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ORIGINAL ARTICLE

Determinants of clinical outcomes of gastric cancer patients treated with neoadjuvant chemotherapy: a sub-analysis of the PRODIGY study

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Abstract

Background In this post hoc analysis of the PRODIGY study, we aimed to investigate factors associated with survival outcomes and provide evidence for designing optimal perioperative treatment strategies for gastric cancer patients receiving neoadjuvant chemotherapy.

Patients and methods A total of 212 patients in the neoadjuvant chemotherapy group of the PRODIGY study were included as the study population. The prognostic impact of clinicopathologic factors, including the initial radiological clinical stage (cStage) and post-neoadjuvant chemotherapy pathological stage (ypStage), was analyzed.

Results The median age was 58 years. The majority of patients (77.4%) had cStage III disease, and about 10% and 25% had ypStage 0 and I disease, respectively. According to the initial cStage, progression-free survival (PFS) and overall survival (OS) were significantly different ($P < 0.01$). PFS and OS were also different according to the ypStage ($P < 0.01$). In multivariate analyses, cStage IIIC disease (vs. cStage II) and ypStage II and III disease (vs. ypStage 0/I) were independent factors for poor survival outcomes. Based on the patterns of PFS and OS according to both cStage and ypStage, three patient groups were defined. These groups showed distinct PFS and OS ($P < 0.01$) with 5-year PFS rates of 95.7%, 77.9%, and 31.3% and 5-year OS rates of 95.7%, 82.4%, and 42.5%, respectively.

Conclusions Both initial cStage and ypStage were independent factors for survival outcomes of gastric cancer patients treated with neoadjuvant chemotherapy. Efforts should be made to develop optimal peri-operative treatment strategies for patients at different risks according to cStage and ypStage.

Keywords Gastric cancer · Neoadjuvant chemotherapy · Clinical stage · Post-neoadjuvant chemotherapy pathological stage

Abbreviations

OS	Overall survival
DOS	Docetaxel oxaliplatin and S-1
PFS	Progression-free survival
ypStage	Post-neoadjuvant chemotherapy pathological stage
cStage	Clinical stage
CSC	Neoadjuvant chemotherapy followed by surgical resection and adjuvant S-1
AJCC	American joint committee on cancer
ECOG	Eastern cooperative oncology group
FAS	Full analysis set
CT	Computed tomography
LN	Lymph node
PD	Progressive disease
CI	Confidence interval
ycStage	Post-neoadjuvant chemotherapy clinical stage
HR	Hazard ratio
ICIs	Immune checkpoint inhibitors
EUS	Endoscopic ultrasound

Introduction

Gastric cancer is the fifth most common cancer and the third leading cause of cancer-related death worldwide [1]. While surgical resection is essential for treating patients with locally advanced resectable gastric cancer, adjuvant

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treatment has been shown to prolong overall survival (OS). Because of the differences in the surgical approach, the proportion of early stage disease, and adverse events caused by the chemotherapy agents between Western and Asian populations, standard adjuvant treatment is regionally different based on the pivotal trials. Peri-operative chemotherapy is standard in European countries based on the MAGIC [2] and more recently reported FLOT4 [3] studies. In North America, post-operative chemoradiation is standard based on the Intergroup 0116 study [4]. In Eastern Asian countries, adjuvant chemotherapy using S-1 or capecitabine plus oxaliplatin is the current standard based on the ACTS–GC [5] or CLASSIC [6] trials, respectively. Recently, it has also been shown that the addition of oxaliplatin or docetaxel to adjuvant S1 in patients with pathological LN positivity or pathological stage III tumors, respectively, improved clinical outcomes in an adjuvant chemotherapy setting [7, 8].

Compared to post-operative adjuvant chemotherapy alone, neoadjuvant chemotherapy has some benefits of intensifying chemotherapy by delivering chemotherapy to reduce the tumor burden, while patients are more medically fit. Recently, the phase 3 PRODIGY [9] and RESOLVE [10] studies demonstrated that neoadjuvant chemotherapy with docetaxel, oxaliplatin and S-1 (DOS) or S-1 and oxaliplatin achieved a significantly higher rate of complete resection (R0 resection) and superior progression-free survival (PFS) (or disease-free survival), respectively, as compared to the standard adjuvant chemotherapy in Asian patients. Based on these results, neoadjuvant chemotherapy is expected to become one of the standard treatments in Asian countries.

Identifying factors associated with clinical outcomes in a neoadjuvant setting is required to optimize the application of peri-operative chemotherapy and develop optimal post-operative treatment strategies. In previous Western studies, a lower post-neoadjuvant chemotherapy pathological stage (ypStage) and a higher degree of pathological tumor regression were shown to be associated with favorable survival outcomes of gastric cancer patients receiving neoadjuvant chemotherapy [11–14]. However, these results cannot be directly extrapolated to Asian populations because of the use of different chemotherapy regimens and surgical approaches. Moreover, these studies mainly focused on analyzing the ypStage, and there have been no studies that have comprehensively evaluated the value of systematically assessing the initial radiological clinical stages (cStage) in a neoadjuvant setting. Given that the clinical benefit brought by neoadjuvant chemotherapy may be different according to the initial clinical stage [9, 15], the prognostic value of the initial clinical stage should be comprehensively assessed based on systematic and consistent clinical staging.

