Original Article

Down-staging depth score could be a survival predictor for locally advanced gastric cancer patients after preoperative chemoradiotherapy

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Abstract

Objective: The predictive effect of preoperative chemoradiotherapy (CRT) is low and difficult in guiding individualized treatment. We examined a surrogate endpoint for long-term outcomes in locally advanced gastric cancer patients after preoperative CRT.

Methods: From April 2012 to April 2019, 95 patients with locally advanced gastric cancer who received preoperative concurrent CRT and who were enrolled in three prospective studies were included. All patients were stage $T_{3/4}N_{+}$. Local control, distant metastasis-free survival (DMFS), disease-free survival (DFS) and overall survival (OS) were evaluated. Clinicopathological factors related to long-term prognosis were analyzed using univariate and multivariate analyses. The down-staging depth score (DDS), which is a novel method of evaluating CRT response, was used to predict long-term outcomes.

Results: The median follow-up period for survivors was 30 months. The area under the curve (AUC) of the receiver operating characteristic (ROC) curve predicted by the DDS was 0.728, which was better than the pathological complete response (pCR), histological response and ypN0. Decision curve analysis further affirmed that DDS had the largest net benefit. The DDS cut-off value was 4. pCR and ypN0 were associated with OS (P=0.026 and 0.049). Surgery and DDS are correlated with DMFS, DFS and OS (surgery: P=0.001, <0.001 and <0.001, respectively; and DDS: P=0.009, 0.013 and 0.032, respectively). Multivariate analysis showed that DDS was an independent prognostic factor of DFS (P=0.021).

Conclusions: DDS is a simple, short-term indicator that was a better surrogate endpoint than pCR, histological response and ypN0 for DFS.

Keywords: Gastric cancer; preoperative chemoradiotherapy; prediction; long-term outcomes

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Introduction

A total of 6,791,000 and 498,000 new cases and deaths, respectively, from gastric cancer occur annually in China, which makes gastric cancer the second leading disease after lung cancer, and the proportion of stage II/III gastric cancer is as high as 70.8% (1,2). Several studies showed the important role of perioperative radiotherapy in locally advanced gastric cancer, but preoperative treatment is more important (3-9).

Pathological complete response (pCR) and ypTNM staging are associated with prognosis. However, these indicators are single assessment methods after neoadjuvant therapy, which do not consider the pretreatment staging. Therefore, these indicators may have some limitations in predicting prognosis comprehensively and accurately. Furthermore, the current evaluation system of response effect is insufficient to evaluate long-term outcomes and guide individualized treatment (10). Down-staging depth score (DDS) has been evaluated in rectal cancer in our previous study. We found that it could be a predictor of survival in patients treated with new adjuvant treatment (11). Here, we conducted this study to further examine the role of DDS as the endpoint for long-term outcomes in locally advanced gastric cancer patients after preoperative chemoradiotherapy (CRT).

Materials and methods

Patients and eligibility

From April 2012 to April 2019, patients with locally advanced gastric cancer who received preoperative concurrent CRT and enrolled in our three prospective studies (ClinicalTrial.gov NCT01291407, NCT03427684 and NCT04062058) were included. The following inclusion criteria were as follows: 1) clinical stage $T_{3-4}N_{+}M_{0}$ gastric cancer or Siewert II/III esophagogastric junction carcinoma; 2) pathologically confirmed adenocarcinoma; 3) 18–75 years old; 4) male or female; 5) Karnofsky score ≥70; 6) white blood cell count $\geq 4\times10^{9}$/L; 7) platelet count $\geq 100\times10^{9}$/L; 8) serum creatinine ≤1× the upper limit of normal; 9) total bilirubin ≤1× the upper limit of normal; 10) alanine aminotransferase and aspartate aminotransferase ≤2.5× the upper limit of normal; and 11) alkaline phosphatase ≤5× the upper limit of normal. The study protocol was approved by the Independent Ethics Committee of the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences (NCC2018S-112). All patients signed informed consent forms.

