Downstaging depth score as a better surrogate endpoint than pCR, histological response and ypN0 for long-term outcomes in locally advanced gastric cancer patients after preoperative chemo-radiotherapy

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Research

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Abstract

Background: The prediction effect of preoperative chemo-radiotherapy(CRT) is not high and difficult to guide individualized treatment. We explored 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 enrolled in 4 prospective studies with locally advanced gastric cancer who received preoperative concurrent radio-chemotherapy were included. All patients were stage T3/4, N+. Local control (LC), distant metastasis-free survival (DMFS), disease-free survival (DFS) and overall survival (OS) were evaluated. The clinicopathological factors related to the long-term prognosis were analysed by uni- and multivariant analyses. The downstaging depth score (DDS), a novel method of evaluating the 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 that of pathological complete response (pCR), histological response and ypN0 (AUC= 0.634, 0.640 and 0.643, respectively). The DDS cut-off value was 4. pCR and ypN0 were associated with OS (p = 0.026, 0.049). Surgery and the DDS were correlated with DMFS, DFS and OS (p = 0.001, 0.000, and 0.000 and 0.009, 0.013, and 0.032, respectively). The multivariate analysis showed that the DDS was an independent prognostic factor of DFS (p = 0.021).

Conclusion: The DDS, a simple, short-term indicator, seems to be a better surrogate endpoint than pCR, histological response and ypN0 for DFS.

Background

In China, 6.791 million and 498 thousand new cases of and deaths from gastric cancer occur per year, respectively, leading to the second after lung cancer, meanwhile, the proportion of stage II/III gastric cancer is as high as 70.8%(1, 2). Several studies have shown the important role of peri-operative radiotherapy in locally advanced gastric cancer, but preoperative treatment is more important(3–9).

However, according to the published literature, the ability to predict the prognosis of gastric cancer patients who receive preoperative chemo-radiotherapy is insufficient, and the power of the prediction effect is not high; therefore, it is difficult to guide individualized treatment(10). The purpose of this study was to explore a surrogate endpoint for long-term outcomes in locally advanced gastric cancer patients after preoperative chemo-radiotherapy.

Methods

Patients and eligibility

From April 2012 to April 2019, patients enrolled in our three prospective studies (ClinicalTrial.gov NCT01291407, NCT03427684 and NCT04062058) with locally advanced gastric cancer who received preoperative concurrent radio-chemotherapy were included. The inclusion criteria were as follows: clinical stage T3–4 N + M0 gastric cancer or Siewert II/III oesophagogastric junction carcinoma; pathologically confirmed adenocarcinoma; 18–75 years old, male or female; Karnofsky score ≥ 70; white blood cell count ≥ 4×10^9/L; platelet count ≥ 100×10^9/L; serum creatinine ≤ 1 × upper limit of normal; total bilirubin ≤ 1 × upper limit of normal; alanine aminotransferase and aspartate aminotransferase ≤ 2.5 × upper limit of normal; and alkaline phosphatase ≤ 5 × upper limit of normal. 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/day on radiotherapy days. Due to requirement of protocols, 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 (iv) on day 1, and S-1 (at 40–60 mg orally BID) was given on days 1–14. An imaging evaluation was performed 3 weeks after neoadjuvant treatment. The radical operation and surgical procedures were determined based on multidisciplinary team (MDT) discussion. Non-operable patients continued with 3 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 CT scan was performed after body film fixation. Using gastroscopy, MRI and CT, we determined the gross tumour volume (GTV) range of primary tumours and lymph nodes (LNs). The clinical target volume (CTV) included the GTV with 2.5 cm expanded in the mucosal direction and the GTV of LNs (GTVnd). According to the location of the primary tumour, the CTV included elective LN regions(11). Peri-gastric LN regions without the GTVnd were excluded from the CTV. The planning target volume (PTV) was based on 7 mm radial and 10 mm proximal and distal expansions from the CTV. Intensity-modulated radiotherapy (IMRT) or volumetric-modulated arc radiotherapy (VMAT) was applied.

