

Potential of clinical staging for long-term prognosis prediction in pathological stage III gastric cancer

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Abstract. In gastric cancer (GC), discrepancies are often observed between the clinical stage (cStage) and pathological stage (pStage). Nevertheless, cStage diagnosis may contribute to outcome predictions even within the same pStage. Therefore, the present study examined the prognostic significance of cStage in patients with pStage III GC who underwent curative gastrectomy. A multicenter retrospective study was conducted on 162 patients with pStage III GC who underwent curative resection at three institutions in Kyoto between April 2010 and May 2020. Patients were stratified into two groups according to cStage (I/II vs. III/IVA), and the clinicopathological features and survival outcomes were compared. Of the 162 patients, 72 (44.4%) were classified as cStage I/II and 90 (55.6%) as cStage III/IVA. The 5-year overall survival rate was significantly lower in the cStage III/IVA group than that in the cStage I/II group (50.0% vs. 63.9%, $P=0.030$), as was the 5-year recurrence-free survival rate (36.7% vs. 51.4%, $P=0.023$). A multivariate analysis identified cStage III/IVA ($P<0.05$, hazard ratio=1.912) as an independent poor prognostic factor for overall survival. In conclusion, preoperative cStage may serve as a complementary prognostic indicator reflecting tumor biological aggressiveness and could assist in postoperative treatment decision-making.

Introduction

Gastric cancer (GC) remains one of the leading causes of cancer-related mortality worldwide despite recent advances in its diagnosis and treatment (1). The accurate staging of GC is essential for selecting treatment strategies and predicting patient outcomes. In clinical practice, the clinical stage (cStage) evaluated by imaging modalities, such as upper gastrointestinal endoscopy, computed tomography (CT), and positron emission tomography-CT (PET-CT), provides critical information for selecting surgical procedures and the need for preoperative chemotherapy. Conversely, the pathological stage (pStage), which is assessed after surgical resection, has conventionally been regarded as the most reliable predictor of outcomes, and has been used as a basis for establishing the necessity of adjuvant chemotherapy after surgery.

cStage and pStage are both important for selecting treatment strategies. However, discrepancies between cStage and pStage are frequently observed in GC in clinical practice (2-4), and pStage, which is considered to be more reliable than cStage for outcome predictions, has been used to evaluate the postoperative prognosis of patients with GC and select treatment strategies (5,6). Several studies have shown that even among patients pathologically diagnosed with advanced GC (AGC), those classified as early GC (EGC) in cStage had a better prognosis than those classified as having advanced disease in cStage (7,8). Another study demonstrated that even within pT4a disease, preoperative CT findings, such as the depth of tumor invasion and tumor size, stratify prognosis (9), suggesting the contribution of a clinical diagnosis to outcome predictions even within the same pStage. Previous studies have evaluated prognostic differences based on the Borrmann classification, which is closely associated with the cT factor, or based on cT factors, and most of these analyses have been conducted in single-center settings.

With this background, we conducted a multicenter retrospective study to evaluate the prognostic significance of

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cStage, incorporating both cT and cN factors, in patients with pStage III GC who underwent curative gastrectomy.

Materials and methods

Patients. This study included 191 patients with pStage III GC who underwent curative gastrectomy at three hospitals in Kyoto (Kyoto Prefectural University of Medicine, North Medical Center Kyoto Prefectural University of Medicine, and Ayabe City Hospital) between April 2010 and May 2020. In accordance with the Japanese Gastric Cancer Treatment Guidelines, curative resection for GC was performed on patients whose cases were not eligible for endoscopic resection and who were determined to have no distant metastases based on preoperative imaging (i.e., cStage I-IVA) (6). The surgical procedures performed were total gastrectomy, distal gastrectomy, and proximal gastrectomy. Patients who received neoadjuvant chemotherapy, were diagnosed preoperatively with cStage IVB disease with distant metastasis, underwent the simultaneous resection of other malignancies, had remnant GC, underwent emergency surgery, or had insufficient clinical records were excluded. Ultimately, 162 patients with GC were included in the analysis. Fig. 1 shows a flowchart of patient selection and classification.

All patient data were collected from medical records and the databases included. The present study was approved by the Kyoto Prefectural University of Medicine Ethical Review Board (approval no. ERB-C-3523). The study was conducted using an opt-out approach for consent as permitted by the Ethics Committee.

Diagnosis. All patients underwent a preoperative clinical diagnosis and postoperative pathological diagnosis according to the 8th Union for International Cancer Control classification (UICC) system (10). Tumor depth in the clinical diagnosis was assessed based on upper gastrointestinal endoscopy and CT findings. Regarding the clinical N stage, LNs that showed a short-axis diameter ≥ 8 mm on CT or abnormal fluorodeoxyglucose accumulation on PET-CT were considered to be positive for LN metastasis. In all cases, the cStage was determined preoperatively before the pathological results were available.