Treatment regimens

All patients were first treated with radiotherapy concurrent with oral S-1 at 80 mg/m^2/d on radiotherapy days. Due to protocol requirements, some patients received neoadjuvant chemotherapy with oxaliplatin and S-1 (SOX) three weeks after radiation. Oxaliplatin was given at a dose of 130 mg/m^2 intravenously on d 1, and S-1 [at 40–60 mg orally twice daily (BID)] was given on d 1–14. An imaging evaluation was performed 3 weeks after neoadjuvant treatment. Radical operation and surgical procedures were determined based on multidisciplinary team (MDT) discussion. Non-operable patients continued with three cycles of chemotherapy, and the chemotherapy regimen could be changed. Adjuvant chemotherapy was recommended after surgery.

Radiotherapy

The patients fasted for more than 4 h before positioning, and a computer tomography (CT) scan was performed after body film fixation. Using gastroscopy, magnetic resonance imaging (MRI) and CT, we determined gross tumor volume (GTV) range of primary tumors and lymph nodes (LNs). Clinical target volume (CTV) included GTV with 2.5 cm expanded in the mucosal direction and GTV of LNs (GTVnd). According to the location of the primary tumor, CTV included elective LN regions (12). Perigastric LN regions without GTVnd were excluded from CTV. Planning target volume (PTV) was based on radial expansions of 7 mm, proximal expansions of 10 mm and distal expansions of 10 mm from CTV. Intensity-modulated radiotherapy (IMRT) or volumetric-modulated arc radiotherapy (VMAT) was used.

Evaluation and endpoints

Preoperative TNM stage was evaluated using thoracic, abdominal and pelvic CT, gastroscopy, endoscopic ultrasonography and gastric MRI. Positron emission computed tomography (PET-CT) scans and diagnostic laparoscopy were not mandatory. Surgical resection specimens were subjected to an overall evaluation of primary lesions and LNs.

Follow-up occurred at 3-month intervals for 2 years,

then at 6-month intervals until 5 years. Diagnostic evaluations were performed using CT of chest and abdomen and MRI or gastroscopy only if necessary. The primary endpoint was disease-free survival (DFS), which was defined as locoregional recurrence (LRR), distant metastasis or any death during follow-up. The secondary endpoints were overall survival (OS), the cumulative incidence of local recurrence, the cumulative incidence of distant metastasis, compliance and safety.

Acute radiation toxicity was assessed and scaled according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

DDS

DDS is a response evaluation method that uses TNM staging system. Stages $T_{0-4}N_0$ were scored as 0–4 points, and stages $T_{0-4}N_+$ were scored as 5–9 points. The score before surgery was evaluated per clinical stage, and the postoperative score was based on pathological findings. Therefore, DDS = pre-score − post-score (*Table 1*).

Statistical analysis

The Kaplan-Meier method was used to calculate survival rate using IBM SPSS Statistics (Version 22.0; IBM Corp., New York, USA). The survival calculation was determined from the date of enrolment to the date of death or the last follow-up visit. The R language software survival ROC package calculated the area under the curve (AUC) of the receiver operating characteristic (ROC) curve, and the maximum Youden index represented the best positive cut-off value. To estimate the clinical usefulness of DDS, a decision curve analysis (DCA), as a comprehensive method for evaluating and comparing between DDS and other factors was conducted by computing net benefits for a range of threshold probabilities.

Table 1 DDS diagram

Stage	Score
T0N0	0
T0N+	5
T1N0	1
T1N+	6
T2N0	2
T2N+	7
T3N0	3
T3N+	8
T4N0	4
T4N+	9

DDS, down-staging depth score (pre-score – post-score).

