

# Lymph node response to neoadjuvant chemotherapy as an independent prognostic factor in gastric cancer

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**Abstract.** Previous studies have revealed the usefulness of neoadjuvant chemotherapy (NAC) followed by surgery for clinical stage III gastric cancer (GC). The tumor volume at the primary tumor site (PT) is sometimes difficult to measure because of the luminal structure; therefore, evaluation of the lymph node (LN) response to NAC may help to more accurately predict survival outcomes. The present study therefore evaluated the LN response to NAC for prediction of survival outcomes in patients with GC. The study involved 160 patients with clinical stage III GC who underwent NAC (n=14) and upfront surgery (n=146). PT and LN responses to NAC were evaluated, various clinicopathological factors were evaluated and Cox proportional hazard regression analyses were performed to determine survival outcomes. Overall survival (OS) and disease-free survival (DFS) were not significantly different between patients who underwent NAC and those who underwent upfront surgery (OS, P=0.71; DFS, P=0.50). However, although there were no significant differences in PT responses, patients classified as LN non-responders to NAC had a significantly worse prognosis compared with patients classified as LN responders in terms of DFS (PT, P=0.93; LN, P<0.01) and OS (PT, P=0.84; LN, P<0.01). Moreover, a higher neutrophil-lymphocyte ratio tended to be associated with poor DFS [univariate: hazard ratio (HR)=4.23, P=0.06; multivariate: HR=6.45, P=0.04]. Finally, an LN response

to NAC was significantly better for prediction of recurrence (univariate, HR=7.79, 95% confidence interval=1.16-63.51, P=0.02; multivariate, HR=7.44, P=0.01). Overall, the current study revealed the clinical importance of the LN response to NAC for predicting survival outcomes in patients with GC. These findings highlight the potential clinical impact of optimizing treatment strategies to improve the selection and management of patients.

## Introduction

Gastric cancer (GC) is the fourth leading cause of cancer death worldwide (1). Although surgical resection with D2 lymphadenectomy is currently a standard strategy for advanced GC, the survival outcome of patients with stage III GC remains poor, with a 5-year overall survival (OS) rate of 40 to 70% (2). Neoadjuvant chemotherapy (NAC) for advanced GC has been used in clinical practice since the 1990s (3). NAC aims to control microscopic metastasis and decrease the tumor volume. For patients with clinically resectable disease at high risk of recurrence, such as patients with extensive lymph node (LN) metastasis or large type 3 or 4 tumors, NAC is more commonly used than adjuvant chemotherapy. Although no randomized trials have been performed to compare these approaches, NAC is more likely to provide maximum response to systemic therapy. NAC is a promising strategy that is associated with significantly higher curative resection and downstaging rates than provided by surgery alone, highlighting its potential to improve the OS of patients with GC (4). The MAGIC trial was a landmark study that evaluated the survival benefit of perioperative chemotherapy plus surgery vs. surgery alone in patients with curative GC (4). The study was concluded by a phase III trial comparing surgery with vs. without perioperative chemotherapy, and the results showed a similar 5-year OS rate in favor of perioperative chemotherapy (5). In the randomized phase II PETRARCA trial, the addition of trastuzumab and pertuzumab in patients with human epidermal growth factor 2-positive resectable esophagogastric adenocarcinoma resulted in a high pathologic complete response rate and significantly improved LN-negative rates (6). Because accumulating reports including the above-mentioned clinical trials have shown that the response to NAC is considered an important factor related to survival outcomes in patients with GC, NAC followed by surgery is more likely to improve disease-free survival (DFS)

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*Abbreviations:* CI, confidence interval; CT, computed tomography; DCS, docetaxel, cisplatin, and S-1; DFS, disease-free survival; GC, gastric cancer; HR, hazard ratio; LCR, lymphocyte-C-reactive protein ratio; LN, lymph node; LNM, lymph node metastasis; NAC, neoadjuvant chemotherapy; NLR, neutrophil-lymphocyte ratio; OS, overall survival; PNI, prognostic nutritional index; PT, primary tumor site; RECIST, Response Evaluation Criteria in Solid Tumors; SOX, S-1 and oxaliplatin

*Key words:* neoadjuvant chemotherapy, lymph node, response prediction marker, gastric cancer, neutrophil-lymphocyte ratio

and OS (7-9). However, optimal methods to predict the therapeutic effect in patients with GC have not been developed, and a novel approach to evaluate the response to NAC for prediction of survival outcomes is required.

