The Research and Analysis of Bring Perigastric Tumor Deposits into The Staging of Primary Gastric Cancer

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Abstract

Background: The current significance of perigastric tumor deposits (TDs) in gastric cancer (GC) for indicating prognosis remains unclear. The aim of this study was to assess the prognostic value of perigastric TDs and a new TNM staging involving TDs for GC.

Methods: The pathological data of 6672 patients with GC who underwent gastrectomy or operation of gastric cancer with other diseases between January 1, 2012 and December 31, 2017 at Chinese PLA General Hospital were analyzed retrospectively. The patients were divided into tumor deposits positive (TD^+) group and tumor deposits negative (TD^-) group. The differences between TD^+ and TD^- were analyzed by binary Logistic regression model. To draw survival curves, we used Kaplan-Meier methods. Multivariate Cox regression model and Log-rank test was used to analyze the data.

Results: Perigastric TDs were found to be positive in 339 (5.09%) of the 6672 patients with GC of which 237 were males (69.91%) and 102 females (30.09%) (2.32:1). The median age was 59 years (ranging from 27 to 78 years). No significant differences were detected between the two groups. Univariate and multivariate survival analysis both indicated that GC patients with positive TDs had poorer prognosis than those with negative TDs ($p<0.05$). The 1-, 3-and 5-year overall survival rates of GC patients with TDs were 68.3%, 19.6%, and 11.2%, respectively, and were significantly poorer than those of the staged matched control group. There was statistical significance between the location of TDs and patient survival in patients with gastric cancer (p□0.05). A new TNM staging was formulated according to the TDs location. When TDs appear on the gastric body, the original T1, T2, T3 stages change to T4a, and T4a, T4b change to T4b; when TDs appear in the lesser curvature, the previous N0, N1, N2, N3 stage change to N3; when the TDs located in the greater curvature or the distant tissue, the patient should be categorized as M1. After using the new stage, the survival curve of patients with TDs was closer to that of patients without TDs in each pTNM staging.

Conclusion: 1. Tumor deposits is a bad prognostic factor in patients with primary gastric cancer. 2. The location of tumor deposits is associated with the prognosis of patients with primary gastric cancer. 3. The new stage is more suitable for patients with tumor deposits of gastric cancer.

Background

Gastric cancer (GC) remains the fifth most common cancer worldwide. More than 70% of cases of GC occur in developing countries, especially in Japan, Korea and China. GC ranks the fourth leading cause of cancer-related deaths both in men and women. It is estimated that in 2012, the mortality rate of gastric cancer in East Asia was the highest (24 male deaths per 100,000 people, 9.8 female deaths), and the lowest in North America (2.8 male deaths and 1.5 female deaths). [1].

The prognosis of GC patients varied with different TNM stages and excise staging of GC is critical for treatment options and indications for prognosis. The TNM (tumor, lymph node, and metastasis) gastric cancer staging system is determined by the extent of primary tumor infiltration depth (pT), number of

metastatic lymph nodes (pN), and distant metastasis (pM) [2]. In the past few years, some other predictors; for example, histological types and lymphatic vessel infiltration, lymphatic wall carcinoma, etc. have been identified as important or even independent predictors of survival [3].

Gabriel was the first clinician to discover Tumor deposits (TDs) in 1935 [4], which is initially defined as the peritumoral nodule clusters in the primary adipose tissue of GC, and no histologically evidence of residual lymph nodes remain in the nodules. It is speculated that TDs may be discontinuous spread, venous invasion and extravascular spread, or complete replacement of lymph nodes [2]. However, the prognostic significance of colon cancer and rectal cancer tumor deposition has been confirmed by several studies [2,5,6,7,8,9]. A series of following studies indicated that TDs were not only correlated with colorectal cancer, they are also positive in other gastrointestinal tumors including biliary tract, gastric cancer, and pancreatic cancer[10,11].