The pathological diagnosis was established by experienced pathologists. Dissected LNs were isolated from resected gastric specimens by surgeons, fixed in formalin, and subsequently submitted for a pathological evaluation.

Surgical procedure, follow-up, and treatments for recurrence. Primary tumor resection and LN dissection were performed according to the Japanese Gastric Cancer Treatment Guidelines (6). Postoperative adjuvant chemotherapy (PAC) was, in principle, administered to all patients in accordance with the guidelines, typically using doublet regimens. However, in patients with a poor general condition for whom standard chemotherapy was difficult to initiate, monotherapy with capecitabine or S-1 was employed or adjuvant chemotherapy was omitted. A postoperative follow-up was also conducted in accordance with the guidelines (6). CT was performed every six months for the first three years after surgery, and annually thereafter. Upper gastrointestinal

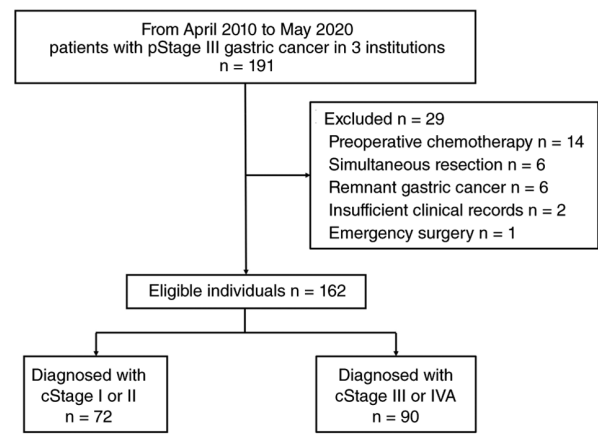


Figure 1. Flowchart for the selection of eligible individuals. A total of 191 patients who underwent the curative resection of gastric cancer and were diagnosed with pStage III between April 2010 and May 2020 were enrolled. Of these, 29 patients were excluded, and 162 were ultimately included in the retrospective study. cStage, clinical stage; pStage, pathological stage.

endoscopy was performed in the first, third, and fifth postoperative years to evaluate recurrence. Additional treatments for recurrence were selected based on the patient's condition, informed consent, and examination findings following the guidelines.

Effects of clinical diagnosis on prognosis. Patients were classified into two groups based on the cStage: those diagnosed as stage I or II and those diagnosed as stage III or IVA. The relationships between cStage and clinicopathological features were analyzed.

The effects of the clinical diagnosis on 5-year overall survival (OS) and 5-year recurrence-free survival (RFS) rates in patients with GC who underwent curative gastrectomy were investigated. Prognostic factors affecting survival in pStage III GC patients were examined using univariate and multivariate analyses. OS was defined as the interval from curative gastrectomy to death from any cause, and RFS was defined as the interval from curative gastrectomy to recurrence of GC or death from any cause.

Statistical analysis. Data processing and statistical analyses for the present study were centrally performed at Kyoto Prefectural University of Medicine. Data were analyzed using JMP version 18 (SAS Institute, Cary, NC, USA). The χ^2 test was used to compare categorical variables between the groups. Survival curves were estimated using the Kaplan-Meier method, and differences were evaluated using the log-rank test. Multivariate analyses were performed using Cox proportional hazards models. Hazard ratios (HR) and 95% confidence intervals for multivariate analysis were subsequently calculated using Cox proportional hazards regression models. In gastric cancer surgery, the surgical procedure and tumor location are closely related; indeed, in this cohort, 'Tumor location' was significantly associated with 'Gastrectomy' (χ^2 test, $P < 0.001$; data not shown). Since 'Tumor location' and 'Gastrectomy' are similar variables, the former was excluded from the multivariate analysis. $P < 0.05$ was considered to indicate a statistically significant difference.

Table I. Clinicopathological characteristics and relationships with cStage in pStage III GC.