Results

Clinical characteristics

Ninety-five patients were included in the entire group, and the follow-up rate was 100%, with 30 (8–84) months of median follow-up for survivors until October 2019. A total of 80.0% of patients were male. The median age was 61 (35–75) years old. Nearly half (47.4%) of the primary sites were located in the junction of the esophagus, and the rest were located in the proximal 1/3 segment (14.7%), middle 1/3 segment (12.6%) and distal 1/3 segment (25.3%). The proportion of clinical T3 and T4 lesions was 97.9%, and the N positive rate was 88.4%.

Most (97.9%) of the patients received 40 Gy or higher doses of preoperative radiotherapy, all concurrent with S-1, and 47.4% of the patients received neoadjuvant chemotherapy with SOX in 2–6 cycles. The median time between neoadjuvant therapy and surgery was 52 (14–174) d. Twenty-two patients (23.2%) did not undergo further surgery because of disease progression or other personal reasons, including 17 patients with distant metastasis (4 peritoneal metastasis), 3 patients who abandoned surgery due to personal reasons, and 2 patients who abandoned surgery for unknown reasons. For patients who received surgery, 62 (84.9%) patients underwent D2 operation (*Table 2*), and pCR rate was 15.1%.

DDS

According to the initial clinical stage, 81 (85.3%) patients had a pre-score of 7 or higher, which indicated that the disease stage was severe. The post-treatment score could not be evaluated in 22 patients who did not receive surgery after neoadjuvant treatment. Therefore, DDS was obtained only from 73 resected patients. Thirty-eight (52.1%) of these patients had a post-score less than 4, and 35 (47.9%) patients had a DDS≥4 (*Table 3*).

The AUC of ROC curve predicted by DDS was 0.728 (*Figure 1A*), which was better than pCR, histological response and ypN0 (AUC=0.634, 0.640 and 0.643, respectively). When DDS was ≥4, the Youden index reached the maximum value. DCA was used to compare the clinical usefulness of DDS to that of other clinical factors. DCA graphically showed that DDS was better than pCR,

Table 2 Patient characteristics (N=95)

Characteristics	n (%)
Sex	
Male	76 (80.0)
Female	19 (20.0)
Median age (year) [median (range)]	61 (35–75)
Segment	
GEJ	45 (47.4)
Proximal	14 (14.7)
Body	12 (12.6)
Distal	24 (25.3)
Pathology	
Well differentiated	2 (2.1)
Moderately differentiated	14 (14.7)
Poorly differentiated	69 (72.6)
Mucinous adenocarcinoma	2 (2.1)
Signet ring cell carcinoma	7 (7.4)
Unknown	1 (1.1)
T stage	
T2	2 (2.1)
T3	39 (41.1)
T4	54 (56.8)
N stage	
N0	11 (11.6)
N+	84 (88.4)
Radiotherapy (Gy)	
<40	2 (2.1)
≥40	93 (97.9)
Duration between neoadjuvant therapy and operation (d) [median (range)]	52 (14–174)
Surgical procedure	
D1+	11 (11.6)
D2	62 (65.3)
No operation	22 (23.1)
Cycles of neoadjuvant chemotherapy	
0	50 (52.6)
2	10 (10.5)
3	6 (6.3)
4	23 (24.2)
6	6 (6.3)
pCR	11 (11.6)
Histological response	
Mild	3 (3.2)
Moderate	27 (28.4)
Severe	33 (34.7)
Unknown	10 (10.5)
Not available	22 (23.2)
pT stage	
T0	14 (14.7)
T1	8 (8.4)
T2	15 (15.8)
T3	20 (21.1)
T4	16 (16.8)
Not available	22 (23.2)
pN stage	
N0	46 (48.4)
N1	17 (17.9)
N2	3 (3.1)
N3	7 (7.4)
Not available	22 (23.2)
Adjuvant chemotherapy	
0	28 (29.5)
1–2	8 (8.4)
3–4	6 (6.3)
5–6	7 (7.4)
>6	6 (6.3)
Unknown	40 (42.1)
Interval between neoadjuvant treatment and surgery (d)	
≤55	49 (51.6)
>55	24 (25.2)
Not available	22 (23.2)

GEJ, gastroesophageal junction; pCR, pathological complete response.

histological response and ypN0 in predicting 3-year DFS (*Figure 1B*) according to a continuum of potential thresholds.