Tumor markers and imaging modalities, such as endoscopy and computed tomography (CT), have been used to evaluate the response to NAC. However, these evaluation methods involve measurement of the tumor volume at the primary tumor site (PT), which is sometimes difficult because of the luminal structure (10). In contrast, LNs have a clearer border and are included in the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Thus, NAC response evaluations that target LNs instead of the PT might provide a useful alternative for predicting survival outcomes in patients with GC. The presence of LN metastasis (LNM) is considered one of the most important prognostic factors after curative resection. More than half of patients with GC have LNM at the time of diagnosis, resulting in a 5-year OS rate of <30% (11). Because LNM is considered to be more closely associated with micro-metastases than is the PT, evaluating the LN response to NAC might be more accurate than assessing the PT for predicting treatment benefits and survival outcomes and managing treatment strategies.

In the present study, by analyzing PT and LN responses to NAC using CT images, we evaluated the clinical use of NAC responses for predicting survival outcomes. Our simple approach may be used in clinical decision-making for patients with GC before and after NAC.

## Materials and methods

**Patient cohorts.** This study involved 1220 patients with GC who underwent standard surgical procedures (gastrectomy and regional lymphadenectomy) at Tokushima University from 1994 to 2020. All patients were diagnosed with GC by pathologists according to the 8th edition of the American Joint Committee on Cancer/Union for International Cancer TNM staging system. Of these 1220 patients, we retrospectively reviewed 160 patients with clinical stage III GC who underwent NAC followed by surgery (n=14) and upfront surgery (n=146). The exclusion criteria were the inability to detect the size of the PT or LNs by CT images, the presence of non-adenocarcinoma, and lack of available clinical information. The pathological findings were evaluated by pathologists of Tokushima University, and the histological grade was determined according to the Japanese classification of GC; the evaluation criteria are provided in Fig. 1 (12). The patients' immunonutritional status was assessed using the neutrophil-lymphocyte ratio (NLR), lymphocyte-C-reactive protein ratio (LCR), and prognostic nutritional index (PNI) (13-15). C-reactive protein levels were assessed by using LABOSPECT 008  $\alpha$  (HITACHI, Tokyo, Japan). Neutrophils were calculated by using SIEMENS ADVIA 2120i Hematology System (Siemens Health care Co., Tokyo, Japan). Present study was approved in advance by the Institutional Review Board of the University of Tokushima Graduate School of Medical Science (TOCMS: 3215-1).

**NAC.** Routine examinations before treatment included a complete physical examination; assessment of medical and surgical history; chest, abdominal, and pelvic CT scans;

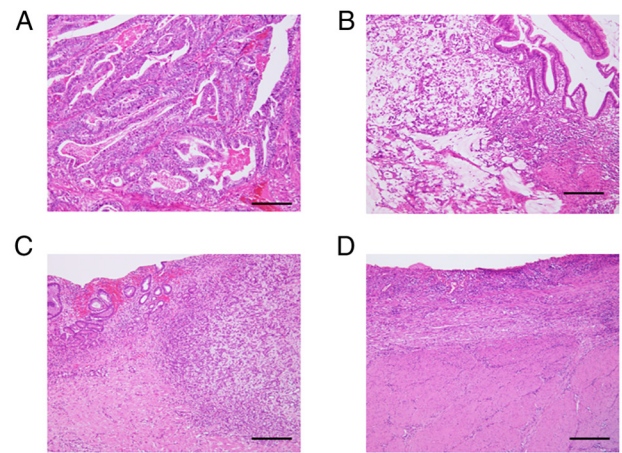


Figure 1. Histological grade of tumor response in patients treated by neoadjuvant chemotherapy. Pathological appearances of histological grades are shown (HE staining). (A) Grade 0 (no effect): No evidence of treatment effect. (B) Grade 1 (slight effect): Viable tumor cells occupy >1/3 of the tumor area. (C) Grade 2 (considerable effect): Viable tumor cells remain in <1/3 of the tumor area. (D) Grade 3 (complete response): No viable tumor cells remain. HE staining (magnification, x20). Scale bar: 50  $\mu$ m. HE, hematoxylin and eosin.

