prognostic marker in ESCC patients.<sup>19,20</sup> In line with previous reports, when responders were defined as those with grade 1b or higher, they showed significantly better prognosis. Then,

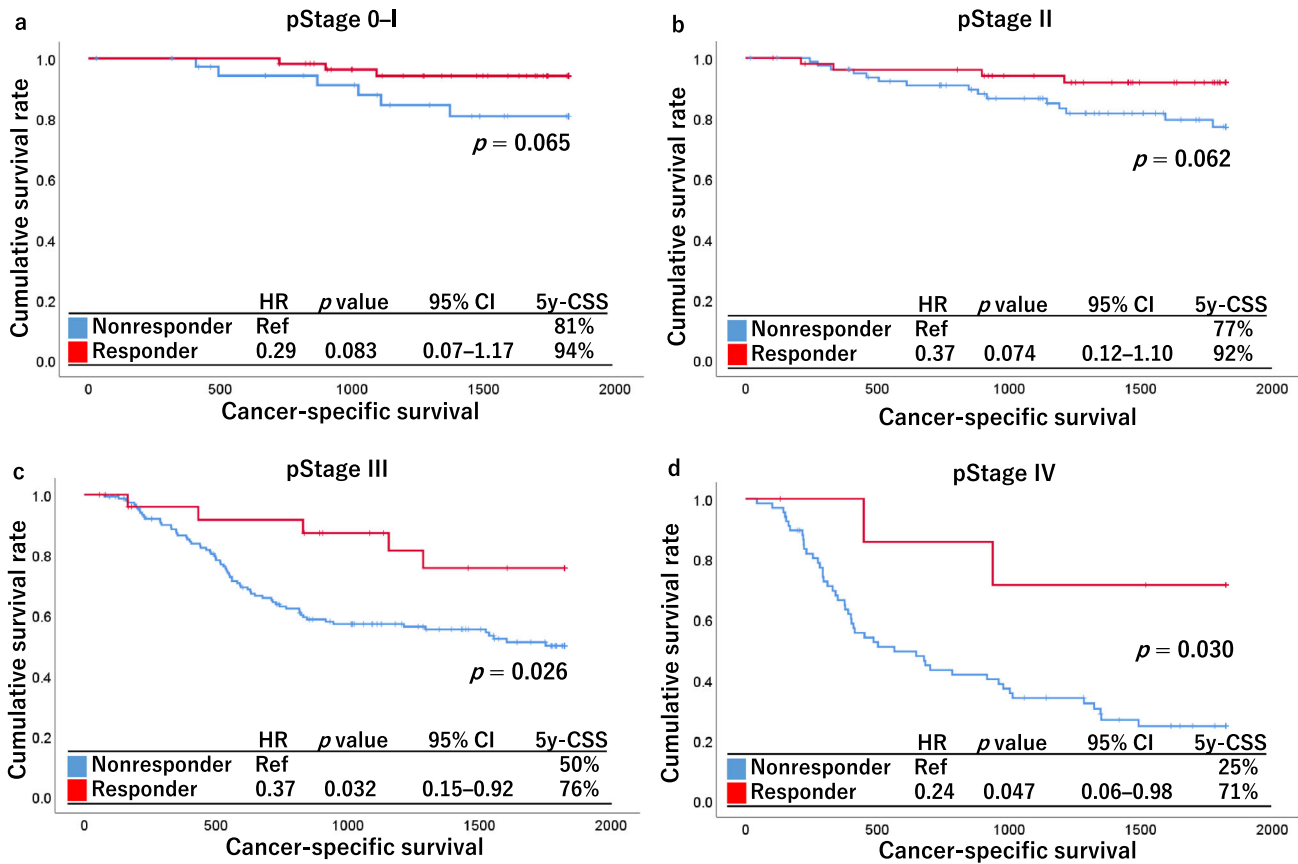
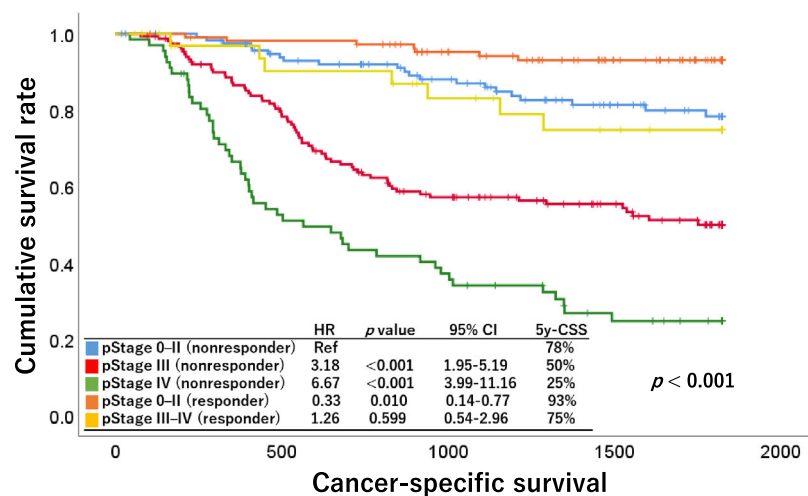