Long-term outcomes

The 3-year local recurrence-free survival (LRFS) rate was 90.2%. The 3-year distant metastasis-free survival (DMFS) rate was 64.0%. The 3-year DFS and OS rates were 60.7% and 62.3%, respectively (*Figure 2*). Univariate analysis showed that sex, tumor location, T stage, N stage, ypT stage, histological response and perioperative chemotherapy were not related to LRFS, DMFS, DFS or OS (P>0.05). pCR and ypN0 were associated with OS

Table 3 DDS score of 73 patients who underwent an operation [n (%)]

Pre-DDS	Post-DDS									
	0	1	2	3	4	5	6	7	8	Total
3	2 (2.1)	1 (1.0)	1 (1.0)	2 (2.1)	–	–	–	–	–	6 (6.3)
4	1 (1.0)	–	1 (1.0)	–	1 (1.0)	–	–	–	1 (1.0)	4 (4.2)
6	1 (1.0)	–	–	–	2 (2.1)	–	–	–	–	3 (3.1)
7	4 (4.2)	3 (3.1)	2 (2.1)	5 (5.3)	3 (3.1)	3 (3.1)	2 (2.1)	3 (3.1)	4 (4.2)	29 (30.5)
8	7 (7.4)	1 (1.0)	5 (5.3)	4 (4.2)	1 (1.0)	2 (2.1)	2 (2.1)	6 (6.3)	3 (3.1)	31 (32.6)
Total	15 (15.8)	5 (5.3)	9 (9.5)	11 (11.6)	7 (7.4)	5 (5.3)	4 (4.2)	9 (9.5)	8 (8.4)	73 (76.8)

DDS, down-staging depth score.

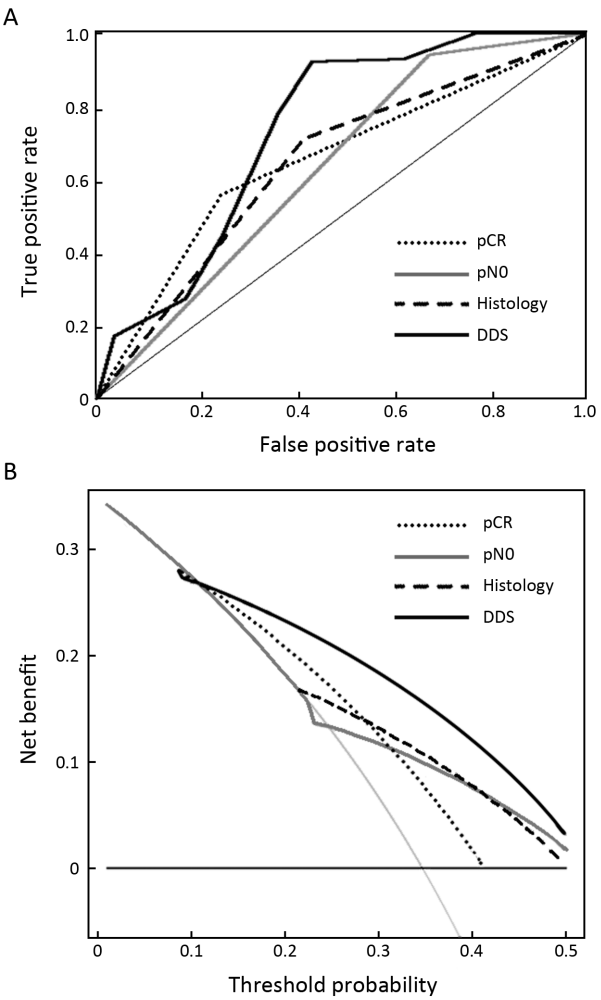

Figure 1 ROC curve for DDS to predict DFS. ROC, receiver operating characteristic; DDS, down-staging depth score; DFS, disease-free survival; pCR, pathological complete response.