and endoscopy. NAC consisted of a docetaxel, cisplatin, and S-1 (DCS) regimen or S-1 and oxaliplatin (SOX) regimen. DCS therapy involved two to six cycles of docetaxel (60 mg/m<sup>2</sup>), cisplatin (60 mg/m<sup>2</sup>), and S-1 (40 mg/m<sup>2</sup> twice daily on days 1-14) every 3 weeks. SOX therapy involved two to six cycles of S-1 (40 mg/m<sup>2</sup> twice daily on days 1-14) and oxaliplatin (130 mg/m<sup>2</sup>) via rapid intravenous infusion every 3 weeks. Radical resection with D2 lymphadenectomy was performed 2 to 4 weeks after NAC.

**Evaluation of response to NAC.** The response to NAC was evaluated by the volume of the PT and the short axis of the LN lesion with the greatest diameter on enhanced thin-slice (1-mm) CT scans before NAC and 2 to 4 weeks after NAC. The response to NAC in the PT and LNs was evaluated as the percent reduction in the PT area and LN length, respectively. We classified positive LNs as those of >8 mm in size because a threshold of 8 mm is often arbitrarily used for perigastric LNs (16). We evaluated the diameter of each LN lesion and the median short axis of the total LN lesions in patients with multiple LNM. Based on the RECIST classification, the patients were classified into a responder group (complete response and partial response) and a non-responder group (stable disease and progressive disease) (10). All patients underwent an abdominal CT scan using a 320-slice Aquilion One scanner (Toshiba, Tokyo, Japan). The CT device had auto exposure control and was linked to a networked medical imaging system through which images were electronically transferred to a centralized data system and then retrieved at a workstation.

**Statistical analysis.** The cutoff thresholds of continuous variables were divided by the median value among the total participants. The nutrition indices (NLR, LCR, and PNI) were also divided by the median value among the total participants. The patients' clinicopathological characteristics were compared between responders and non-responders using the chi-square

test for categorical data. DFS and OS were analyzed by the Kaplan-Meier method using a weighted test. Univariate and multivariate Cox proportional hazard regression models were used to identify independent prognostic markers. A P-value of <0.05 was considered statistically significant. Statistical analyses were performed using MedCalc 16.2.0 statistical software (MedCalc Software bvba, Ostend, Belgium) and JMP Pro 13 statistical software (SAS Institute Japan, Tokyo, Japan).

## Results

**Patient characteristics and CT measurements.** We retrospectively reviewed 160 patients with clinical stage III GC who had been diagnosed with one or more positive LNs before treatment. Among these 160 patients, 14 underwent NAC followed by surgery and 146 underwent standard radical surgery (gastrectomy and D2 lymphadenectomy). The patients' detailed clinicopathological characteristics are provided in Table I. There were no significant differences in the clinicopathological characteristics between the two groups. The median PT area before and after NAC was 924 mm<sup>2</sup> (range: 600-2649 mm<sup>2</sup>) and 665 mm<sup>2</sup> (range: 332-1956 mm<sup>2</sup>), respectively. The median short axis of LN lesions before and after NAC was 11 mm (range: 8-20 mm) and 7 mm (range: 5-12 mm), respectively. We divided the patients into responder and non-responder groups based on the RECIST criteria; six patients were PT responders and eight were PT non-responders, and eight patients were LN responders and six were LN non-responders. We then examined the difference in the response to NAC between PTs and LNs (Table II).

**Prognostic potential of NAC response for predicting survival outcomes in patients with GC.** To evaluate the prognostic potential of NAC responses, we performed a survival analysis to compare OS and DFS between patients who underwent NAC and those who underwent upfront surgery. There were no significant differences in survival outcomes between the two groups (OS: P=0.71, DFS: P=0.50) (Fig. 2A and B). We then investigated the prognostic potential of NAC responses between patients categorized as responders and non-responders for PTs and LNs. The results showed no significant differences in the 5-year DFS rate between the PT non-responder and responder groups (64.3% vs. 66.7%, P=0.93) (Fig. 3A). More importantly, we observed that LN non-responders had significantly worse DFS than LN responders (30.0% vs. 100%, P<0.01) (Fig. 3B). Moreover, LN non-responders had significantly worse OS, whereas no significant difference in OS was observed between PT responders and non-responders (PT: 62.5% vs. 50.0%, P=0.84; LN: 26.7% vs. 100%, P<0.01) (Fig. 3C and D). These findings highlight the clinical importance of LN responses to NAC.