Clinical characteristics	All patients (n=162)	cStage I/II ^a (n=72)	cStage III/IVA ^a (n=90)	P-value ^b
Age, years				0.086
<65	37 (22.8%)	21 (29.2%)	16 (17.8%)	
≥65	125 (77.2%)	51 (70.8%)	74 (82.2%)	
Sex				0.444
Male	113 (69.8%)	48 (66.7%)	65 (72.2%)	
Female	49 (30.2%)	24 (33.3%)	25 (27.8%)	
BMI, kg/m ²				0.292
<22	84 (51.8%)	34 (47.2%)	50 (55.6%)	
≥22	78 (48.2%)	38 (52.8%)	40 (44.4%)	
Tumor location				0.724
Upper	45 (27.8%)	19 (26.4%)	26 (28.9%)	
Middle/lower	117 (72.2%)	53 (73.6%)	64 (71.1%)	
CEA, ng/ml				0.777
<5	121 (74.7%)	53 (73.6%)	68 (75.6%)	
≥5	41 (25.3%)	19 (26.4%)	22 (24.4%)	
CA19-9, U/ml				0.697
<37	137 (84.6%)	60 (83.3%)	77 (85.6%)	
≥37	25 (15.4%)	12 (16.7%)	13 (14.4%)	
Lymphatic invasion				0.530
Presence	141 (87.0%)	64 (88.9%)	77 (85.6%)	
Absence	21 (13.0%)	8 (11.1%)	13 (14.4%)	
Venous invasion				0.200
Presence	140 (86.4%)	65 (90.3%)	75 (83.3%)	
Absence	22 (13.6%)	7 (9.7%)	15 (16.7%)	
Tumor differentiation				0.830
Differentiated	66 (40.7%)	30 (41.7%)	36 (40.0%)	
Undifferentiated	96 (59.3%)	42 (58.3%)	54 (60.0%)	
Gastrectomy				0.720
Partial	97 (59.9%)	42 (58.3%)	55 (61.1%)	
Total	65 (40.1%)	30 (41.7%)	35 (38.9%)	
Postoperative adjuvant chemotherapy				0.196
Presence	112 (69.1%)	46 (63.9%)	66 (73.3%)	
Absence	50 (30.9%)	26 (36.1%)	24 (26.7%)	
Postoperative complication				0.904
≤CD-I	120 (74.1%)	53 (73.6%)	67 (74.4%)	
≥CD-II	42 (25.9%)	19 (26.4%)	23 (25.6%)	

^aAccording to the 8th edition of the Tumor, Node, and Metastasis staging classification. ^bP-value derived from the χ^2 test. BMI, body mass index; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CD, Clavien-Dindo classification; cStage, clinical stage; pStage, pathological stage.

Results

Relationship between clinical diagnosis and clinicopathological features. A total of 162 patients were included in the analysis. Of these, 113 were male and 49 were female. The median age was 63 years (range, 29-94 years). Sixty-five patients (40.1%) underwent total gastrectomy, while 97 (59.9%) underwent partial gastrectomy. PAC was administered to 112 patients (69.1%). According to the clinical diagnosis,

20 patients were classified as cStage I, 16 as cStage IIA, 36 as cStage IIB, 87 as cStage III, and 3 as cStage IVA. The three cStage IVA cases consisted of one patient with cT4bN0M0 disease and two patients with cT4bN+M0 disease, all of whom were classified as stage IVA according to the 8th UICC system. Seventy-two patients were categorized into the cStage I/II group and 90 into the cStage III/IVA group. The clinicopathological characteristics of patients with GC are summarized in Table I. cStage did not correlate with clinical characteristics.

Table II. Discrepancy between clinical and pathological stage.

Clinical classification	Accuracy rate	Over diagnosis rate	Under diagnosis rate
cT factor	34.0%	13.6%	52.4%
cN factor	64.8%	0.2%	35.0%

cN, clinical N; cT, clinical T.

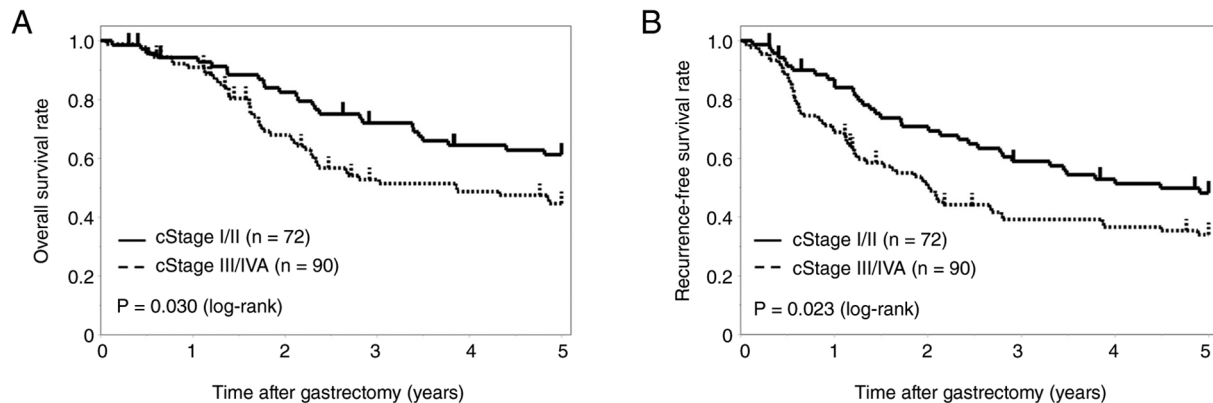


Figure 2. The clinical diagnosis predicts outcomes after gastric cancer surgery. (A) Overall survival of patients following the curative resection of gastric cancer based on cStage. (B) Recurrence-free survival of patients following the curative resection of gastric cancer based on cStage. cStage, clinical stage.