(P=0.026 and 0.049, respectively). Surgery and DDS were correlated with DMFS, DFS and OS (surgery: P<0.001, =0.001, and <0.001, respectively; and DDS: P=0.032, 0.013, and 0.009, respectively) (*Table 4*, *Figure 3*). Multivariate analysis showed that DDS was an independent prognostic factor of DFS (P=0.021).

Discussion

The optimal treatment for locally advanced gastric cancer is surgery-based comprehensive treatment, which includes radiotherapy and chemotherapy. The value of concurrent CRT in preoperative treatment was confirmed in an increasing number of studies. The 3-year DFS of all enrolled patients after neoadjuvant therapy was good. pCR is a good prognostic indicator, but its predictive ability is not ideal. The AUC of 3-year DFS was less than DDS, which is a novel prognosis indicator that was published in our study. To the best of our knowledge, the present study is the first study to examine a more effective and simple surrogate endpoint to predict long-term prognosis compared with pCR.

Preoperative radiotherapy is a promising treatment for locally advanced gastric cancer. The phase 3 randomized controlled study from National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College compared the prognosis of preoperative radiotherapy with surgery alone. The preoperative radiotherapy group received a 40 Gy dose of radiotherapy prior to surgery. The 5-year and 10-year OS rates in the preoperative radiotherapy group were 30.1% and 19.75%, respectively, which were significantly better than the surgery alone group (20.3% and 13.3%, respectively; P=0.009) (8). The CROSS study reached a similar conclusion (5). These two prospective phase III studies showed that preoperative radiotherapy or concurrent CRT significantly improved long-term outcomes compared to surgery alone. Recent investigators examined the value of total neoadjuvant CRT in the treatment of locally advanced gastric cancer. Although Stahl's study closed earlier than expected due to a slow