Evaluation and endpoints

The preoperative TNM stage was evaluated via thoracic, abdominal and pelvic CT, gastroscopy, endoscopic ultrasonography and gastric MRI. PET 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 and then at 6-month intervals until 5 years. Diagnostic evaluations were performed using CT of the chest and abdomen and MRI or gastroscopy only if necessary. The primary endpoint was disease-free survival (DFS), defined as locoregional recurrence

(LRR), distant metastasis or any death during the 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.

Downstaging depth score (DDS)

The DDS is a response evaluation method that uses the TNM staging system. Stages T0–4N0 were scored as 0 to 4 points, while stages T0–4N + were scored as 5 to 9 points. The score before surgery was evaluated per the clinical stage, and the postoperative score was based on pathological findings. Hence, the DDS = pre-score – post-score (Table 1).

Statistical analysis

The Kaplan-Meier method was used to calculate the survival rate using SPSS 22.0 software (IBM, New Orchard Road Armonk, New York 10504). 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 SurvivalROC package calculates the area under the curve (AUC) of the receiver operating characteristic (ROC) curve, and the maximum Youden index represents the best positive cut-off value.

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 period for survivors till October 2019. In total, 80.0% of patients were male. The median age was 61 (35–75) years. Nearly a half (47.4%) of primary site was located in the junction of the oesophagus, and the rests 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 N positive was 88.4%.

Majority (97.9%) of patients received 40 Gy or higher doses of preoperative radiotherapy, all concurrent with S-1, and 47.4% of patients received neoadjuvant chemotherapy with SOX in 2–6 cycles. The median time between neoadjuvant therapy and the operation was 52 (14–174) days. Twenty-two patients (23.1%) did not undergo a further operation because of disease progression or other personal reasons, in which 17 had distant metastasis, including 4 peritoneal metastasis, 3 abandoned the operation due to personal reasons, and 2 abandoned the operation due to unknown reasons. Among the patients who received surgery, sixty-two patients (84.9%) underwent the D2 operation (Table 2), and pathologic complete response (pCR) rate was 15.1%.

DDS

According to the initial clinical stage, as all, 81 patients (85.3%) 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 twenty-two patients who did not receive surgery after neoadjuvant treatment, so according to this situation, DDS was obtain from the rest of 73 resected patients. Among these patients, 40 (54.8%) had a post-score less than 4, 34 patients (45.6%) had a DDS ≥ 4 (Table 3).

The AUC of the ROC curve predicted by the DDS was 0.728 (Fig. 1), which was better than that of pCR, histological response and ypN0 (AUC = 0.634, 0.640 and 0.643, respectively). When the DDS was ≥ 4, the Youden index reached the maximum value.

Long-term outcomes

The 3-year local recurrence-free survival 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 (Fig. 2).

The univariate analysis showed that sex, tumour location, T stage, N stage, ypT stage, histological response and perioperative chemotherapy were not related to local recurrence-free survival (LRFS), DMFS, DFS or OS ($p > 0.05$). pCR and ypN0 were associated with OS ($p = 0.026$, 0.049, respectively). Surgery and the DDS were correlated with DMFS, DFS and OS ($p = 0.001$, 0.000, and 0.000 and 0.032, 0.013, and 0.009, respectively) (Table 4) (Fig. 3). The multivariate analysis showed that the DDS was an independent prognostic factor of DFS ($p = 0.021$).

Discussion

The standard treatment for locally advanced gastric cancer is surgery-based comprehensive treatment, which includes radiotherapy and chemotherapy. The value of concurrent chemo-radiotherapy in preoperative treatment has been confirmed by an increasing number of studies. pCR is a good prognostic indicator, but the predictive ability is not ideal. AUC of 3-year DFS was only 0.634, less than that of DDS which was 0.728. To the best of our knowledge, this was the first study to explore a more effective and simple surrogate endpoint to predict long-term prognosis compared with pCR.