The clinicopathological characteristics of patients with pStage IIIA, IIIB, and IIIC disease are summarized in Table SI. No imbalance in the substages of pStage III was observed between the cStage I/II and cStage III/IVA groups (Table SII). In addition, no marked differences were observed between the two groups in terms of adjuvant chemotherapy regimens or completion rates (Table SIII). The association between postoperative adjuvant chemotherapy regimens and cStage is summarized in Table SIV. No significant differences were observed between the cStage I/II and cStage III/IVA groups in the proportions of patients who received no chemotherapy, monotherapy, or doublet therapy.

Discrepancy between cStage and pStage. Regarding the discrepancy between clinical and pathological diagnoses, diagnostic accuracy rates for the T and N factors were 34.0 and 64.8%, respectively. The cT factor was underestimated more than the pT factor in 52.4% of cases, while cN factor was underestimated in 35.0% of cases (Table II).

Clinical diagnosis as a prognostic factor in GC. The prognostic impact of the clinical diagnosis on patients with GC who underwent curative resection was evaluated using a Kaplan-Meier survival analysis (Fig. 2A and B). Among patients with pStage III disease, the 5-year OS rate was significantly lower in the cStage III/IVA group than in the cStage I/II group (50.0% vs. 63.9%, $P=0.030$). Similarly, the 5-year RFS rate was significantly lower in the cStage III/IVA group than in the cStage I/II group (36.7% vs. 51.4%, $P=0.023$). Prognostic factors affecting survival in patients with GC were assessed using a Cox proportional hazards regression analysis. In the univariate analysis of

5-year OS rates, tumors in the upper stomach, total gastrectomy, the absence of PAC, and the clinical diagnosis were identified as significant poor prognostic factors. Tumor location and surgical procedure were highly confounded; therefore, the surgical procedure was selected as the explanatory variable in the multivariate analysis to avoid multicollinearity. In the multivariate analysis of 5-year OS rates, total gastrectomy ($P<0.05$, $HR=1.934$), the absence of PAC ($P<0.05$, $HR=1.818$), and cStage III/IVA ($P<0.05$, $HR=1.912$) were identified as independent poor prognostic factors (Table III). In the univariate analysis of 5-year RFS rates, tumors in the upper stomach, total gastrectomy, the absence of PAC, and the clinical diagnosis were identified as significant poor prognostic factors. In the multivariate analysis of 5-year RFS rates, total gastrectomy ($P<0.05$, $HR=1.953$) and the clinical diagnosis ($P<0.05$, $HR=1.728$) were identified as independent poor prognostic factors, as shown in Table IV. Survival analyses were performed for the pStage IIIA-IIIC subgroups in the present cohort (Fig. S1). Although no statistically significant differences were observed in the pStage IIIA-IIIC subgroup analyses, patients with cStage III/IVA generally showed poorer OS and RFS than those with cStage I/II.

Discussion

In the present study, when patients with pStage III GC were stratified into cStage I/II and cStage III/IVA groups, those diagnosed preoperatively with more advanced disease had significantly worse OS and RFS. Furthermore, the multivariate analysis identified cStage III/IVA as a poor prognostic factor for both OS and RFS after curative

Table III. Prognostic factors for OS in patients with pStage III gastric cancer in univariate and multivariate analyses.

Variable	All patients (n=162)	Univariate		Multivariate	
		5-year OS, %	P-value ^a	HR (95% CI)	P-value ^b
Age, years			0.094		
<65	37	64.9			
≥65	125	53.6			
Sex			0.675		
Male	113	54.9			
Female	49	59.2			
BMI, kg/m ²			0.250		
<22	84	61.9			
≥22	78	50.0			
Tumor location			0.004 ^c		NA
Upper	45	40.0			
Middle/lower	117	62.4			
CEA, ng/ml			0.393		
<5	121	57.0			
≥5	41	53.7			
CA19-9, U/ml			0.456		
<37	137	57.7			
≥37	25	48.0			
Lymphatic invasion			0.203		
Presence	141	54.6			
Absence	21	66.7			
Venous invasion			0.302		
Presence	140	57.9			
Absence	22	45.5			
Tumor differentiation			0.654		
Differentiated	66	56.1			
Undifferentiated	96	56.3			
Gastrectomy			0.005 ^c		0.006 ^c
Partial	97	66.0		1	
Total	65	41.5		1.934 (1.208-3.095)	
Postoperative adjuvant chemotherapy			0.025 ^c		0.020 ^c
Presence	112	58.0		1	
Absence	50	52.0		1.818 (1.101-3.002)	
Postoperative complication			0.134		
≤CD-I	120	59.2			
≥CD-II	42	47.6			
cStage ^d			0.030 ^c		0.010 ^c
≤II	72	63.9		1	
≥III	90	50.0		1.912 (1.168-3.132)	

^aP-value derived from the log-rank test; ^bP-value derived from the Cox's proportional hazards model; ^cP<0.05, significant difference; ^dAccording to the 8th edition of the Tumor, Node, and Metastasis staging classification. BMI, body mass index; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CD, Clavien-Dindo classification; CI, confidence interval; cStage, clinical stage; HR, hazard ratio; NA, not available; OS, overall survival; pStage, pathological stage.

resection. These results indicate that even in pStage III GC, the preoperative clinical diagnosis may function as a useful tool for predicting postoperative outcomes.