The 7th Edition of the American Joint Committee on Cancer (AJCC) Gastric Staging System is currently used in general. It considers all gastric metastasis nodules without residual lymph node tissue as regional lymph node metastasis [5]. However, the AJCC TNM staging system failed to distinguish between lymph node metastasis and peri-weekly TDs. The prognostic value of TDs in GC has not been extensively studied and confirmed. To date, no studies have studied the prognostic significance of gastric cancer tumor deposits (TDs) in detail [13,14,15]. In this study, we aimed to assess the prognostic value of perigastric TDs and a new TNM staging involving TDs for GC.

Methods

This study was approved by the Medical Ethics Committee of the Chinese PLA General Hospital (S2017-059-042). Patients provided their written informed consent before enrollment. Retrospective cohort study was conducted to evaluate the clinicopathologic data of 6672 gastric cancer patients who underwent surgical procedures in Chinese PLA General Hospital between January 2012 to December 2017. A tumor deposit was defined as previously reported[13, 14]. Briefly, a discrete focus of tumor which were found in the perigastric fat or in an adjacent ligament away from the leading edge of the tumor and showing no evidence of residual lymph node tissue but within the drainage area of the primary cancer were considered as TDs. The control group included patients who underwent non-gastric cancer surgeries during the same period. The postoperative adjuvant therapy was performed for patients who needed according to the Japanese Gastric Cancer Treatment Guidelines.

Tumor deposits (TDs) are defined as satellite peritumoral nodules in the peritumoral adipose tissue of a primary carcinoma without histologic evidence of residual lymph node in the nodule[24]. The locations of TD were classified into cardia of stomach, gastric body and antrum of stomach.

The 7th AJCC TNM staging system were adopted in this study. The clinical characteristics including sex, age, time of gastrectomy, differentiation type, location, T stage, the number of node metastases, N stage, and the type of operation were collected. Patients with and without TDs were compared for overall

survival rates. Survival curves of different pTNM stages were compared, including TDs positive and TDs negative. And an additional content of the seventh edition of TNM staging of gastric cancer UICC/AJCC was designed and validated. As for multivariate analysis, clinicopathological characteristics including sex, age, operation method, histological grade, TNM stage and TD, and survival data were analyzed.

Follow-up

GC patients who underwent gastrectomy must be followed-up every 6 months during the first year and every 6 or 12 months thereafter. The general follow-up included physical examination, laboratory tests, chest X-ray, abdominal and pelvic ultrasonography and computed tomography scan as previously reported. Overall survival was calculated from the date of diagnosis to last contact, date of death, or date when the survival information was collected.

Statistical analysis

All statistical analyses and graphics were performed with the IBM SPSS version 22.0 statistical package (International Business Machines Corp., New Orchard Road Armonk, New York 10,504 914–499-1900, USA) for Windows. For comparisons of clinicopathologic characteristics between the two-propensity score-matched groups, the Logistic test was used for categorical variables as appropriate. Overall survival rates were determined using the Kaplan–Meier estimator, the Log-rank test was used to identify differences between the survival curves of different patient groups. In the univariate analysis and the multivariate analysis, Cox's proportional hazard model was used to identify independent factors correlated with prognosis. The confidence interval (CI) method was used to compare differences in means between the predictive accuracy estimates for models that either included or did not include TDs. All p values were two-sided with p values < 0.05 considered statistically significant.

Result

Patients' demographics

6672 patients with GC were enrolled in this study of which 339 (5.09%) were positive with TDs from January 2012 to December 2017. For patients with positive TDs, 237 ones were male and 102 ones were female (P=0.527). For patients with negative TDs, 256 ones were male and 83 ones were female (P=0.492). The clinical characteristics of patients with TDs and without TDs were comparable.

Survival analysis

1. Kaplan–Meier curves were performed to evaluate the overall survival rates for patients with TDs and without TDs. The 1-year, 3-year, and 5-year survival rates of patients with tumor deposits were 68.3%, 19.6%, and 11.2%, respectively, and those for patients without TDs were 81.7%, 56.3%, and 26.3%, respectively.