In this post hoc analysis of PRODIGY, we aimed to evaluate the prognostic value of clinicopathological factors in gastric cancer patients treated with neoadjuvant chemotherapy and provide evidence for designing optimal peri-operative treatment strategies for future studies.

Patients and methods

Study patients and treatments

The study population was derived from patients in PRODIGY who received neoadjuvant chemotherapy followed by surgical resection and adjuvant S-1 (the CSC group). The following were the key eligibility criteria for PRODIGY: 20–75 years of age, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, histological confirmation of primary gastric or gastroesophageal junction adenocarcinoma, and resectable and locally advanced disease as defined by cT2,3/N (+) or cT4/Nany stage by the American Joint Committee on Cancer (AJCC) 7th edition. Patients in the CSC group received three cycles of neoadjuvant DOS (docetaxel 50 mg/m^2 and oxaliplatin 100 mg/m^2 iv day 1, S-1 40 mg/m^2 po bid days 1–14 q3w), D2 surgery, and eight cycles of adjuvant S-1 (40–60 mg po bid days 1–28 q6w).

Among the 238 patients in the full analysis set (FAS) of the CSC group, 16 patients who did not receive surgery, 3 who received microscopically incomplete surgical resection (R1 resection) and 3 who received palliative surgery due to overt metastasis confirmed during surgery were excluded; thus, 212 patients were included as the final study population for this sub-analysis.

Clinical and pathological staging

As per the original PRODIGY, the initial clinical stage was determined based on the computed tomography (CT) scans that were uploaded to the study website by a central reviewer (JSL, a board-certified abdominal radiologist with more than 10 years of experience in abdominal imaging). Initial clinical T and post-neoadjuvant chemotherapy clinical T stages were determined according to the depth of invasion according to AJCC 7th edition by the central radiologist [16]. Clinical lymph node (LN) stage was determined based on the number of clinically positive LN. LNs were considered positive when the short axis was ≥ 8 mm (irrespective of the LN shape) or the shortest diameter was ≥ 5 mm with central necrosis, a round shape, perinodal infiltration, and/or prominent enhancement [17–19]. Post-neoadjuvant chemotherapy pathological ypStage was determined by analyzing post-chemotherapy pathological specimens based on the AJCC 7th edition.

In a subset of patients ($n = 107$), tumor regression grade (TRG) was assessed using the post-neoadjuvant chemotherapy pathological specimens of the primary tumor bed according to Becker's criteria [20]: TRG 1a, complete

pathological tumor regression; TRG1b, < 10% residual tumor per tumor bed; TRG 2, 10–50% residual tumor per tumor bed; and TRG 3, > 50% residual tumor per tumor bed.

Tumor assessment and follow-up

Tumor assessment was performed based on physical examination, abdominal–pelvic CT scan, and esophagogastroduodenoscopy. A physical examination was performed every 3 months for the first year and every 6 months after that. An abdominal–pelvic CT scan was performed every 6 months, and esophagogastroduodenoscopy was performed every 12 months. An additional evaluation was performed in clinical circumstances, where progressive disease (PD) was suspected.

Statistical analysis

Survival outcomes were analyzed with regard to the clinicopathologic factors, including histological classification, clinical staging, and post-treatment ypStage. PFS was defined as the interval from randomization to the PD date or death. The cutoff date for survival outcomes was the same as in the original PRODIGY study. PD was determined using RECIST v1.1 during neoadjuvant chemotherapy for patients in the CSC group. Recurrence/distant metastasis during follow-up after R0 resection was considered a PD event. OS was defined as the time from randomization to the date of death from any cause. The Kaplan–Meier method was used to estimate survival outcomes, and the log-rank test was used to compare these survival outcomes among the subgroups. Cox proportional hazard modeling was used to assess the association between the examined factors and PFS and OS. A P value of < 0.05 was considered statistically significant. Statistical analyses were performed using R software version 3.6.2 (R Foundation for Statistical Computing).

Results

Study patients

The baseline patient characteristics are summarized in Table 1. The median age was 58 years, and most patients (92.9%) had primary gastric tumors. A majority of patients (77.4%) had cStage 3 disease at initial radiological evaluation. By pathological evaluation following neoadjuvant chemotherapy, about 10 and 25% of patients had ypStage 0 (pathological complete response) and ypStage I disease, respectively. In the overall study population, the 5-year PFS and OS rates were 66.3% (95% confidence interval [CI] 59.4–74.0%) and 72.0% (95% CI 65.2–79.5%), respectively (Supplementary Fig. 1).