Subgroup analyses according to pStage IIIA-IIIC showed generally consistent trends, although no statistically significant differences were observed.

Table IV. Prognostic factors for RFS in patients with pStage III gastric cancer in univariate and multivariate analyses.

Variable	All patients (n=162)	Univariate		Multivariate	
		5-year RFS (%)	P-value ^a	HR (95% CI)	P-value ^b
Age, years			0.086		
<65	37	51.4			
≥65	125	40.8			
Sex			0.443		
Male	113	45.1			
Female	49	38.8			
BMI, kg/m ²			0.640		
<22	84	45.2			
≥22	78	41.0			
Tumor location			0.003 ^c		NA
Upper	45	26.7			
Middle/lower	117	49.6			
CEA, ng/ml			0.318		
<5	121	44.6			
≥5	41	39.0			
CA19-9, U/ml			0.551		
<37	137	43.7			
≥37	25	40.0			
Lymphatic invasion			0.198		
Presence	141	41.8			
Absence	21	52.4			
Venous invasion			0.060		
Presence	140	45.7			
Absence	22	27.3			
Tumor differentiation			0.714		
Differentiated	66	42.4			
Undifferentiated	96	43.8			
Gastrectomy			0.003 ^c		0.002 ^c
Partial	97	54.6		1	
Total	65	26.2		1.953 (1.292-2.951)	
Postoperative adjuvant chemotherapy			0.165		
Presence	112	43.8			
Absence	50	42.0			
Postoperative complication			0.310		
≤CD-I	120	44.2			
≥CD-II	42	40.5			
cStage ^d			0.023 ^c		0.012 ^c
≤II	72	51.4		1	
≥III	90	36.7		1.728 (1.131-2.642)	

^aP-value derived from the log-rank test; ^bP-value derived from the Cox's proportional hazards model; ^cP<0.05, significant difference; ^dAccording to the 8th edition of the Tumor, Node, and Metastasis staging classification. BMI, body mass index; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CD, Clavien-Dindo classification; CI, confidence interval; cStage, clinical stage; HR, hazard ratio; NA, not available; pStage, pathological stage; RFS, recurrence-free survival.

The discrepancy between clinical and pathological diagnoses has been frequently discussed (2-4). Regarding the T factor, a previous study suggested that inconsistencies arise

because a pathological evaluation is not always performed at the site of deepest invasion (11). In addition, the location and size of tumors have been reported as risk factors for

discordance between clinical and pathological diagnoses of the T factor (2,8). Regarding the N factor, findings suggestive of LN metastasis on CT imaging include: i) A short-axis diameter of 6-8 mm in perigastric LNs, ii) a round shape, iii) central necrosis, and iv) heterogeneous or high enhancement (12). Although the size criteria for metastatic lymph nodes vary among studies, several reports, including the present study, have commonly adopted 8 mm as the cutoff value (3,9,13). CT sensitivity for N staging varies across studies (62.5-91.9% in systematic reviews) (14), indicating limitations in detecting LN metastasis using CT.

In the present cohort, an underestimation was observed in 52.4% of cases for the T factor and in 35% for the N factor, and diagnostic accuracy rates for the T and N factors were 34.0 and 64.8%, respectively. In previous studies, the diagnostic accuracy rate for the T factor was 35.8-38.8%, while that for the N factor was approximately 63.6%, which are consistent with the present results (11,13). The limited accuracy of clinical staging in GC, including more frequent underestimations than pathological staging, has been widely recognized as a major clinical issue (2,4). Several mechanisms may explain this underestimation. Peritumoral inflammation and fibrosis may obscure the true depth of tumor invasion on preoperative imaging. Fat stranding and serosal enhancement observed on CT are often difficult to distinguish from true serosal invasion, potentially resulting in both an underestimation and overestimation of the T factor. These inflammatory changes, particularly in advanced disease, may compromise the accuracy of a depth-of-invasion assessment (15,16). Furthermore, tumor morphology has a large impact on diagnostic accuracy. Diffuse-type or linitis plastica-like GC often present as uniform wall thickening without a distinct mass, making an accurate assessment of tumor depth challenging and predisposing these tumors to underestimation (17). In addition, LN micrometastases are often difficult to detect using conventional imaging modalities because of limited spatial resolution (18), which may lead to an underestimation of the N factor. Collectively, these factors suggest that the clinical staging of GC based on imaging modalities generally underestimates tumor progression.