Furthermore, we conducted univariate and multivariate Cox proportional hazard regression analyses to identify prognostic factors, and patients categorized as LN non-responders to NAC had significantly worse DFS than patients categorized as LN responders [univariate: hazard ratio (HR)=7.79, 95% confidence interval (CI)=1.16-63.51, P=0.02; multivariate: HR=7.44, 95% CI=1.45-56.78, P=0.01] (Table III). In contrast, PT responders and non-responders to NAC showed no significant differences in DFS (univariate: HR=2.35, 95%

Table I. Clinicopathological characteristics of patients who underwent upfront surgery vs. NAC followed by surgery.

Factors	Upfront surgery (n=146)	NAC (n=14)	P-value
Age			0.19
≥70 years	79	5	
<70 years	67	9	
Sex			0.75
Male	109	11	
Female	37	3	
Tumor location			0.96
Upper/Middle	84	8	
Lower	62	6	
Tumor size			0.62
≥50 mm	83	7	
<50 mm	63	7	
Differentiation			0.08
Well/Moderate	74	3	
Poor	58	7	
Others	14	4	
cT stage			0.75
T1-3	76	6	
T4	70	8	
cN stage			0.73
N0-1	80	7	
N2-3	66	7	
Surgical procedure			0.62
DG	62	5	
TG	84	9	
NAC regimen			-
DCS	-	9	
SOX	-	5	
Histological grade			-
0, 1	-	6	
2, 3	-	8	

DCS, docetaxel + cisplatin + S-1; DG, distal gastrectomy; NAC, neoadjuvant chemotherapy; SOX, S-1 + oxaliplatin; TG, total gastrectomy.

CI=0.62-8.85, P=0.21). Among the clinicopathological factors, an elevated NLR tended to be associated with poor DFS (univariate: HR=4.23, 95% CI=0.57-31.42, P=0.06; multivariate: HR=6.45, 95% CI=1.23-45.34, P=0.04). These results indicate that the LN response to NAC and the NLR have prognostic potential in predicting the survival outcomes of patients with GC.

## Discussion

Radical resection with D2 lymphadenectomy is currently the gold standard for advanced GC worldwide (12,17-19).

Table II. Clinicopathological characteristics according to PT and LN responses to NAC.

Factors	Primary tumor			Lymph node		
	Res (n=6)	Non-res (n=8)	P-value	Res (n=8)	Non-res (n=6)	P-value
Age						0.33
≥70 years	3	2		2	3	
<70 years	3	6	0.33	6	3	
Sex						0.35
Male	6	5		7	4	
Female	0	3	0.10	1	2	
Tumor location						0.12
Upper/Middle	5	3		6	2	
Lower	1	5	0.09	2	4	
Tumor size						0.12
≥50 mm	2	5		2	4	
<50 mm	4	3	0.28	6	2	
Differentiation						0.08
Well/Moderate	1	2		2	1	
Poor	4	3		5	2	
Others	1	3	0.54	1	3	
cT stage						0.53
T1-3	3	3		4	2	
T4	3	5	0.64	4	4	
cN stage						0.28
N1	2	5		3	4	
T2-3	4	3	0.28	5	2	
Surgical procedure						0.33
DG	2	3		2	3	
TG	4	5	0.87	6	3	
NAC regimen						0.87
DCS	4	5		5	4	
SOX	2	3	0.87	3	2	
Histological grade						0.12
0, 1	2	4		2	4	
2, 3	4	4	0.53	6	2	
LCR						0.53
High	4	2		4	4	
Low	2	6	0.12	4	2	
NLR						0.35
High	5	2		7	2	
Low	1	6	0.71	1	4	
PNI						0.20
High	5	4		4	1	
Low	1	4	0.20	4	5	

DCS, docetaxel + cisplatin + S-1; DG, distal gastrectomy; LCR, lymphocyte-C-reactive protein ratio; LN, lymph node; NAC, neoadjuvant chemotherapy; NLR, neutrophil-lymphocyte ratio; Non-res, nonresponse; PNI, prognostic nutritional index; PT, primary tumor site; Res, response; SOX, S-1 + oxaliplatin; TG, total gastrectomy.