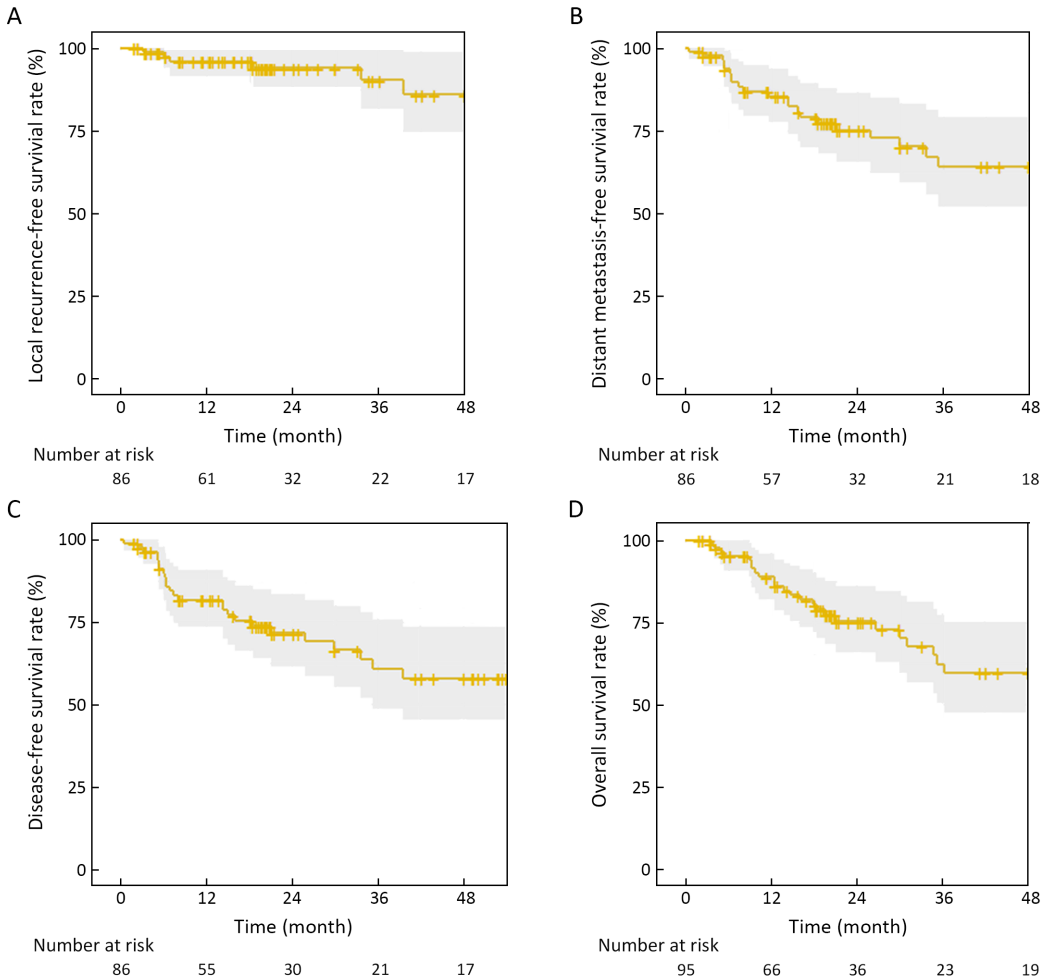

Figure 2 Kaplan-Meier plots for (A) LRFS; (B) DMFS; (C) DFS; and (D) OS. LRFS, local recurrence-free survival; DMFS, distant metastasis-free survival; DFS, disease-free survival; OS, overall survival.

recruiting speed, total neoadjuvant CRT significantly improved the pCR rate (15.6% *vs.* 2%) and the pathologic N0 rate (64.4% *vs.* 37.7%) compared to chemotherapy alone, which accordingly improved the 5-year OS rate (39.5% *vs.* 24.4%, P=0.055) (13). Our previous study examined the prognosis of preoperative radiotherapy compared to preoperative chemotherapy. Seventy-five patients were enrolled in that study. The pCR rate of preoperative CRT group was 14.1%, which was better than the neoadjuvant chemotherapy group (11.1%). The 2-year DFS and LRFS rates were better in the CRT group than in the neoadjuvant chemotherapy group (87.1% and 100% *vs.* 63.9% and 79.3%, P=0.005 and 0.014) (14). The present study examined the therapeutic modalities of concurrent CRT and perioperative chemotherapy plus radical surgery. The pCR rate was 15.1% in patients who underwent surgery. The 3-year DFS and OS rates were 60.7% and 62.3%, respectively.

However, there is still a lack of accurate early prognosis indicators to guide the treatment modality and intensity after neoadjuvant treatment. The clinicopathological factors that predict prognosis were discussed in several studies, and histological response and ypTNM stage after neoadjuvant therapy are generally considered effective predictors (15-23). Yukinori's study, which included 100 patients in the JCOG0210 and JCOG0405 studies, indicated that the histological response was the best surrogate endpoint for OS in these neoadjuvant trials of gastric cancer compared to the Response Evaluation Criteria in Solid Tumors (RECIST) standard and the Japanese Classification of Gastric Cancer (JCGC) standard (24). Stahl *et al.* found that patients who achieved pCR or

Table 4 Univariant analysis of long-term prognosis of gastric cancer patients after preoperative concurrent radiotherapy and chemotherapy