Improvements in cStage accuracy have been reported through the use of additional imaging modalities. Previous studies demonstrated that the incorporation of endoscopic ultrasonography (EUS) may improve the diagnostic accuracy of cT stage (19). Systematic reviews showed that EUS provided an overall accuracy of 65-92.1% for cT staging, with a sensitivity of 77.8-100% for identifying serosal invasion (20). Although preoperative EUS was not mandatory in the present study, its addition may have further improved diagnostic performance. Although several studies have suggested that magnetic resonance imaging and EUS improve the diagnostic performance of cStage (21-23), these examinations are often omitted unless the findings obtained are expected to markedly affect the treatment strategy. As described above, although advances in imaging modalities may increase the concordance between cStage and pStage and may theoretically lessen the extent to which cStage functions as a complementary prognostic indicator, the current diagnostic performance still allows cStage to serve as a prognostic indicator, as demonstrated in the present study.

We discuss how cStage may function as a prognostic factor. Although the present results suggest the opposite, it is conceivable that an underestimation of cStage may result in less extensive lymph node dissection, thereby potentially leading to poorer oncologic outcomes. However, only 18 cases (11.1%, data not shown) in the cStage I/II group in the present study were classified as cT1bN0M0 or lower, which are not indicated for D2 dissection, and D2 dissection was appropriately performed in most cases where it was required. Therefore, this underestimation did not adversely affect prognosis. Previous studies on preoperative underestimations reported that patients with AGC who were preoperatively diagnosed as having EGC exhibited better OS and disease-free survival than those preoperatively diagnosed with AGC (7,8,24,25), which supports the present results. Taking these points into consideration, concerns that an underestimation of cStage may lead to insufficient lymph node dissection and thereby worsen prognosis, contradicting the results of the present study, may be alleviated. In addition, there were no significant differences between the two groups in the distribution of adjuvant chemotherapy regimens or completion rates, suggesting that treatment heterogeneity is unlikely to have influenced the observed differences in prognosis.

In advanced GC, a clinical diagnosis based on CT or PET-CT findings plays an important role. Imaging modalities have been shown to enable the spatial and non-invasive visualization of the biological characteristics of tumors, such as size, vascularity, and necrosis (26). In GC, several imaging-based prognostic factors have been reported in addition to conventional pathological indicators, such as tumor depth and the number of metastatic LNs. For example, a larger primary tumor size and diffuse wall thickening observed on CT have been associated with a poor prognosis (9,27,28). Furthermore, the size of LN on imaging has been reported to reflect the biological aggressiveness of the tumor (29,30). On CT, findings of gastric wall thickening, an irregular outer surface, or perigastric fat stranding are often interpreted as tumor invasion beyond the serosa (12). Similarly, in the assessment of LN metastasis, CT is used to estimate metastasis based on the morphology and size of LNs, while PET-CT evaluates the presence of nodal metastasis by reflecting the biological characteristics of LNs (12). A clinical diagnosis based on imaging assessments may inherently integrate various factors reflecting the biological aggressiveness of the tumor. The staging system of GC is based on two variables, the depth of invasion of the primary tumor and the number of metastatic LNs, and this method has the advantage of providing a simple and practical assessment of disease progression. However, this prognostic classification does not take into account other potential prognostic elements that are less directly related to the T and N factors, such as tumor size, lateral tumor extent (tumor volume), tumor characteristics, and LN morphology. Consequently, variations in prognosis may occur even among patients within the same pStage. cStage may integrate radiological surrogates of tumor burden, infiltrative growth pattern, and nodal morphology, which are not fully captured by pathological TNM classification. Based on these considerations, cStage may serve as a useful tool for a prognostic assessment within the cohort of patients with pStage III GC.

The present study has several limitations. This was a retrospective study with a small sample size and was therefore subject to potential selection bias. Therefore, we analyzed a large cohort from three centers to overcome this limitation; however, the present results require validation in a larger prospective patient cohort from many institutions. As clinical diagnoses and treatment decisions were performed by surgeons at each institution, potential concerns regarding interobserver variability in imaging modality and heterogeneity in treatment strategies cannot be entirely excluded. However, all participating surgeons underwent standardized training at the Department of Gastrointestinal Surgery, Kyoto Prefectural University of Medicine, ensuring consistency in imaging assessment and treatment decision-making. In addition, no central radiological or pathological review was performed. Furthermore, although local inflammation was suggested as an explanation for why a clinical diagnosis may serve as a prognostic factor, the possibility that other factors may also be involved needs to be considered. Further clinical and basic studies are required to clarify this.

The present study demonstrated that cStage is a useful prognostic factor for patients with pStage III GC following curative resection and may provide an independent and complementary perspective for outcome predictions. To the best of our knowledge, most previous studies have focused on the prognostic significance of the cT factor alone in single-center settings. This is one of the few studies to demonstrate the prognostic significance of cStage, incorporating both cT and cN factors, in patients with pStage III GC in a multicenter cohort. Previous studies evaluating Borrmann classification, gross tumor appearance, or cT-related findings have shown that patients preoperatively assessed as having less advanced disease tend to have better postoperative outcomes than those assessed as having more advanced disease (7,8,24,25). Consistent with these reports, the present study demonstrated that patients with pStage III GC classified as cStage I/II had more favorable OS and RFS than those classified as cStage III/IVA. However, whereas previous studies mainly focused on Borrmann classification, gross tumor appearance, or other cT-related factors, the present study evaluated cStage, a TNM-based clinical staging system determined according to the 8th UICC system that incorporates both cT and cN factors. Unlike the Borrmann classification, cStage represents an integrated clinical staging system rather than a morphological classification. Therefore, our findings support and extend previous observations by showing that a more comprehensive TNM-based preoperative clinical staging system can also provide complementary prognostic information within a multicenter cohort of patients with pStage III GC.