Table 1 Clinical characteristics of the study patients

Variables	CSC group ($n = 212$)
Age (years)	58 (27–75)
Male sex	163 (76.9)
ECOG performance status	
0	135 (63.7)
1	77 (36.3)
Primary tumor location	
GEJ	15 (7.1)
Gastric	197 (92.9)
Lauren classification[a]	
Intestinal subtype	74 (38.1)
Diffuse subtype	63 (32.5)
Mixed subtype	36 (18.6)
Indeterminate	21 (10.8)
Initial cStage	
IIA	8 (3.8)
IIB	40 (18.9)
IIIA	52 (24.5)
IIIB	75 (35.4)
IIIC	37 (17.5)
Post-neoadjuvant ypStage	
0	23 (10.8)
I	55 (25.9)
IIA	47 (22.2)
IIB	33 (15.6)
IIIA	18 (8.5)
IIIB	23 (10.8)
IIIC	13 (6.1)
Type of gastrectomy	
Subtotal gastrectomy	92 (43.4)
Total gastrectomy	120 (56.6)
Number of lymph nodes dissected[b]	38 (0–72)
Hospital stay during surgery (days)[c]	9 (7–43)

Data are presented as median (range) or number (percentage)

ECOG Eastern cooperative oncology group; *GEJ* Gastroesophageal junction

[a]For 194 patients whose data on Lauren classification were available

[b]For 44 patients whose data on the number of dissected lymph node were available

[c]For 168 patients whose data on hospital stay during surgery were available

Neoadjuvant and adjuvant chemotherapy

The proportion of patients completing the full course of neoadjuvant (3 cycles) and adjuvant chemotherapy (8 cycles) was 94.8% and 80.2%, respectively, with about one-fourth of patients having dose modification for both neoadjuvant and adjuvant chemotherapy (Table 2).

Table 2 Profiles of perioperative chemotherapy and response to neoadjuvant chemotherapy

Variables	CSC group ($n=212$)
Neoadjuvant chemotherapy	
Completion of 3 cycles of neoadjuvant chemotherapy	201 (94.8)
Dose modification of neoadjuvant chemotherapy	50 (23.6)
Adjuvant chemotherapy	
Completion of 8 cycles of adjuvant chemotherapy	170 (80.2)
Dose modification of adjuvant chemotherapy	58 (27.4)

Data are presented as number (percentage)

Following neoadjuvant chemotherapy, the proportion of patients with clinical T4 disease decreased from 67.5 (initial clinical T4) to 57.2% (post-neoadjuvant chemotherapy clinical T4), whereas that of patients with clinical lymph node negative disease increased from 1.9 (initial clinical N0) to 29.2% (post-neoadjuvant chemotherapy clinical N0) (Supplementary Table 1). Accordingly, 29.2% of patients with initial cStage II achieved down-staging to post-neoadjuvant chemotherapy clinical stage (ycStage) I, and 42.5% with initial cStage IIIA/B achieved down-staging to ycStage I/II, whereas most of the patients (89.2%) with initial cStage IIIC disease still had ycStage III disease (Supplementary Table 2). A comparison between cStage and ypStage is presented in Supplementary Table 3.

Clinical outcomes according to the clinical characteristics

There were no differences in PFS and OS according to the primary tumor location. In addition, PFS and OS were not different according to the Lauren classification, and the proportion of patients achieving a pathologic complete response was not significantly different according to the Lauren classification (4.1% vs. 8.1% for intestinal vs. diffuse/mixed subtypes, respectively; $P=0.36$).

While PFS and OS were significantly different according to the initial cStage, similar patterns of survival outcomes were observed between those with cStage IIA and IIB and those with cStage IIIA and IIIB (Supplementary Fig. 2A). Based on these findings, the patients were divided into 3 groups according to their cStage (i.e., cStage II, cStage IIIA/B and cStage IIIC), showing distinct PFS (5-year PFS rates of 84.5%, 65.9% and 44.6%, respectively; $P<0.01$) and OS (5-year OS rates of 88.5%, 72.6% and 52.3%, respectively; $P<0.01$) (Fig. 1A).

Similarly, based on the comparable survival outcomes between those with ypStage 0 and ypStage I (Supplementary Fig. 2B), the patients were grouped into 3 groups by their ypStage (i.e., ypStage 0/I, ypStage II and ypStage III), and they exhibited distinct PFS (5-year PFS rates of 86.8%, 65.7%, and 35.0%, respectively; $P<0.01$) and OS (3-year OS rates of 89.0%, 70.5%, and 47.3%, respectively; $P<0.01$) (Fig. 1B).

Multivariate analysis for survival outcomes

Multivariate Cox proportional analyses for PFS and OS (Table 3) revealed that cStage IIIC disease (vs. cStage II) was independently associated with a poor PFS (hazard ratio [HR] 3.53, 95% CI 1.28–9.76, $P=0.02$) and OS (HR 4.55, 95% CI 1.29–16.01, $P=0.02$), while cStage IIIA/B disease (vs. cStage II) showed a trend toward a poor PFS (HR 1.97, 95% CI 0.76–5.09, $P=0.16$) and OS (HR 2.41, 95% CI 0.72–8.05, $P=0.15$). In addition, ypStage II and III diseases (vs. ypStage 0/I) were independent factors for a poor PFS (HR 3.11, 95% CI 1.31–7.40, $P=0.01$ and HR 6.98, 95% CI 2.98–16.36, $P<0.01$, for ypStage II and III disease, respectively) and OS (HR 3.49, 95% CI 1.27–9.58, $P=0.02$ and HR 6.89, 95% CI 2.54–18.65, $P<0.01$ for ypStage II and III disease, respectively).