Factors	n	3-year OS (%)	P	3-year DFS (%)	P	3-year DMFS (%)	P	3-year LC (%)	P
Sex			0.890		0.147		0.036		0.891
Male	76	64.1		67.9		72.1		92.6	
Female	19	56.1		36.6		36.6		80.0	
Segment			0.939		0.465		0.583		0.765
GEJ	45	71.8		63.9		65.8		89.2	
Proximal	14	64.0		36.3		40.1		90.9	
Body	12	70.7		77.8		77.8		100	
Distal	24	53.6		58.8		64.2		86.9	
T stage			0.485		0.339		0.433		0.466
T2	2	100		100		100		100	
T3	39	68.7		71.8		75.8		96.0	
T4	54	55.9		51.9		54.9		86.0	
N stage			0.072		0.183		0.282		0.369
N0	11	100		87.5		87.5		100	
N+	84	58.8		57.9		61.7		89.0	
Operation			<0.001		0.001		<0.001		0.375
Yes	73	71.4		67.4		71.6		89.1	
No	22	29.6		19.3		17.9		100	
Neoadjuvant chemotherapy			0.261		0.324		0.135		0.683
Yes	50	40.4		45.1		48.2		92.4	
No	45	72.9		74.8		74.9		89.4	
Interval between neoadjuvant treatment and surgery (d)			0.196		0.884		0.651		0.445
≤55	49	69.2		69.4		78.3		86.3	
>55	24	74.8		63.9		63.9		91.7	
pCR			0.026		0.057		0.141		0.146
Yes	11	100		85.7		85.7		100	
No	84	64.0		61.5		66.6		85.6	
ypT			0.148		0.375		0.510		0.416
ypT0	14	100		83.3		83.3		100	
ypT1	8	100		83.3		83.3		100	
ypT2	15	65.5		58.4		58.4		85.7	
ypT3	20	57.1		65.5		76.9		85.1	
ypT4	16	58.6		51.2		613		90.0	
ypN0			0.049		0.051		0.240		0.240
Yes	46	89.4		79.1		79.1		92.3	
No	27	51.5		52.2		64.4		77.2	
Histological response			0.099		0.071		0.124		0.033
Mild	3	66.7		75.0		100		75.0	
Moderate	27	58.0		54.1		57.7		82.2	
Severe	33	85.1		83.1		86.5		96.9	
Adjuvant chemotherapy			0.923		0.797		0.612		0.631
Yes	27	67.5		66.6		73.2		86.2	
No	28	69.2		62.3		65.1		89.9	
DDS			0.009		0.013		0.032		0.367
<4	38	54.8		52.2		60.2		85.0	
≥4	35	93.6		82.1		82.1		90.9	

GEJ, gastroesophageal junction; pCR, pathological complete response; DDS, down-staging depth score; OS, overall survival; DFS, disease-free survival; DMFS, distant metastasis-free survival; LC, local control.