However, GC is one of the most aggressive malignancies; it has high metastatic potential, and the 5-year OS rates of patients after D2 lymphadenectomy remain poor (18). Therefore, a

multi-treatment strategy consisting of NAC has been suggested for GC because NAC reportedly reduces the tumor volume and micrometastases and improves the R0 resection rate (4).

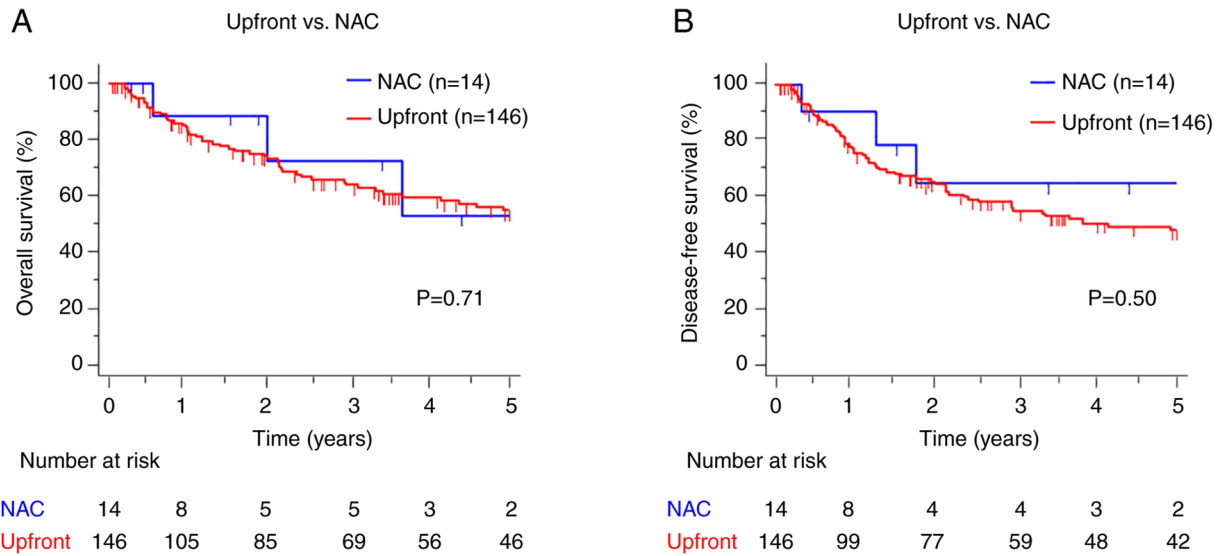


Figure 2. Prognosis of patients after upfront surgery and NAC. Comparison of (A) OS and (B) DFS in patients with clinical stage III gastric cancer who underwent upfront surgery (n=146) and NAC followed by surgery (n=14). The OS and DFS times were calculated from the date of surgery to the date of death of any cause, recurrence, or the last follow-up. OS and DFS were estimated using the Kaplan-Meier method. NAC, neoadjuvant chemotherapy; OS, overall survival; DFS, disease free survival.