The phase 3 randomized controlled study from our centre compared the prognosis of preoperative radiotherapy with that of 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 those in the surgery alone group (20.3% and 13.3%, respectively; $p = 0.009$)(8). In the CROSS study, a similar conclusion was obtained(12). These 2 prospective phase III studies have shown that either preoperative radiotherapy or concurrent chemo-radiotherapy could significantly improve long-term outcomes compared with surgery alone. In recent years, investigators even explored the value of total neoadjuvant chemo-radiotherapy in the treatment of locally advanced gastric cancer. Although Stahl's study closing earlier than expected due to

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

The neo-adjuvant treatment of gastric cancer is promising, however, there is still a lack of accurate early prognosis indicators to guide the treatment modality and intensity after neo-adjuvant treatment. The clinicopathological factors that predict prognosis have been discussed in several studies, and histological response and ypTNM stage after neoadjuvant therapy are generally considered effective predictors (15–23)..Yukinori compared the prognostic value of evaluation criteria, the Response Evaluation Criteria in Solid Tumors (RECIST) standard, the Japanese Classification of Gastric Cancer (JCGC) standard and the histological response. A total of 100 patients were included in the JCOG0210 and JCOG0405 studies. The result indicates that the histological response was the best surrogate endpoint for OS in these neoadjuvant trials of gastric cancer. Stahl et al found that patients who achieved pathological N0 stage after the operation had better 3-year OS rates than those who did not (64.2% vs. 38.8%, P < 0.001). Moreover, the DFS rate of patients with pCR was 100%(6). However, in our study, we did not obtain similar results with these indicators. The prediction of treatment response should consider the dynamic change in primary tumours(24). It may not be comprehensive and accurate to evaluate prognosis only by the tumour 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 analyse patients in the NSABP R-04 trial(25). It is concluded that the NAR score, rather than pCR and tumour regression grade (TRG), offers an opportunity to incorporate a novel surrogate endpoint into early-phase rectal cancer clinical trials. The DDS, a new evaluation method could obtain the depth index of downstaging by considering four factors: T and N stages before and after the operation. Our previous studies showed the prognostic value of the DDS in rectal cancer, which was better than that of pCR(26). In the present study, the DDS was applied to the neoadjuvant treatment of gastric cancer patients, and similar results were obtained. A DDS of 4 was used as a cut-off value to predict 3-year DFS, and the AUC reached 0.728, which was better than that of the histological response and ypN0.

On the other hand, in neo-adjuvant studies of GI cancer, investigators have been exploring the necessity and indications of adjuvant chemotherapy. However, no definite results had been concluded. In our further analysis, adjuvant chemotherapy was used as a stratified factor for survival analysis. The results showed that the DFS of the DDS favor patients with adjuvant chemotherapy was 100%, which was better than that of the DDS favor patients without chemotherapy (74.1%), the DDS un-favor patients with

chemotherapy (50.4%) and the DDS un-favor patients without chemotherapy (57.6%) (P = 0.025). This result suggests that adjuvant chemotherapy can improve the long-term prognosis of patients in DDS favor group. But in the insensitive patients, the value of adjuvant chemotherapy is uncertain. Therefore, we believe that the greater DDS is, the better the sensitivity of treatment and thus the better the long-term prognosis. And it can be used as an indicator to guide treatment. More samples are needed to support this conclusion.

There were also some limitations to this study. First, clinical staging without diagnostic laparoscopy might not be accurate and could affect decisions regarding treatment and lead to prognostic bias. Second, there are many clinicopathological factors that might be related to prognosis that were not fully included in this study. Third, although the treatment modality of all patients was the same, the peri-operative chemotherapy intensity was inconsistent, which might have affected the long-term prognosis. Finally, the case data in the present study were obtained from a single centre, and the number of patients might be insufficient. The results should be verified by enlarging the sample size.

Conclusions

In conclusion, preoperative chemo-radiotherapy is effective for locally advanced gastric cancer, and the long-term outcome is good. The DDS, a simple, short-term indicator, seems to be a better surrogate endpoint than pCR, histological response and ypN0 for DFS in gastric cancer patients who receive preoperative radio-chemotherapy, and may guide the consequential treatment.