2. Univariate analysis:

Univariate analysis was used to assess the clinicopathological variables. As shown in Table 1, the status of TD was significantly correlated with age ($P = 0.011$), Operation method ($P \leq 0.001$), histologic grading ($P = 0.003$), depth of invasion ($P \leq 0.001$), lymph node metastasis ($p \leq 0.001$), distant metastases ($P \leq 0.001$), and TDs ($P \leq 0.001$) (Table 1).

Table 1. Univariate and multivariate survival analysis of the patients after operation for gastric cancer.

Characteristic	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Sex		0.772	/	/
Male	0.97(0.80,1.18)			
Female	1.00(ref)			
Age		0.011		0.009
≥65 y	1.26(1.05,1.50)		1.27(1.06,1.53)	
65 y	1.00(ref)		1.00(ref)	
Operation method		≤ 0.001		0.076
Proximal gastrectomy	0.56(0.45,0.70)	≤ 0.001	0.76(0.60,0.97)	0.026
Distal gastrectomy	0.57(0.46,0.70)	≤ 0.001	0.84(0.67,1.05)	0.118
Total gastrectomy	1.00(ref)		1.00(ref)	
Histologic grade		0.003		0.456
Low	1.41(1.12,1.76)		1.09(0.86,1.39)	
High	1.00(ref)		1.00(ref)	
AJCC 7 TNM T category		≤ 0.001		0.034
T4b	2.28(1.58,3.28)	≤ 0.001	1.19(0.79,1.78)	0.410
T4a	1.92(1.34,2.75)	≤ 0.001	0.92(0.62,1.37)	0.679
T3	1.65(1.15,2.36)	0.006	0.85(0.58,1.27)	0.429
T2	0.93(0.59,1.48)	0.766	0.70(0.44,1.12)	0.138
T1	1.00(ref)		1.00(ref)	
AJCC 7 TNM N category		≤ 0.001		≤ 0.001
N3	3.64(2.86,4.64)	≤ 0.001	2.72(2.07,3.59)	≤ 0.001
N2	2.01(1.54,2.63)	≤ 0.001	1.66(1.24,2.22)	0.001
N1	1.43(1.06,1.94)	0.019	1.37(1.00,1.89)	0.052
N0	1.00(ref)		1.00(ref)	
AJCC 7 TNM M category		≤ 0.001		≤ 0.001
M1	3.70(2.89,4.74)		2.78(2.15,3.60)	
M0	1.00(ref)		1.00(ref)	
Tumor Deposits		≤ 0.001		≤ 0.001
Yes	2.09(1.72,2.53)		1.64(1.32,2.03)	
No	1.00(ref)			

3.Multivariate analysis:

Cox multivariate analysis was use to exclude the confounding factors. As shown by multivariate analysis, age, depth of invasion, lymph node metastasis, distant metastases, and perigastric TDs were all

independent prognostic factors for GC ($p < 0.05$) (Table 1).

4. We performed the survival curves of the TNM staging between TDs and without TDs (Fig. 2). And the differences in the Kaplan-Meier survival curve were observed between different pTNM categories (except IV) without TDs and with TDs (Fig. 3). Patients with TDs exhibited poorer survival probability than those without TDs in each stage.

5. Kaplan-Meier survival curves were plotted to evaluate the prognostic value of TDs. As shown in Fig. 4c, patients with positive TDs and N3 stage without positive TD exhibited similar survival rates.

6. The significance of TDs location in the prognosis of gastric cancer patients has not been studied. The location of TDs is not fixed in pathological reports. According to the anatomical relationship of the stomach and the principle of lymph node metastasis, the TDs were divided into 4 groups: gastric body, lesser curvature, greater curvature and distant tissue. And the prognosis survival of the 4 groups were compared (Fig 5).Then we Compared the survival curves between patients with TDs'different location and those without TDs in pT, pN, pM stage category (Fig 6).