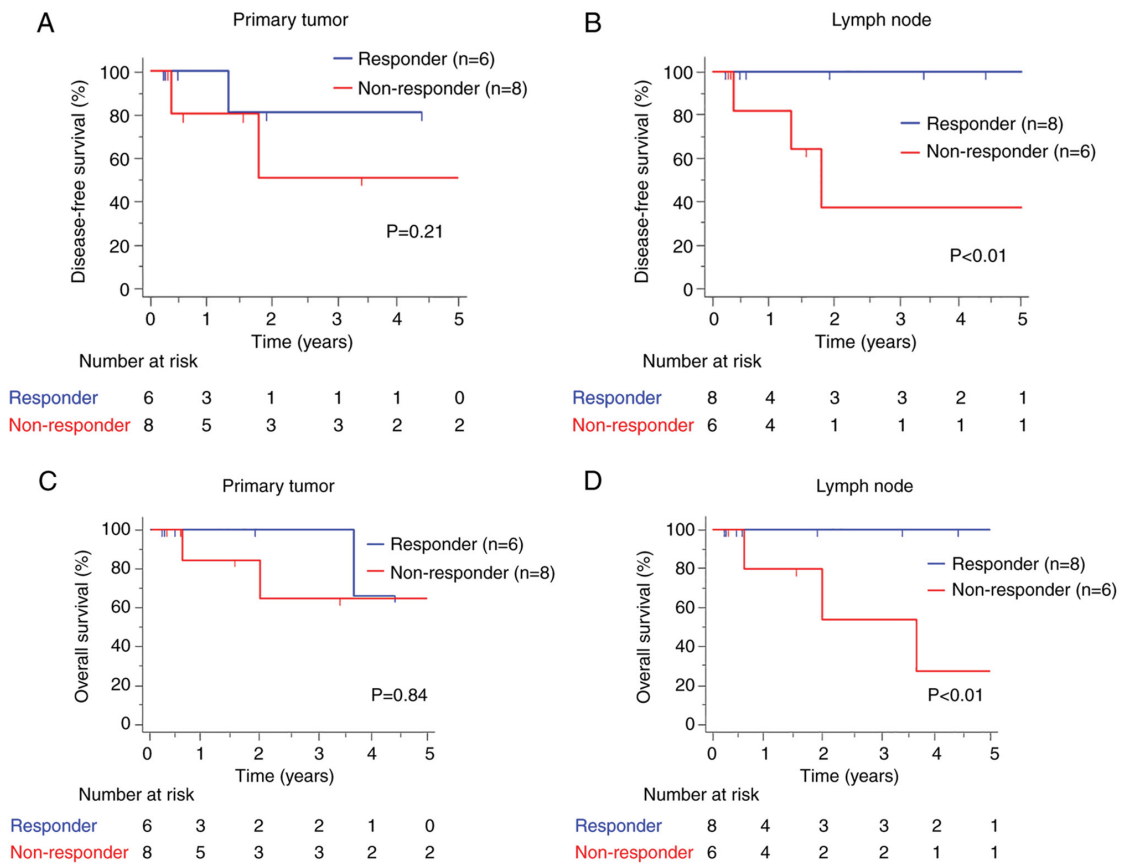


Figure 3. Prognosis of patients in responder and non-responder groups based on PT and LN responses to NAC. Comparison of DFS between the responder and non-responder groups according to (A) PT and (B) LN responses to NAC. Comparison of OS between patients in the responder and non-responder groups according to (C) PT and (D) LN responses to NAC. OS and DFS were estimated using the Kaplan-Meier method using a weighted test. PT, primary tumor site; LN, lymph node; NAC, neoadjuvant chemotherapy; DFS, disease-free survival; OS, overall survival.

Since the 1990s, NAC has been used in clinical practice for advanced GC (3). Furthermore, several clinical studies on the efficacy of NAC or different chemotherapeutic regimens have

recently demonstrated survival benefits compared with surgery alone in patients with advanced GC (4,5,20), emphasizing the clinical significance of predicting the response to NAC.

Table III. Univariate and multivariate Cox proportional hazard regression analyses for disease-free survival.

Factors	Univariate analysis			Multivariate analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
Age (≥70 vs. <70 years)	2.10	0.59-7.43	0.25			
Gender (Male vs. Female)	0.31	0.04-2.53	0.28			
Tumor location (Upper/Middle vs. Lower)	1.45	0.37-5.77	0.59			
Tumor size (≥50 mm vs. <50 mm)	0.64	0.16-2.56	0.53			
Differentiation (Well/Moderate vs. Poor/Others)	1.13	0.28-4.41	0.88			
cT (T4 vs. <T3)	2.61	0.73-9.40	0.14			
cN (≥N2 vs. <N1)	1.18	0.31-4.48	0.81			
Surgical procedure (TG vs. DG)	1.29	0.33-5.08	0.71			
NAC regimen (DCS vs. SOX)	3.27	0.78-13.73	0.09	2.37	0.67-8.98	0.45
Histological grade (0, 1 vs. 2, 3)	1.71	0.32-9.00	0.53			
LCR (Low vs. High)	2.53	0.67-9.60	0.17			
NLR (High vs. Low)	4.23	0.57-31.42	0.06	6.45	1.23-45.34	0.04 <sup>a</sup>
PNI (Low vs. High)	1.90	0.45-8.07	0.39			
PT response (Non-res vs. Res)	2.35	0.62-8.85	0.21			
LN response (Non-res vs. Res)	7.79	1.16-63.51	0.02 <sup>a</sup>	7.44	1.45-56.78	0.01 <sup>a</sup>

<sup>a</sup>P<0.05. CI, confidence interval; DCS, docetaxel + cisplatin + S-1; DG, distal gastrectomy; HR, hazard ratio; LCR, lymphocyte-C-reactive protein ratio; LN, lymph node; NAC, neoadjuvant chemotherapy; NLR, neutrophil-lymphocyte ratio; Non-res, nonresponse; PNI, prognostic nutritional index; PT, primary tumor site; Res, response; SOX, S-1 + oxaliplatin; TG, total gastrectomy.