Abbreviations

CRT
chemo-radiotherapy
LC
Local control
DMFS
distant metastasis-free survival
DFS
disease-free survival
OS
overall survival
DDS
downstaging depth score
AUC
area under the curve
pCR
pathological complete response
MDT

multidisciplinary team

ROC

receiver operating characteristic

GTV

gross tumour volume

CTV

clinical target volume

PTV

planning target volume

IMRT

intensity-modulated radiotherapy

VMAT

volumetric-modulated arc radiotherapy

CTCAE

common terminology criteria for adverse events

NAR

neoadjuvant rectal

TRG

tumour regression grade

Declarations

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Availability of data and materials

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

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Contributions

JJ and NL conceived the study; NL, XW, YT, DZ, YC, LY, LJ and JJ collected data; NL analyzed and interpreted data, wrote manuscript and provided statistical analyses; JS, WL, HR, YT, BC, NL, HJ, SQ, SW YL, YS and YL provided critical review and revision of manuscript; All authors reviewed the results and approved the final version of the manuscript.

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Ethics declarations

Ethics approval and consent to participate

The study protocol was approved by the Independent Ethics Committee of National Cancer Center/ /Cancer Hospital, Chinese Academy of Medical Sciences (NCC2018S-112).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1. Downstaging depth score (DDS) diagram

	N0	N+
T0	0	5
T1	1	6
T2	2	7
T3	3	8
T4	4	9
DDS = pre-score – post-score		

Table 2. Patient characteristics

	n. (%)
Sex	
Male	76 (80.0)
Female	19 (20.0)
Median age	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 (14.8)
Poorly differentiated	69 (72.6)
Mucinous adenocarcinoma	2 (2.1)
Signet ring cell carcinoma	7 (7.4)
Unknown	1 (1.0)
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	
< 40 Gy	2 (2.1)
>=40 Gy	93 (97.9)
Duration between neoadjuvant therapy and the operation	52 (14–174) days
Surgical procedure	

	n. (%)
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 Not available	10 (10.5) 22 (23.2)
pT stage	
T0	14 (14.7)
T1	8 (8.4)
T2	15 (15.8)
T3	20 (21.1)
T4 Not available	16 (16.8) 22 (23.2)
pN stage	
N0	46 (48.4)
N1	17 (17.9)
N2	3 (3.1)
N3 Not available	7 (7.4) 22 (23.2)

	n. (%)
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)

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

Post-DDS Pre-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)

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

or	n.	3-y OS (%)	*p*	3-y DFS (%)	*p*	3-y DMFS (%)	*p*	3-y LC (%)	*p*
			0.890		0.147		0.036		0.891
	76	64.1		67.9		72.1		92.6	
	19	56.1		36.6		36.6		80.0	
			0.939		0.465		0.583		0.765
	45	71.8		63.9		65.8		89.2	
al	14	64.0		36.3		40.1		90.9	
	12	70.7		77.8		77.8		100.0	
	24	53.6		58.8		64.2		86.9	
			0.485		0.339		0.433		0.466
	2	100.0		100.0		100.0		100.0	
	39	68.7		71.8		75.8		96.0	
	54	55.9		51.9		54.9		86.0	
			0.072		0.183		0.282		0.369
	11	100.0		87.5		87.5		100.0	
	84	58.8		57.9		61.7		89.0	
n			0.000		0.001		0.000		0.375
	73	71.4		67.4		71.6		89.1	
	22	29.6		19.3		17.9		100.0	
vant erapy			0.261		0.324		0.135		0.683
	50	40.4		45.1		48.2		92.4	
	45	72.9		74.8		74.9		89.4	
			0.026		0.057		0.141		0.146
	11	100.0		85.7		85.7		100.0	
	84	64.0		61.5		66.6		85.6	
			0.148		0.375		0.510		0.416
	14	100.0		83.3		83.3		100.0	
	8	100.0		83.3		83.3		100.0	
	15	65.5		58.4		58.4		85.7	
	20	57.1		65.5		76.9		85.1	
	16	58.6		51.2		61.3		90.0	
			0.049		0.051		0.240		0.109
	46	89.4		79.1		79.1		92.3	
	27	51.5		52.2		64.4		77.2	
ical			0.099		0.071		0.124		0.033
	3	66.7		75.0		100.0		75.0	
ate	27	58.0		54.1		57.7		82.2	
	33	85.1		83.1		86.5		96.9	
			0.923		0.797		0.612		0.631
erapy									
	27	67.5		66.6		73.2		86.2	
	28	69.2		62.3		65.1		89.9	
			0.009		0.013		0.032		0.367
	38	54.8		52.2		60.2		85.0	
	35	93.6		82.1		82.1		90.9	