Survival outcomes considering both cStage and ypStage

Given that cStage and ypStage were independently associated with PFS and OS, survival outcomes for both stages were analyzed. Among patients with initial cStage II disease, those whose tumors were ypStage 0/I showed an excellent PFS and OS (5-year PFS and OS rates of 95.7%) (Fig. 2A). In the patient subgroup with cStage IIIA/B, those with ypStage 0/I and II showed similar PFS and OS, whereas those with ypStage III had a prominently poor PFS (5-year PFS rate 32.9%) and OS (5-year OS rate 46.5%) (Fig. 2B). In the subgroup with initial cStage IIIC, except for those who had ypStage 0/I, the PFS and OS were poor, with 5-year PFS rates of 48.6% and 18.2% or less (due to censoring of the last patient before 5 years) and OS rates of 45.7% and 36.4%, for ypStage II and ypStage III, respectively (Fig. 2C).

Subsequently, according to the similar patterns of PFS and OS by cStage and ypStage, 3 patient groups were defined: group 1 with cStage II and ypStage 0/I; group 2 with cStage II and ypStage II/III, cStage IIIA/B and ypStage 0–II, and cStage IIIC and ypStage 0/I; and group 3 with

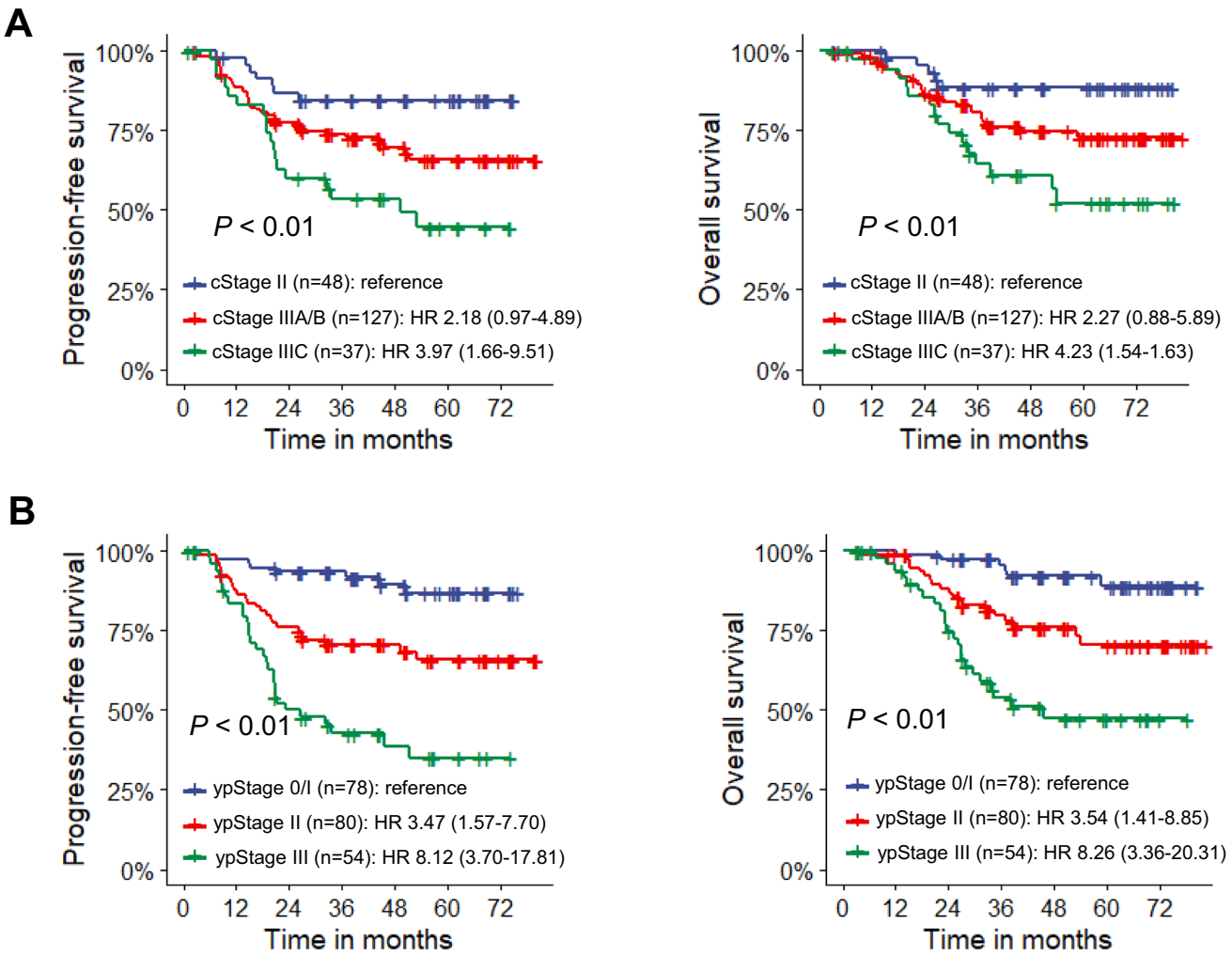

Fig. 1 Survival outcomes according to the initial clinical stage (cStage) and post-neoadjuvant chemotherapy pathological stage (ypStage). Progression-free survival and overall survival according to cStage (**A**) and ypStage (**B**). Hazard ratio (HR) of each group is represented with 95% confidence interval

cStage III/AB and ypStage III, and cStage IIIC and ypStage II/III (Fig. 3A). These groups showed a clear segregation in terms of PFS and OS with 5-year PFS rates of 95.7%, 77.9% and 31.3% ($P < 0.001$) and 5-year OS rates of 95.7%, 82.4% and 42.5% ($P < 0.001$) for groups 1, 2 and 3, respectively (Fig. 3B).