7.So we put forward an additional content which based on the seventh edition of TNM staging of gastric cancer UICC/AJCC: when TDs appear on the gastric body, the original T1, T2, T3 stages change to T4a, and T4a, T4b change to T4b; when TDs appear in the lesser curvature, the previous N0, N1, N2, N3 stage change to N3; when the TDs located in the greater curvature, the patient should be categorized as M1; when the TDs appear in the distant tissue, the patient should be categorized as M1. We used the new TNM staging to analyze the Kaplan-Meier survival curve for patients with TDs (Fig 7).

Discussion

TDs first appeared in the UICC/AJCC Tumor Staging Guide in the fifth edition of colorectal cancer staging in 1997, followed by the appearance of TDs in the 6th and 7th editions of colorectal cancer staging. However, the definition of TDs in each stage of colorectal cancer is different. The criteria and histological features of TDs have been modified several times. In the 7th edition of UICC/AJCC colorectal cancer staging, the TDs are defined as non-contiguous with the primary tumor and there is no evidence of lymphoid tissue structure, but the TDs in the lymph node drainage area, and the TDs have been included as N1c staging becomes an independent factor affecting prognosis[16]. However, there is no evidence to suggest which version of the TDs is the most suitable for the actual survival of the patient. In gastric cancer, the TDs of the 8th edition of UICC/AJCC are classified as lymph node metastasis, the regional lymph node metastasis with no residual lymph node tissue evidence[11].

The pathophysiological causes of cancer nodules are still unclear, and most studies have shown that the appearance of TDs is associated with lymph node metastasis, neurovascular invasion, and microvascular system[5,8]. In terms of the cause of gastric TDs, there is no credible research report. We refer to the report of TDs in the field of colorectal cancer to study the classification of TDs. A study reported that they divided the invasive non-continuous tumor infiltration into four types, including

scattered infiltration, vascular infiltration, neurological infiltration, and nodular infiltration[17]. Subsequently, Goldstein et al. reported that the TDs were classified into three types: the nerve disseminated type, the vascular disseminated type, and the intravascular tumor[18]. It is also reported that when the TDs are located in the mesorectum, they should be divided into intravascular, intratympanic, perineural, and isolated TDs[19]. Some studies have found that the formation of TDs may be related to the de-interstitialization of tumor cells[13]. The changes in the secretion of snail, twist, and epithelial cadherin promote the ability of tumors to metastasize and spread through lymph nodes[20]. In summary, we found that the formation of TDs is associated with tumor invasive growth. In the three previous reports, the probability of developing TDs in gastric cancer patients was 17.8%, 23.9%, and 24%, respectively (sorted by publication time). It has been reported that the probability of TDs is related to tumor size, Borrmann classification, and to the extent of tumor infiltrating lymphatic vessels, lymphatic metastasis and expansion, and the survival of TDs and gastric cancer patients is significantly correlated[21].

In this study, we analyzed the status of TDs and the clinical physiology of patients, and found that the presence of TDs was associated with tumor infiltration (T), lymph node metastasis (N), tumor location, and neurovascular invasion, statistically significant ($P < 0.05$). The relationship between patient age (whether greater than 61 years), gender, body mass index, pTNM stage, M stage, and degree of differentiation was not statistically significant ($P < 0.05$). This indicates that the TDs are related to the invasive ability of tumor cells, and the tumor cells in the TDs often have strong migration ability, which may be migration through the lymphatic pathway or sudden infiltration of tumor cells of unknown cause.