FIG. 2 Comparison between responders and nonresponders for each pathological stage

FIG. 3 Development of prognostic risk stratification system of cancer-specific survival combining pStage and response to neoadjuvant chemotherapy



Patients at risk

pStage 0-II (nonresponder)	119	112	99	83	63	48
pStage III (nonresponder)	153	126	91	70	54	33
pStage IV (nonresponder)	67	43	28	21	13	8
pStage 0-II (responder)	109	105	103	89	73	46
pStage III-IV (responder)	35	29	27	21	17	15

based on the histological response, the patients were further stratified into two groups for each pStage. The difference between the responders and nonresponders was

remarkable, especially in pStage III-IV. The current stratification could be beneficial to exclude patients who have lower risk of cancer-related death in the same

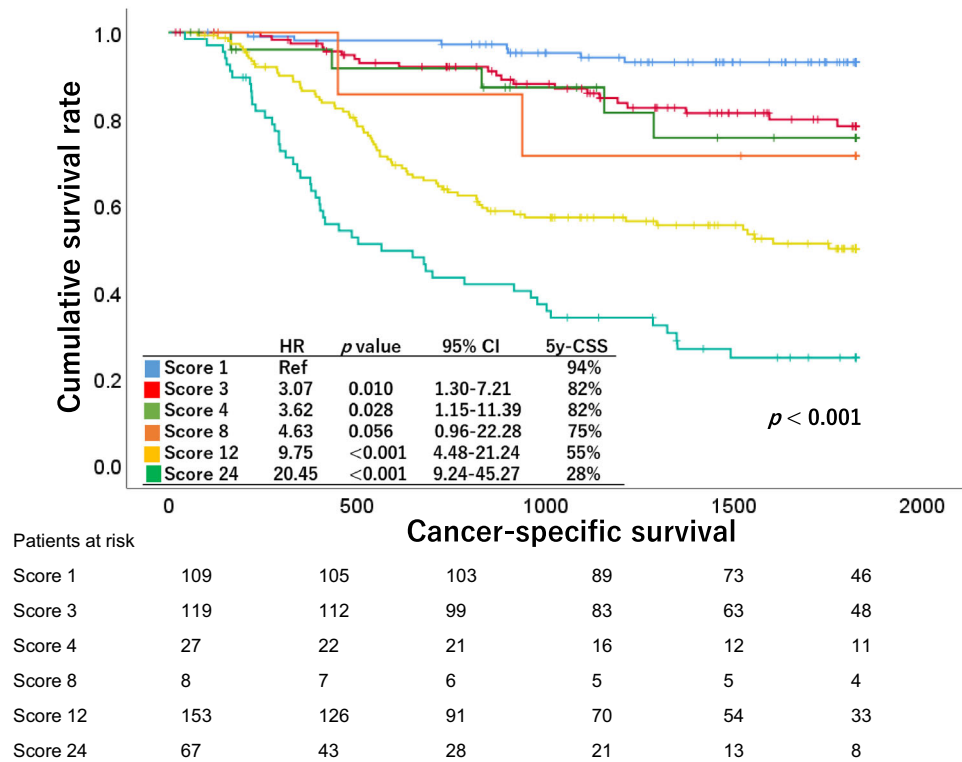


**TABLE 2** Clinicopathological factors, histological response, and cancer specific survival: uni- and multivariate analysis

<i>n</i> = 483	Univariate analysis			Multivariate analysis		
	HR	<i>p</i> value	95% CI	HR	<i>p</i> value	95% CI
Age	1.01	0.373	0.99–1.03			
Location						
Ce/Ut	Ref					
Mt	0.8	0.420	0.47–1.38			
Lt	0.9	0.538	0.64–1.26			
pStage						
pStage 0/I	Ref			Ref		
pStage II	1.56	0.272	0.71–3.45	1.25	0.579	0.56–2.79
pStage III	5.7	< 0.001	2.85–11.40	3.71	< 0.001	1.82–7.57
pStage IV	11.7	< 0.001	5.75–23.82	7.59	< 0.001	3.66–15.75
Histological response						
Responder	Ref			Ref		
Nonresponder	5.3	< 0.001	3.06–9.18	3.07	< 0.001	3.07–5.44
Postoperative pneumonia						
(–)	Ref					
(+)	0.81	0.37	0.51–1.28			
Postoperative anastomotic leakage						
(–)	Ref					
(+)	1.91	0.63	0.58–2.43			

HR hazard ratio

**FIG. 4** Development of risk scoring system using pStage and response to neoadjuvant chemotherapy



pathological stage. Several previous studies have shown a survival advantage for pathological responders within the same TNM class.<sup>24</sup> However, this is the first multicenter study to elucidate the clinical significance of the combination of pStage and histological response in patients who receive esophagectomy after NAC.