To further investigate the prognostic value of a pathological tumor response, we analyzed pathological tumor regression as represented by TRG in relation to the survival outcomes. The baseline clinicopathologic characteristics were comparable between the subgroups with ($n = 107$) and without TRG information ($n = 105$) (Supplementary Table 4). Patients with a pathological complete response (TRG1a) had favorable survival outcomes, but there was a trend toward worse survival outcomes for those with < 10% residual tumor (TRG1b) than those with 10–50% residual tumor (TRG2) (Supplementary Fig. 3A). Survival outcomes were similar between TRG1a/TRG1b and TRG2/TRG3 (Supplementary Fig. 3B).

Discussion

In this post hoc analysis of PRODIGY, we investigated the factors associated with survival outcomes of gastric cancer patients treated with neoadjuvant chemotherapy based on a systematic assessment of the clinical and pathological stages. We found that both the initial radiological cStage and post-neoadjuvant treatment ypStage were independently associated with PFS and OS, and taking both these stages into account enabled better patient stratification. To our knowledge, this is the first study to comprehensively evaluate the prognostic value of both cStage and ypStage, which were systematically assessed in a neoadjuvant setting

Table 3 Factors associated with progression-free survival and overall survival

Variables	Progression-free survival				Overall survival			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age ≥ 60 years	1.59 (0.93–2.70)	0.09	1.14 (0.66–1.96)	0.63	1.53 (0.83–2.80)	0.17	1.08 (0.58–1.99)	0.81
Female sex	1.62 (0.91–2.88)	0.10	1.38 (0.77–2.49)	0.28	1.94 (1.03–3.65)	0.04	1.64 (0.86–3.12)	0.13
ECOG PS 0 (vs.1)	1.37 (0.77–2.43)	0.29	–	–	1.44 (0.75–2.76)	0.28	–	–
GEJ location (vs. gastric)	1.36 (0.49–3.76)	0.56	–	–	1.75 (0.62–4.91)	0.29	–	–
Lauren classification intestinal (reference)	–	–	–	–	–	–	–	–
Diffuse/Mixed subtype	1.28 (0.71–2.29)	0.42			1.27 (0.66–2.43)	0.47		
Indeterminate	1.13 (0.45–2.86)	0.79			0.91 (0.3–2.74)	0.87		
cStage II (reference)	–	–	–	–	–	–	–	–
cStage IIIA/B	2.56 (1.00–6.55)	0.05	1.97 (0.76–5.09)	0.16	3.15 (0.95–10.42)	0.06	2.41 (0.72–8.05)	0.15
cStage IIIC	4.68 (1.71–12.78)	< 0.01	3.53 (1.28–9.76)	0.02	6.22 (1.79–21.64)	< 0.01	4.55 (1.29–16.01)	0.02
ypStage 0–I (reference)	–	–	–	–	–	–	–	–
ypStage II	3.41 (1.44–8.07)	< 0.01	3.11 (1.31–7.40)	0.01	3.86 (1.41–10.54)	0.01	3.49 (1.27–9.58)	0.02
ypStage III	8.39 (3.64–19.3)	< 0.01	6.98 (2.98–16.36)	< 0.01	8.75 (3.30–23.23)	< 0.01	6.89 (2.54–18.65)	< 0.01

HR Hazard ratio; *CI* Confidence interval; Eastern cooperative oncology group; *PS* Performance status; *GEJ* Gastroesophageal junction