PAC is generally recommended for patients with pStage III GC and cStage may be regarded as one of the factors in postoperative decision-making. Further investigations are warranted to confirm these results and examine their potential clinical applications.

In conclusion, despite discrepancies with pathological staging, preoperative cStage may serve as a complementary prognostic indicator reflecting tumor biological aggressiveness.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

NN, HI, TKu, TKo, KNi, KT, SS, JH, KK, HKu, JK, TI, KNa, HS, TA, YY, HKo, RM, HF, TO and AS contributed to the conception and design of this study. NN, SS and JH acquired the data and confirm the authenticity of all the raw data. NN, HI and TKu contributed to data analysis and interpretation. NN and HI drafted the manuscript. TKo, KNi, KT, KK, HKu, JK, TI, KNa, HS, TA, YY, HKo, RM, HF, TO and AS made critical revisions. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Medical Ethics Review Committee of Kyoto Prefectural University of Medicine (approval no. ERB-C-3523). All experiments performed in this study involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was conducted using an opt-out approach for consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 71: 209-249, 2021.
2. Janczewski LM, Shah D, Wells A, Bentrem DJ, Abad JD and Chawla A: The inaccuracies of gastric adenocarcinoma clinical staging and its predictive factors. *J Surg Oncol* 127: 1116-1124, 2023.
3. Kim DJ, Hyung WJ, Park YK, Lee HJ, An JY, Kim HI, Kim HH, Ryu SW, Hur H, Kim MC, *et al*: Accuracy of preoperative clinical staging for locally advanced gastric cancer in KCLASS-02 randomized clinical trial. *Front Surg* 9: 1001245, 2022.
4. Papageorge MV, de Geus SWL, Zheng J, Woods AP, Ng SC, Cassidy MR, McAneny D, Tseng JF and Sachs TE: The discordance of clinical and pathologic staging in locally advanced gastric adenocarcinoma. *J Gastrointest Surg* 25: 1363-1369, 2021.
5. Ajani JA, D'Amico TA, Bentrem DJ, Corvera CU, Das P, Enzinger PC, Enzler T, Gerdes H, Gibson MK, Grierson P, *et al*: Gastric cancer, version 2.2025, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 23: 169-191, 2025.
6. Japanese Gastric Cancer Association: Japanese gastric cancer treatment guidelines 2021 (6th edition). *Gastric Cancer* 26: 1-25, 2023.