Figures

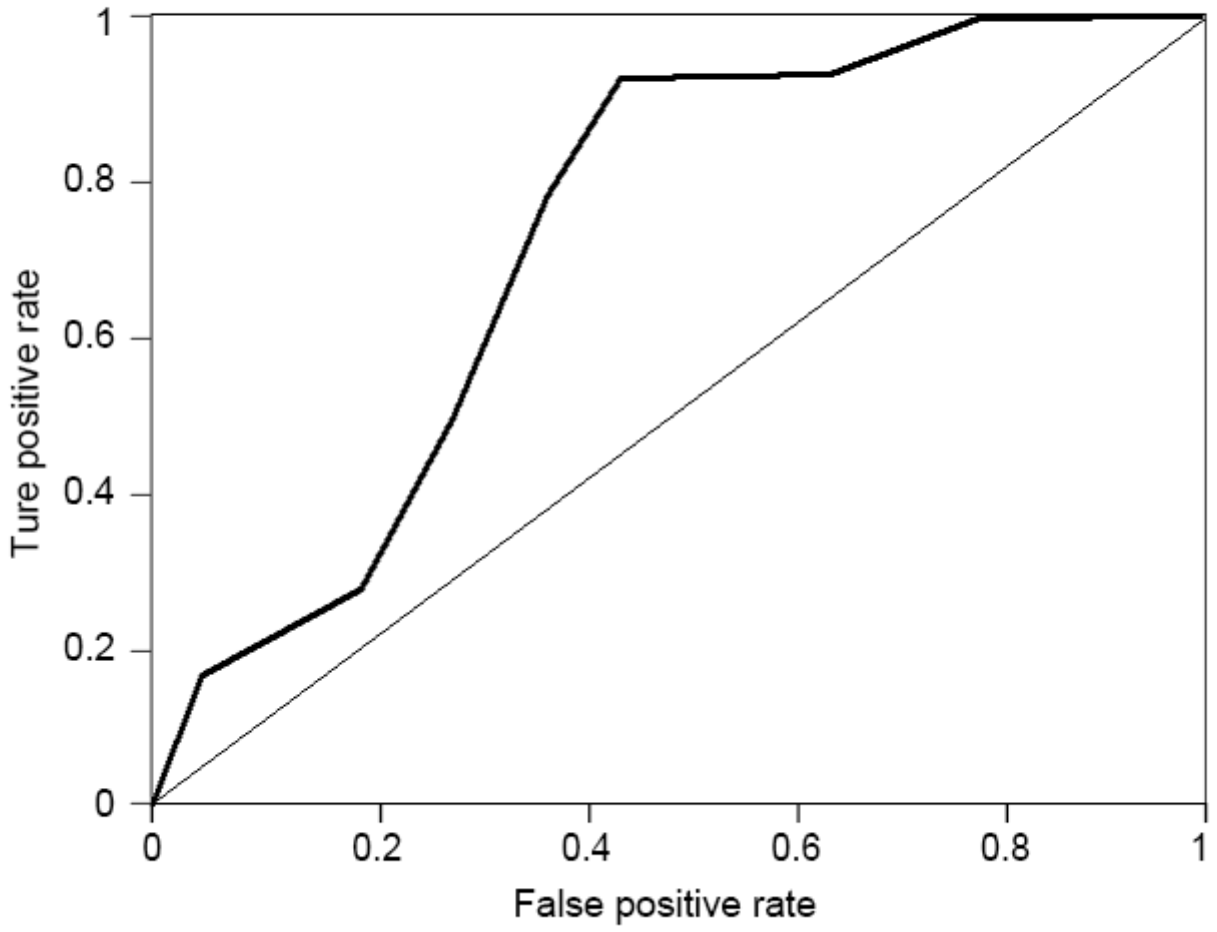

Figure 1

ROC curve for the DDS to predict DFS

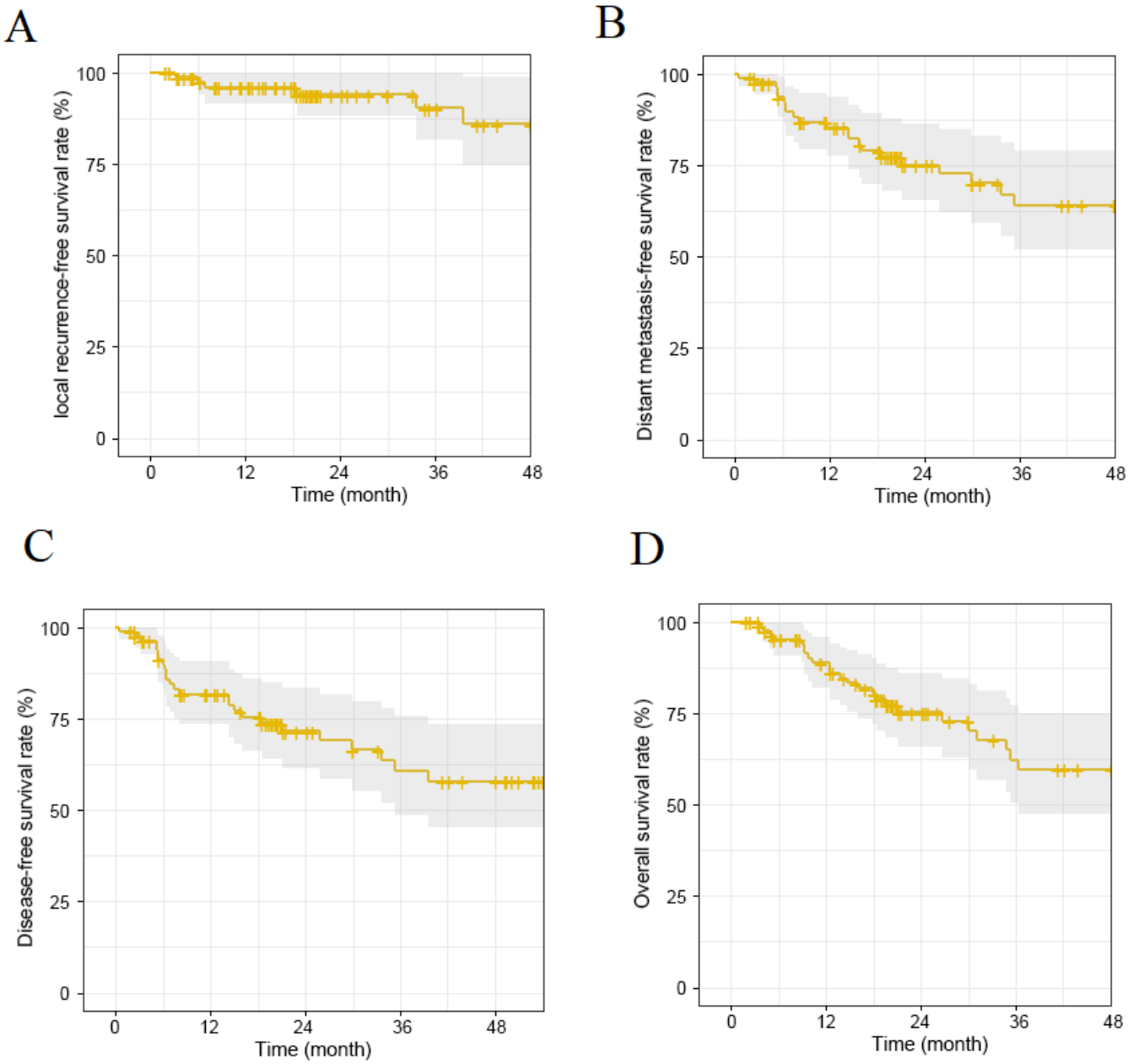

Figure 2