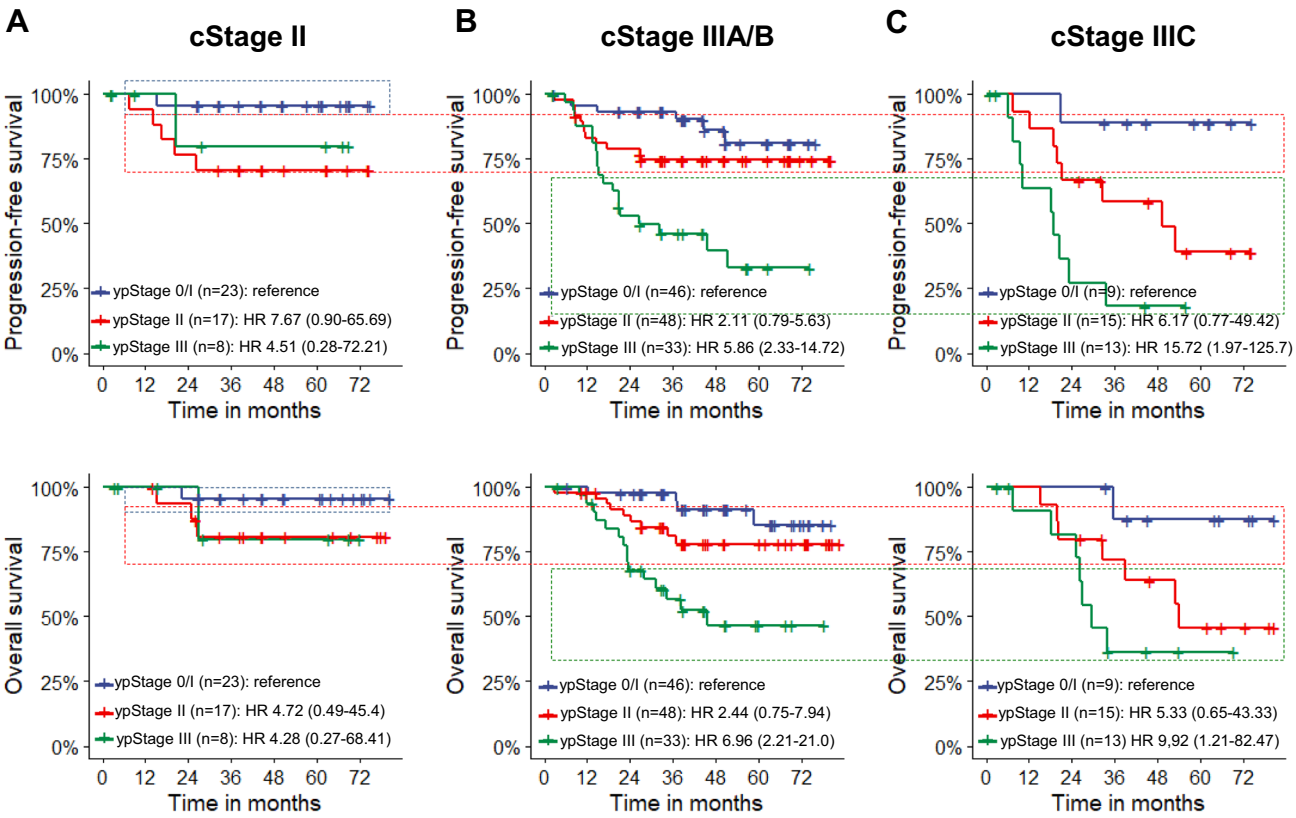

Fig. 2 Survival outcomes according to post-neoadjuvant chemotherapy pathological stage [ypStage in each initial clinical stage (cStage)]. Progression-free survival and overall survival in subgroups with cStage II (**A**), cStage IIIA/B (**B**), and cStage IIIC (**C**). Hazard ratio (HR) of each group is represented with 95% confidence interval

A

Group	Group 1 (n=23 10.8%)	Group 2 (n=128, 60.4%)			Group 3 (n=61, 28.7%)	
Initial cStage	II	II	IIIA/B	IIIC	IIIA/B	IIIC
ypStage	0/I	II/III	0/I or II	0/I	III	II/III

B

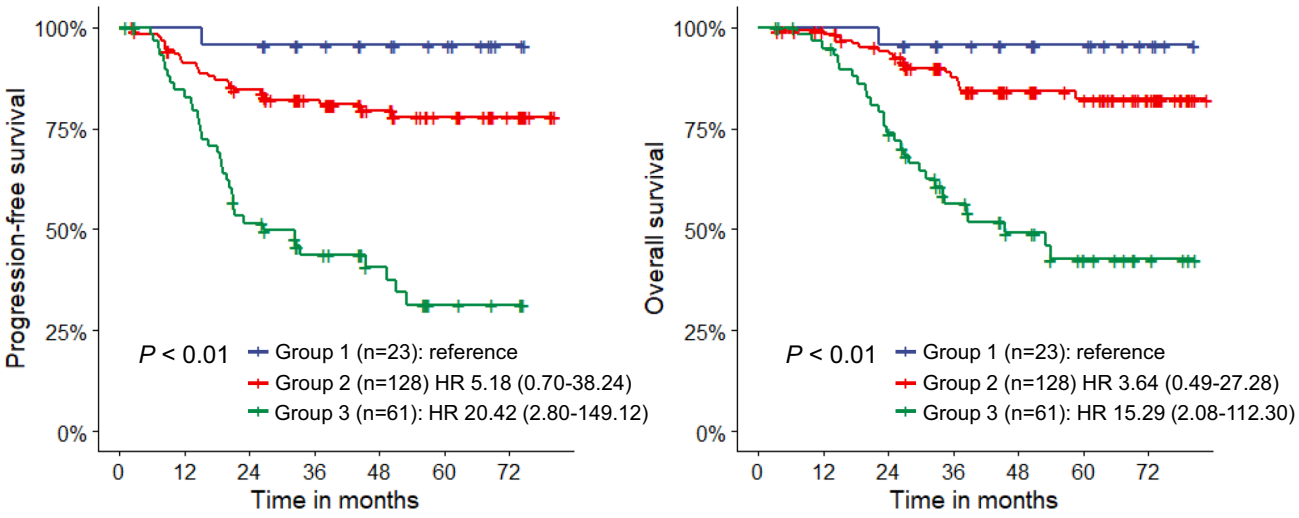

Fig. 3 Survival outcomes of different groups were determined by the initial clinical stage (cStage) and post-neoadjuvant chemotherapy pathological stage (ypStage). **A** classification of groups by cStage and ypStage. **B** Progression-free survival and overall survival of each group. Hazard ratio (HR) of each group is represented with 95% confidence interval

of locally advanced gastric cancer. Our results may provide evidence for designing future studies to optimize peri-operative treatment strategies based on the initial tumor burden and pathological stage in response to neoadjuvant treatment. In particular, our findings will provide novel practical insights into applying neoadjuvant chemotherapy to Asian populations.