Although the overall survival rate of patients with gastric cancer has improved significantly over the past few decades, there are still many questions to be answered about histopathology and predictive factors. Studies have shown that TDs have independent prognostic value in colorectal cancer, however, only a few studies have reported the gastric TDs. Several studies have shown that the appearance of TDs predicts a poor prognosis, which is similar to our findings. Kaplan-Meier survival curves were used to map the survival of patients with positive and negative TDs. It was found that there was a significant difference between the two, which was statistically significant. Analysis of TDs and survival using multivariate Cox regression revealed that TDs positivity was not an independent risk factor for the prognosis of gastric cancer, which may be related to the presence of TDs in patients with more late stages. Using Cox regression to analyze the survival of all patients, only lymph node metastasis (N), age (more than 61 years old) were significantly different, and the other items were not significantly different. One study found that the presence or absence of TDs was not an independent factor when using Cox regression analysis[22]. Studies have pointed out that gastric TDs are an important prognostic indicator and hope to incorporate TDs into lymph node staging. In addition, they classified TDs as metastatic lymph nodes and then re-staged patients with colorectal cancer and advanced gastric cancer using UICC/AJCC's 7th edition guidelines, and found TDs in patients with the same lymph node staging (pN). The appearance of this can lead to a worse prognosis. However, only 6 of the T1 and T2 TDs included in this study were not convincing[23]. In a recent study, the histological typing of tumors and the extent of vascular invasion

were important causes of TDs, and TDs were more common in intestinal tumors. Combined with current research, evidence for TDs in gastric cancer as an independent influencing factor is not sufficient.

We included 6,672 patients with gastric cancer surgery or gastric cancer with other pathological reports of TDs, a total of 341 cases, the TDs positive rate was 5.11%, lower than previously reported. There were 193 patients with positive deposits and 297 patients with negative deposits. Among them, 5 patients (2.59%) in stage I, 2 patients (14.51%) in stage II, 139 (72.02%) in stage III, and 21 (10.88%) in stage IV. The proportion of TDs in gastric cancer patients with a late stage is greater, suggesting that the appearance of TDs may indicate a later stage and a worse prognosis. We found that patients with the same TNM stage had a median survival of the TDs-positive group that was lower than the TDs-negative group, but there was no difference in stage IV patients. Kaplan-Meier survival curves were used to test the survival of the two groups. The prognosis of the patients with stage I TDs was worse than that of the negative group ($P<0.000$). The prognosis of the patients with stage II and III cancer deposits was lower than that of the negative group. The prognosis of the TDs positive group in the IV stage was better than that in the negative group, and the difference was not significant. At the same time, according to the location of the TDs suggested in the pathological report, the positive components of the TDs were the small curved group, the corpuscular group, the large curved group and the distal group. The median survival time was 37.0 months in the small curved group, the overall median survival time was 36.0 months in the corpus group, the median survival time was 15.2 months in the large curved side, and the median overall survival time was 9.9 months in the distal patient. The difference was significant and statistically significant.

It was found that when the TDs appeared on the large curved side of the stomach or the omental fat connective tissue, the patient's survival time was significantly reduced. When TDs appear on the small curved side of the stomach or on the stomach wall, there is no significant difference in survival between the two. Therefore, we believe that when the TDs appear on the small curved side of the stomach or on the stomach wall, it is limited by the anatomical positional relationship of the small omental sac and the lymphatic drainage path, and the invasion range is limited, and the possibility of distant metastasis is small. When the TDs appears in the large curved side of the stomach, the tumor cells may be transferred distally through the gastric colon ligament. When the TDs appears in the distal fat connective tissue or lymph node, it should not be considered as a N stage, but should be directly classified into the M1 stage. For patients with TDs with different TNM stages, only the Kaplan-Meier survival curves of patients with stage III were significantly different, and the Kaplan-Meier survival curves of the other three patients were not significantly different. In order to verify the influence of the location of cancer nodules on the staging of gastric cancer patients, and to find the staging that is more in line with the true survival of TDs positive patients, we made the following attempts. We compared the T-stage and N-stage of the TDs-positive small curved group with the TDs-negative group, and found that the survival curve of the TDs-positive small curved group was similar to that of the negative group of N1 and N2 staging patients. A valid conclusion is drawn. Comparing the T stage and N stage of the cancer nodule positive group and the TDs negative group, it was found that the survival curve of the TDs positive gastric group coincides with the

negative group T3, T4b, N2 staging curve, we It is believed that when a TDs appears on the stomach wall, the T stage at this time should not be lower than the T3 stage, and the N stage has no conclusion.