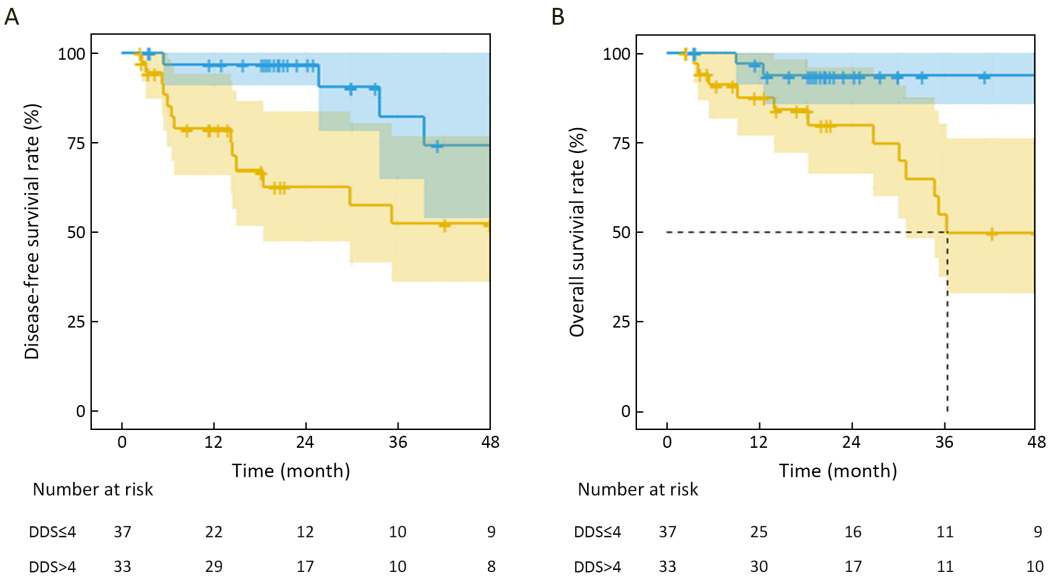

Figure 3 Kaplan-Meier plots for (A) DFS (P=0.013) and (B) OS (P=0.009) according to DDS group. DFS, disease-free survival; OS, overall survival; DDS, down-staging depth score.

pathological N0 stage had better 3-year survival rates (6). However, conclusions of studies are not consistent. Our study did not obtain similar results using these indicators. The prediction of treatment response should consider the dynamic change in primary tumors (25). For example, the prognosis of patients with ypN0 is different between clinical stage N0 and N+. The long-term outcomes of pCR patients with cT3N0 may not be better than ypT1N0 patients with cT4N3. It may not be comprehensive and accurate to evaluate prognosis using only the tumor state before or after treatment alone. Thomas used three indexes, preoperative clinical T stage, postoperative pathological T stage and N stage of rectal cancer, for the neoadjuvant rectal (NAR) score system to analyze patients in the NSABP R-04 trial (26) and concluded that NAR score, rather than pCR and tumor regression grade (TRG), offered an opportunity to incorporate a novel surrogate endpoint into clinical trials of early-phase rectal cancer. DDS is a new evaluation method that obtains the depth index of down-staging by considering four factors: the T and N stages before and after surgery. Our previous studies established predictive models and showed the prognostic value of DDS in rectal cancer, which was better than pCR (11). The present study applied DDS to the neoadjuvant treatment of gastric cancer patients and obtained similar results. A DDS of 4 was used as a cut-off value to predict 3-year DFS, and AUC reached 0.728, which was better than the histological response and ypN0.

DDS score may further guide individualized treatment. Investigations of neoadjuvant studies of gastrointestinal cancer examined the necessity and indications of adjuvant chemotherapy. However, no definite results were concluded. In our further analysis, adjuvant chemotherapy was used as a stratified factor for survival analysis. The results showed that DFS of DDS-favored patients with adjuvant chemotherapy were 100%, which was better than DDS-favored patients without chemotherapy (74.1%), DDS-unfavored patients with chemotherapy (50.4%) and the DDS-unfavored patients without chemotherapy (57.6%) (P=0.025). This result suggests that adjuvant chemotherapy improves the long-term prognosis of patients in DDS-favored group. However, the value of adjuvant chemotherapy is uncertain in the insensitive patients. Therefore, a higher DDS likely indicates better sensitivity to treatment and a better long-term prognosis. DDS may be used as an indicator to guide treatment. However, more samples are needed to support this conclusion.

Although this study was a pilot study on a novel prognostic indicator of gastric cancer, there were also some limitations that may influence the results. First, clinical staging without diagnostic laparoscopy may not be accurate and could affect treatment decisions and lead to prognostic bias. Second, there are many clinicopathological factors that may be related to prognosis that were not fully included in this study. Third, although the treatment

modality of all patients was the same, the perioperative chemotherapy intensity was inconsistent, which may have affected the long-term prognosis. Finally, the case data in the present study were obtained from a single center, and the number of patients may be insufficient. The results should be verified in a larger sample size.

Conclusions

Preoperative CRT was effective for locally advanced gastric cancer, and the long-term outcome was good. DDS is a simple, short-term indicator and is a better surrogate endpoint than pCR, histological response and ypN0 for 3-year DFS in gastric cancer patients who received preoperative CRT, and it may guide the consequential treatment.

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Footnote

Conflicts of Interest: The authors have no conflicts of interests to declare.

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