Kaplan-Meier plots for (a) local recurrence-free survival (LRFS), (b) distant metastasis-free survival (DMFS), (c) disease-free survival (DFS) and (d) overall survival (OS)

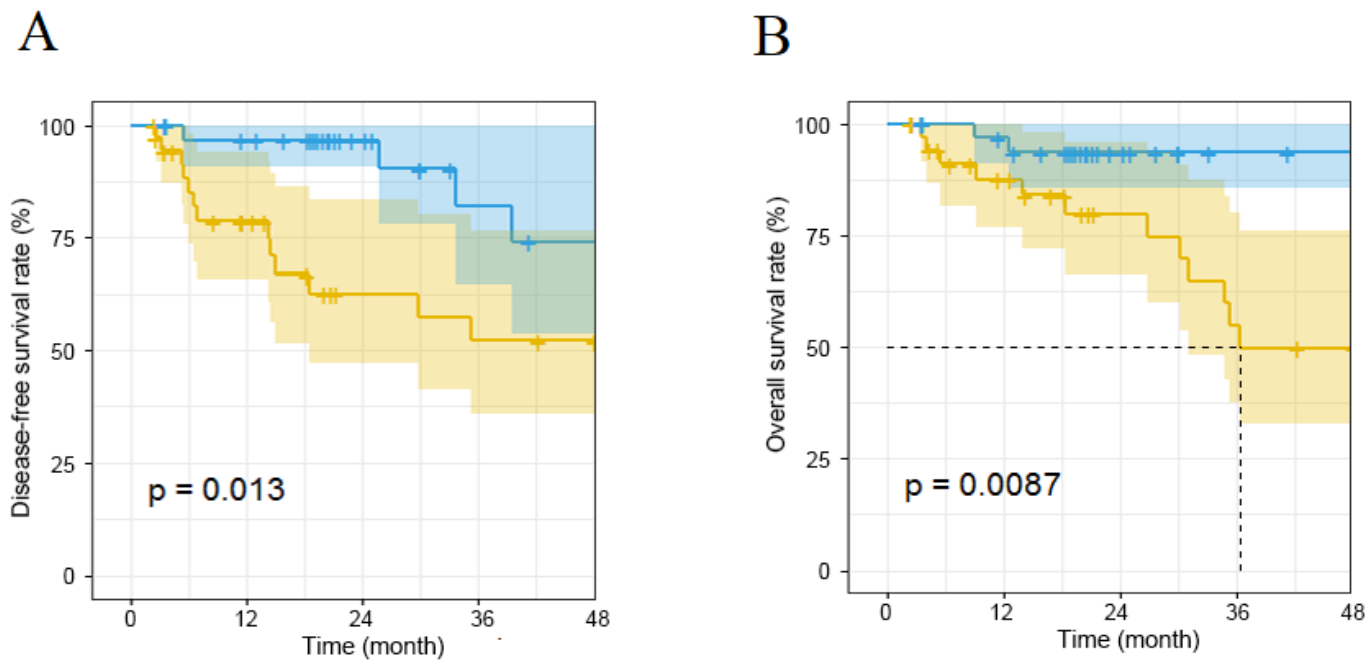

Figure 3

Kaplan-Meier plots for (a) disease-free survival (DFS) and (b) overall survival (OS) according to the DDS group