Comparing the N staging of the TDs-positive large curved group with the cancer nodule negative group, it was found that the survival curve of the positive large curved group and the survival curve of the N3 phase of the negative group were higher, and we thought that the large curved side appeared. In the case of TDs, the N stage at this time, regardless of the number of lymph node metastases, is classified as N3. The M stage of the TDs-positive distal group and the TDs-negative group were compared, and the survival curve of the positive distal group was found to be close to the survival curve of the negative group M1. In this regard, we believe that when the pathological report suggests a TDs on the stomach (stomach wall), the T stage at this time should be no less than the T3 stage; when the TDs appears in the large curved side of the stomach, the N at this time The stage should be no less than N3; when prompted to see a cancer nodule in the distal tissue, the patient should be classified as M1.

Our study confirmed the adverse effects of TDs on the prognosis of gastric cancer. However, because this study was a single-center retrospective study, the number of cases was limited and the follow-up time was short. How to properly incorporate TDs into tumor staging still requires more large-scale clinical analysis, and also requires more in-depth basic research and exploration on the mechanism of TDs.

Conclusion

Tumor deposits serves as a bad prognostic factor in patients with primary gastric cancer and the new stage system combining TNM and TD is more suitable for patients with gastric cancer.

Abbreviations

TD: tumor deposit

GC: gastric cancer

TNM: tumor-node-metastasis

Declaration

Ethics approval and consent to participate

This study was approved by the Medical Ethics Committee of the Chinese PLA General Hospital (S2017-059-042).

Consent for publication

Not Applicable.

Availability of data and materials section

All data generated or analysed during this study are included in this published article.

Competing interests

All the authors declared no interest in this study.

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None.

Authors' contributions

WY, CL designed the study. WXX, WZY, XTY, LS collected the samples of individuals. WD and GX performed statistical analysis. All the authors read and approved the final manuscript.

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Figures

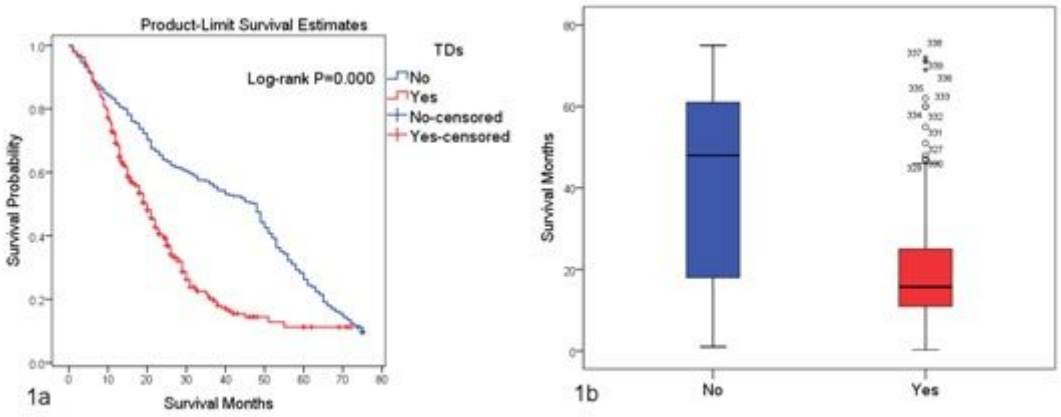

Figure 1

Comparison of prognosis survival between patients with tumor deposits (TDs) and without TDs.