Whereas previous studies have focused on the prognostic value of ypStage [11–14], our results indicate that both cStage and ypStage are prognostically important in a neoadjuvant setting. While a previous study showed that there was no prognostic difference between cStage II and III diseases after adjusting for other variables, their clinical staging might likely have been suboptimal and inconsistent, considering that the clinical staging was completed over 15 years as part of the routine clinical practice along with various regimens of neoadjuvant treatment [13]. Another study showed an association between a higher clinical T stage and poor recurrence-free survival, but the interpretation of the data is limited by its clinical staging using only endoscopic ultrasonography [14]. In our analysis, while the patient groups stratified according to cStage and ypStage showed distinct survival outcomes, considering both stages together enabled the identification of those with excellent (group 1) and particularly poor (group 3) survival outcomes. Patients in group 1 are characterized by an initially smaller tumor burden in conjunction with successful down-staging (into ypStage 0/I) by neoadjuvant chemotherapy. In contrast, those with initial cStage IIIA/B and ypStage III or cStage IIIC and ypStage II/III (group 3) are characterized by an initially large tumor burden and a failure to achieve effective down-staging. In particular, poor survival outcomes of the patients with initial cStage IIIC down-staged to ypStage II (which belong to group 3) suggest that patients with cStage IIIC disease showed prominently poor PFS and OS unless their tumors are effectively down-staged into ypStage 0/I. This highlights the prognostic importance of the initial cStage.

Importantly, taking both cStage and ypStage into account indeed recapitulates the degree of down-staging by neoadjuvant chemotherapy. We found a more favorable PFS and OS according to the degree of down-staging among the subgroups of each cStage. This accords well with a previous study of neoadjuvant chemoradiation therapy that highlighted the clinical value of the degree of down-staging following preoperative treatment [21]. However, the important issue that should be considered is the inaccurate aspects of

cStage in terms of predicting the exact pStage. Among the patients who received up-front surgery in the PRODIGY whose tumors could be pathologically evaluated, the overall concordance rate between clinical and pathological stages was only 64.3% with cStage II and IIIA/B tumors having a concordant pStage in only one-third and two-thirds of the cases, respectively (Supplementary Table 5). This issue has been raised by several studies [15, 22, 23], and the inaccuracy of clinical staging was also problematic in terms of inadvertently including patients with pathologically early stage disease in the recent phase 3 neoadjuvant studies [9, 10]. To this end, efforts are being made to better select candidates for neoadjuvant chemotherapy by minimizing the inclusion of patients with pathologically stage I disease [15, 23]. Therefore, given the inaccurate aspects of cStage, 'downward stage migration from cStage to ypStage' may not actually be the result of tumor down-staging by neoadjuvant chemotherapy, and thus, we did not directly assess the impact of down-staging from cStage to ypStage. Efforts should be made to develop a systematic tool, while considering the inaccurate aspects of cStage, to assess the degree of down-staging following neoadjuvant chemotherapy.

Pathological tumor response as represented by TRG is reportedly associated with favorable survival outcomes [11–13], and TRG might be a useful tool to assess tumor down-staging by neoadjuvant chemotherapy. However, its clinical value has not been firmly established and validated for gastric cancer, especially in an Asian setting. Indeed, there are some limitations of TRG to be considered: (1) since TRG is determined based on the pathological specimens without considering the initial tumor burden, it may not be fully representative of the degree of 'tumor down-staging'. Moreover, because of the abundant stromal component in the gastric cancer microenvironment [24], accurate assessment of pathologic tumor regression may be complicated among gastric cancers having different proportions of stromal components; (2) TRG only focuses on the evaluation of the primary tumor bed and may not comprehensively recapitulate the overall response to neoadjuvant chemotherapy. Given the prognostic importance of the presence of LN metastasis following neoadjuvant chemotherapy [11, 12], systematically assessing ypStage within the TNM system may better reflect the degree of overall tumor response to neoadjuvant chemotherapy, especially when considered together with cStage; (3) albeit present in a small proportion, there remains a possibility that any remaining viable tumor cells following neoadjuvant chemotherapy could serve as a reservoir for tumor recurrence. In our analysis, although patients with a pathological complete response (TRG1a) had favorable survival outcomes as expected, those with TRG1b exhibited a trend for worse survival outcomes than those with TRG2. This suggests that the degree of pathological response was not exactly correlated with the survival outcomes in our analysis. Although the discrepancy between our results and those of previous studies that showed the clinical value of a pathological response may be due in part to the use of different systems to evaluate a pathological response, these results are in line with the limitations of TRG as a factor predicting the survival outcomes as discussed above. Therefore, our results of the patient stratification according to cStage per se, albeit imperfect, and ypStage determined within the TNM system may comprehensively represent the initial tumor burden as well as the degree of response to neoadjuvant chemotherapy. In particular, our results highlight the previously unrecognized value of the initial clinical stage to reflect the responsiveness to neoadjuvant chemotherapy.