7. Oh SE, An JY, Choi MG, Sohn TS, Bae JM, Kim S and Lee JH: Long term oncological outcome of patients with grossly early gastric cancer-mimicking advanced gastric cancer. *Eur J Surg Oncol* 46: 1262-1268, 2020.
8. Nanishi K, Shoda K, Kubota T, Kosuga T, Konishi H, Shiozaki A, Fujiwara H, Okamoto K and Otsuji E: Diagnostic accuracy of the gastric cancer T-category with respect to tumor localization. *Langenbecks Arch Surg* 405: 787-796, 2020.
9. Park CJ, Seo N, Hyung WJ, Koom WS, Kim HS, Kim MJ and Lim JS: Prognostic significance of preoperative CT findings in patients with advanced gastric cancer who underwent curative gastrectomy. *PLoS One* 13: e0202207, 2018.
10. Brierley JD, Gospodarowicz MK and Wittekind C: TNM classification of malignant tumors 8th edition, 2017.
11. Zhu Z, Gong Y and Xu H: Clinical and pathological staging of gastric cancer: Current perspectives and implications. *Eur J Surg Oncol* 46: e14-e19, 2020.
12. Giandola T, Maino C, Marrapodi G, Ratti M, Ragusi M, Bigioger V, Talei Franzesi C, Corso R and Ippolito D: Imaging in gastric cancer: Current practice and future perspectives. *Diagnostics (Basel)* 13: 1276, 2023.
13. Fukagawa T, Katai H, Mizusawa J, Nakamura K, Sano T, Terashima M, Ito S, Yoshikawa T, Fukushima N, Kawachi Y, *et al*: A prospective multi-institutional validity study to evaluate the accuracy of clinical diagnosis of pathological stage III gastric cancer (JCOG1302A). *Gastric Cancer* 21: 68-73, 2018.
14. Smyth EC, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D and Committee EG: Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 27: v38-v49, 2016.
15. Kim TU, Kim S, Lee JW, Lee NK, Jeon TY and Park DY: MDCT features in the differentiation of T4a gastric cancer from less-advanced gastric cancer: Significance of the hyperattenuating serosa sign. *Br J Radiol* 86: 20130290, 2013.
16. Sun RJ, Tang L, Chen Y, Li XT, Sun Y, Li ZY and Sun YS: Feasibility of differentiating T3 from T4a gastric cancer in different Lauren classification by determining serosa invasion: Diagnostic performance of high enhanced serosa sign. *Chin J Cancer Res* 30: 263-271, 2018.
17. Morgant S, Artru P, Oudjit A, Lourenco N, Pasquer A, Walter T, Gornet JM, Rouquette A, Lledo G, Brezault C, *et al*: Computed tomography scan efficacy in staging gastric linitis plastica lesion: A retrospective multicentric French study. *Cancer Manag Res* 10: 3825-3831, 2018.
18. Stabile Ianora AA, Telegrafo M, Lucarelli NM, Lorusso V, Scardapane A, Niccoli Asabella A and Moschetta M: Comparison between CT Net enhancement and PET/CT SUV for N staging of gastric cancer: A case series. *Ann Med Surg (Lond)* 21: 1-6, 2017.
19. Lee KG, Shin CI, Kim SG, Choi J, Oh SY, Son YG, Suh YS, Kong SH, Lee HJ, Kim SH, *et al*: Can endoscopic ultrasonography (EUS) improve the accuracy of clinical T staging by computed tomography (CT) for gastric cancer? *Eur J Surg Oncol* 47: 1969-1975, 2021.
20. Kwee RM and Kwee TC: Imaging in local staging of gastric cancer: A systematic review. *J Clin Oncol* 25: 2107-2116, 2007.
21. Kim KW, Huh J, Urooj B, Lee J, Lee J, Lee IS, Park H, Na S and Ko Y: Artificial intelligence in gastric cancer imaging with emphasis on diagnostic imaging and body morphometry. *J Gastric Cancer* 23: 388-399, 2023.
22. Qiao X, Li Z, Li L, Ji C, Li H, Shi T, Gu Q, Liu S, Zhou Z and Zhou K: Preoperative T2-weighted MR imaging texture analysis of gastric cancer: Prediction of TNM stages. *Abdominal Radiology* 46: 1487-1497, 2020.
23. Uema R, Hayashi Y, Kizu T, Igura T, Ogiyama H, Yamada T, Takeda R, Nagai K, Inoue T, Yamamoto M, *et al*: A novel artificial intelligence-based endoscopic ultrasonography diagnostic system for diagnosing the invasion depth of early gastric cancer. *J Gastroenterol* 59: 543-555, 2024.
24. Saito H, Miyatani K, Takaya S, Matsunaga T, Fukumoto Y, Osaki T, Wakatsuki T and Ikeguchi M: Clinicopathologic characteristics and prognosis of advanced gastric cancer simulating early gastric cancer. *Yonago Acta Med* 56: 73-78, 2013.
25. Sun Z, Wang ZN, Zhu GL, Huang BJ, Li K, Xu Y, Li DM and Xu HM: Advanced gastric cancer with early cancer macroscopic appearance: Is it worthy of D2 lymphadenectomy? *Ann Surg Oncol* 17: 1278-1290, 2010.
26. Garcia-Figueiras R, Baleato-Gonzalez S, Padhani AR, Luna-Alcala A, Vallejo-Casas JA, Sala E, Vilanova JC, Koh DM, Herranz-Carnero M and Vargas HA: How clinical imaging can assess cancer biology. *Insights Imaging* 10: 28, 2019.
27. Li C, Oh SJ, Kim S, Hyung WJ, Yan M, Zhu ZG and Noh SH: Risk factors of survival and surgical treatment for advanced gastric cancer with large tumor size. *J Gastrointest Surg* 13: 881-885, 2009.
28. Li H, Chen XL, Li JR, Li ZL, Chen TW, Pu H, Yin LL, Xu GH, Li ZW, Reng J, *et al*: Tumor volume of resectable gastric adenocarcinoma on multidetector computed tomography: Association with N categories. *Clinics (Sao Paulo)* 71: 199-204, 2016.
29. Katayama H, Tsuburaya A, Mizusawa J, Nakamura K, Katai H, Imamura H, Nashimoto A, Fukushima N, Sano T and Sasako M: An integrated analysis of two phase II trials (JCOG0001 and JCOG0405) of preoperative chemotherapy followed by D3 gastrectomy for gastric cancer with extensive lymph node metastasis. *Gastric Cancer* 22: 1301-1307, 2019.
30. Kurokawa Y, Doki Y, Kitabayashi R, Yoshikawa T, Nomura T, Tsuji K, Goto M, Cho H, Hihara J, Hiki N, *et al*: Short-term outcomes of preoperative chemotherapy with docetaxel, oxaliplatin, and S-1 for gastric cancer with extensive lymph node metastasis (JCOG1704). *Gastric Cancer* 27: 366-374, 2024.



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