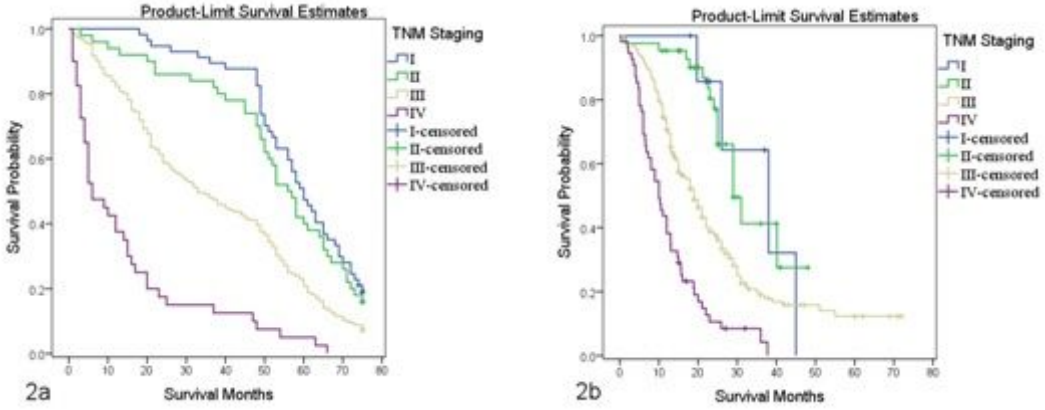

Figure 2

Kaplan-Meier curves of the TNM staging survival.a,TNM staging survival among postoperative patients without tumor depositof gastric cancer. b, TNM staging survival among postoperative patients with tumor depositof gastric cancer.

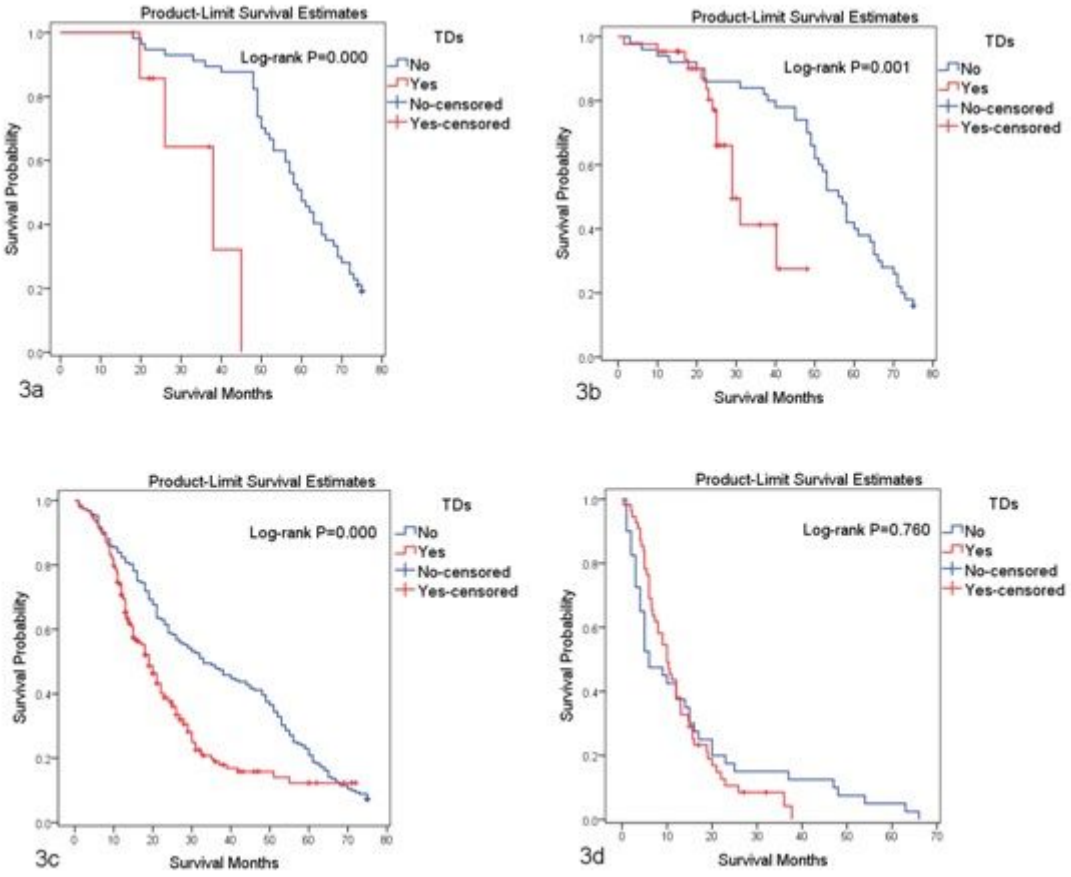

Figure 3

Overall survival of different TNM staging patients with TDs and without TDs.a, stage I survival among postoperative patients with and withoutTDs. b, stage II patients with and withoutTDs. c, stage III patients. d, stage IV patients.