The responders showed favorable prognosis within the same pT and pN groups. Even though the locoregional tumor was completely resected by surgery, microscopic residual tumor cells inside the operative field or micrometastases to distant organs can cause recurrence. When NAC was effective, the residual tumors or micrometastases could be eradicated, resulting in lower cancer recurrence even in pStage III–IV. The current results are consistent with our recent report showing that pathological responders after NAC had less incidence of distant failure.<sup>19</sup> In the CROSS trial, neoadjuvant chemoradiotherapy reduced not only locoregional recurrence but also distant metastases. Besides, pCR was a favorable prognostic factor for both locoregional and systemic recurrence.<sup>25</sup>

Risk stratification methods such as TNM staging must be simple and accurate to be used in daily clinical practice. When patients are classified as responders and nonresponders in the same pStage, the more detailed classification can be proposed, although the number of groups is doubled and becomes more complex, which may decrease the external validity of the stratification. In the current analysis, they were classified to be in the same group because of the almost identical CSS in pStage 0–II and III–IV. Validation using a larger dataset is required for clinical application. In terms of the novelty of the current combination, several studies have reported the clinical significance of combining pathological findings and histological response. However, they primarily used pN stage and the presence of downstaging.<sup>21,22,24</sup> Nevertheless, especially in pStage III/IV, the prognosis of pathological responders was notably better within the same pStage in our dataset. Therefore, combining pStage and histological response would benefit these populations. Furthermore, since interinstitutional consistency is vital for establishing a new prognostic classification, the current first multiinstitutional study can be informative to predict prognosis in esophageal cancer patients who receive NAC.

Esophagectomy is a highly invasive procedure, and postoperative complications may slow down a patient's recovery, making it challenging to receive effective adjuvant therapy. Furthermore, postoperative complications negatively impact cancer relapse and overall survival.<sup>26</sup> Our group previously reported that the postoperative systemic inflammatory response is associated with disease recurrence independent of infectious complications.<sup>27</sup> These previous findings further suggested the importance

of reducing the number of tumor cells before esophagectomy, therefore leading to the introduction of neoadjuvant treatment. However, adjuvant treatment combined with neoadjuvant therapy can further improve survival. In 2020, the CheckMate-577 trial showed remarkable improvement of disease-free survival using adjuvant nivolumab.<sup>13</sup> Because of the fewer gastrointestinal adverse events, immune checkpoint inhibitors may be better tolerated by patients after transthoracic esophagectomy than cytotoxic agents. However, since immune-related adverse events can be crucial, the immunotherapy indication should be carefully chosen, especially in patients with better prognosis. On the other hand, the current stratification cannot predict the efficacy of chemotherapy. Regardless of the prognosis, adjuvant chemotherapy can potentially improve the prognosis of all patients. The current prognostic stratification would be a novel guide to predict long-term outcomes after surgery and determine the indication for adjuvant chemotherapy regardless of the group involved. Based on the fact that immunotherapy will not be the only adjuvant treatment option, further investigation is needed to establish the ideal treatment strategy, including cytotoxic chemotherapy for those with unfavorable prognosis.

This study had several limitations. First, the potential selection bias cannot be fully excluded because of its retrospective nature. However, consecutive patients who underwent transthoracic esophagectomy after NAC were reviewed to minimize the bias. Furthermore, the current dataset was obtained from two Japanese high-volume esophageal centers. A multicenter trial would help improve the external validity of the current analysis. Second, the definition of the histological response to chemotherapy is another limitation. Several classifications have been proposed to evaluate the histological responses. Although the criteria were clearly stated in the JES classification, the diagnosis was provided by only two pathologists. In general, tumor size before NAC needs to be guessed to calculate the percentage of residual tumor cells, resulting in variation among investigators. However, the cutoff between grade 1a and 1b was set in the current analysis, which was relatively clear. Furthermore, the current separation would not greatly affect the results because of the remarkable difference in CSS between responders and nonresponders, with consistency between institutions (Supplementary Fig. 1). While the efficacy of neoadjuvant chemotherapy followed by surgery was proven in a randomized phase III trial,<sup>6</sup> with comparable survival to neoadjuvant chemoradiotherapy reported in the CROSS trial,<sup>5</sup> the application of an NAC-centered treatment strategy is limited. Therefore, the external validity of the current study is limited. On the other hand, given that triplet chemotherapy with higher response rates potentially



improved the prognosis further in the JCOG1109 trial, intensified NAC treatment could be adopted as one of the treatment options in the future.

In conclusion, this novel risk stratification combining pathological stage and histological response was proven to be effective. The current risk stratification system will contribute to selecting appropriate candidates for adjuvant therapy.

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