Substantially, heterogeneous outcomes based on the cStage and ypStage suggest the need for different strategies when applying peri-operative chemotherapy. As for post-operative treatment, patients in group 1 showed excellent survival outcomes (5-year PFS and OS rates of 95.7%) that corresponded to those of stage IA disease [25], in which the role of adjuvant chemotherapy has not been established. These results raise the possibility that some selected patients in this group may be able to undergo surveillance without adjuvant treatment. Nevertheless, this aspect should be cautiously considered, because the information about the exact pathological stage prior to neoadjuvant chemotherapy is not available for these patients, and tumors downstaged to stage IA may not exactly correspond to pathological stage IA tumors without neoadjuvant chemotherapy. Patients in group 2 appeared to be sufficiently treated with adjuvant S-1 alone, which was the post-operative regimen in PRODIGY. On the other hand, those in group 3 may require post-operative systemic therapy regimens with an improved efficacy to reduce the rate of recurrence. Given the reduced tolerability to chemotherapy following gastrectomy [26] and the neuropathy associated with oxaliplatin and/or docetaxel given during neoadjuvant treatment [9], the regimen for the intensification of chemotherapy will need to be cautiously selected. Furthermore, the fact that these patients did not achieve substantial down-staging suggests at least suboptimal responses to the triplet DOS regimen, pointing to the need for the use of different chemotherapy agents. In particular, adding immune checkpoint inhibitors (ICIs) may be considered in the post-operative context for these patients, especially for those with a high PD-L1 combined positive score.

On the other hand, patients with cStage IIIC disease showed distinctly poor outcomes. Although those who achieved down-staging into ypStage 0/I had a relatively favorable PFS and OS, only about one-quarter of patients with cStage IIIC achieved such a response, and these patients were still at a moderate risk of recurrence. Therefore, augmenting the efficacy of neoadjuvant treatment by strategies such as adding ICIs to the triplet regimen may be particularly relevant for patients with cStage IIIC. Since several

clinical trials of ICI-based peri-operative chemotherapy are currently ongoing, whether such ICI-added regimens could enhance the degree of down-staging, increase the proportion of patients achieving substantial down-staging to ypStage 0/I, and ultimately result in an improvement of survival outcomes will be of interest, especially in patients with cStage IIIC.

In our recent post hoc analysis of PRODIGY, we found that patients with cT4 disease showed a minimal proportion of pathological stage I disease (≤5%) in the up-front surgery group, and the relative risk reduction in PFS by neoadjuvant chemotherapy was most prominent in these patients [15]. This suggests the potential usefulness of cT4-based radiological criteria to select candidates for neoadjuvant chemotherapy. In the subgroup analysis of patients with cT4 disease, similar patterns of survival outcomes according to the cStage and/or ypStage were noted (data not shown). This indicates that both cStage and ypStage remain prognostically important in patients with cT4 stage who may preferentially benefit from neoadjuvant chemotherapy.

Other than cStage and ypStage, no other factor was found to be associated with survival outcomes in our analysis. A diffuse histologic subtype by the Lauren classification was reported to reduce the efficacy of adjuvant chemoradiation treatment in the updated analysis of the Intergroup 0116 study [27]. In the neoadjuvant setting, a diffuse subtype has been shown to be associated with a reduced degree of tumor regression by preoperative chemotherapy [20, 28]. In particular, in the phase 2 part of the FLOT study, a pathological complete response was more frequently noted in those with an intestinal subtype than in those with a diffuse subtype [29]. In addition, in the original PRODIGY study, the relative risk reduction of PFS by neoadjuvant chemotherapy was less prominent in those with a diffuse/mixed subtype than in those with an intestinal subtype [9]. However, the proportion of patients achieving a pathologic response was not different between the intestinal and diffuse/mixed subtypes in this study. Moreover, among the patients who received neoadjuvant chemotherapy, it did not have a significant prognostic impact in our analysis. The exact impact of the histological subtypes will need to be further determined in future studies of neoadjuvant chemotherapy.

There are some limitations of the current study to be discussed. First, our findings were not validated in an independent cohort, although there is no appropriate cohort for validation at this time. Second, because of the suboptimal accuracy of clinical radiological staging and the inconsistency of the clinical lymph node evaluation methods among studies [15, 23], our patient classification may not be directly applied to other cohorts, especially Western populations. Endoscopic ultrasound (EUS), which may be considered for further T staging and differentiation between early stage versus locally advanced disease [17, 30], was not used as a modality to evaluate disease extent in our study. However, the diagnostic accuracy of EUS is operator-dependent, ranging from 57 to 88% for T staging [31]. Moreover, the diagnostic yield of EUS in the assessment of T-stage is reportedly comparable to that of CT [32–34], and EUS does not improve the diagnostic accuracy of T staging compared with CT [23] Because of these aspects, EUS is not considered a standard staging work-up modality for resectable gastric cancer. Furthermore, our analysis was based on systematic clinical staging; therefore, our findings will provide novel insights into the value of cStage in a neoadjuvant setting.

In conclusion, both initial cStage and ypStage are independent factors for survival outcomes of gastric cancer patients treated with neoadjuvant chemotherapy. Therefore, in future studies, efforts should be made to develop optimal peri-operative treatment strategies for gastric cancer patients at substantially different risks as determined by the initial tumor burden and pathological stage in response to neoadjuvant treatment.

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