Imaging modalities, including fluoroscopy, CT, and endoscopy, are standard tools for confirming the efficacy of NAC (21-23). Although the most accurate approach for evaluating the response to NAC is pathological classification, some studies have shown that the pathological grading scores of PTs have no predictive value for survival outcomes, and the predictive effect of the pathological complete response rate is not associated with that of the LNM rate (24,25). In the present study, we investigated the clinicopathological factors and PT/LN responses to NAC by CT imaging. The results showed that the PT response to NAC had no predictive significance, whereas patients classified as LN responders to NAC had a significantly higher 5-year DFS rate (30.0% vs. 100%, P<0.01) and 5-year OS rate (26.7% vs. 100%, P<0.01) than non-responders. Accumulating reports have shown that the

rate of LNM predicts survival outcomes and local recurrence in patients with GC (26-28), emphasizing that the LN response to NAC has prognostic potential.

Additionally, we evaluated the LCR, PNI, and NLR, which have been suggested to reflect the balance between the pro-tumor inflammatory status and anti-tumor immune status. In previous studies, patients with several cancers (including GC) who had an increased NLR showed neutrophilic leukocytosis and lymphocytopenia (29-33). In the present study, an elevated NLR was associated with recurrence in patients with GC before treatment and with the LN response to NAC, emphasizing the clinical importance of this nutritional index. Several reports have also shown that cancer-related systemic inflammatory responses are associated with increased numbers of circulating neutrophils. Neutrophils secrete cytokines and

chemokines, which play an important role in cancer progression (34), and the NLR is one of the most robust biomarkers for predicting the prognosis of various types of cancer (35,36). In the present study, an elevated NLR tended to be associated with poor DFS. However, other nutritional indices (lower PNI and LCR) were not associated with poor survival. A lower PNI and LCR have also been reported to be independently associated with poor survival (33,37-40). Therefore, additional studies involving more patients are needed to address the potential prognostic value of nutritional indices in GC.

This study has several limitations. First, its retrospective and single-institute design may have resulted in selection bias. Thus, a prospective clinical trial is required to confirm our findings. However, the patient population was uniform, and all patients received the same treatment strategy [i.e., NAC (DCS or SOX regimen) followed by distal or total gastrectomy with D2 lymphadenectomy]. Second, we analyzed a small number of patients who underwent gastrectomy with NAC. As a result, the findings of the present study are only applicable to patients with positive LNM who undergo NAC followed by surgery. We must confirm the accuracy of our findings in larger numbers of patients, and future studies should evaluate the feasibility of targeting distant metastatic lesions in addition to LNs to predict the response to chemotherapy. Third, we validated the predictive potential of LN responses to NAC by analyzing CT images and clinicopathological factors. Future experiments investigating other previously reported prognostic factors, such as the microsatellite instability status and GC subtypes (41-44), are needed to increase the convenience and prognostic accuracy of our approach. Finally, diagnosing clinical stage III GC by imaging modalities is difficult. However, our study provides important evidence for predicting survival outcomes in patients with GC, and these findings may be a significant step toward the management of lethal malignancies.

In conclusion, we have revealed the clinical importance of the LN response to NAC with CT imaging for prediction of survival outcomes in patients with GC. Our findings highlight the potential clinical impact of optimizing treatment strategies and improving the selection and management of patients with this malignancy.

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### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Authors' contributions

YW, MN and MS designed the study. YW, MN, KY, CT, TT and TN performed the data analyses. YW, MN, MS, HK and TY acquired the clinical data and drafted the manuscript. MS

revised the manuscript. All authors read and approved the final manuscript. YW and MN confirm the authenticity of all the raw data.

### Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the University of Tokushima Graduate School (approval no. 3215). Consent to participate was not applicable.

### Patient consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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