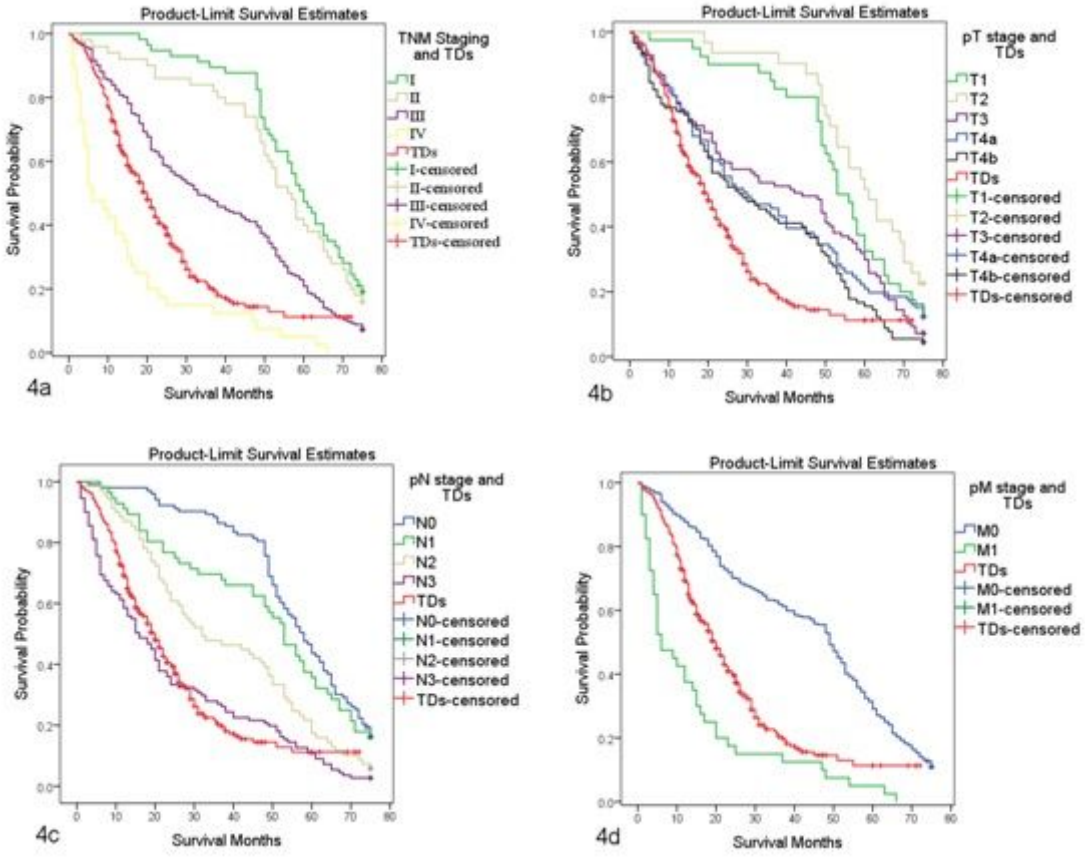

Figure 4

Comparison of survival curves between patients with TDs and those without TDs in TNM category. a,survival curves between patients with TDs and those without TDs in pTNM category. b, survival curves between patients with TDs and those without TDs in pT category. c, survival curves between patients with TDs and those without TDs in pN category. d, survival curves between patients with TDs and those without TDs in pM category.

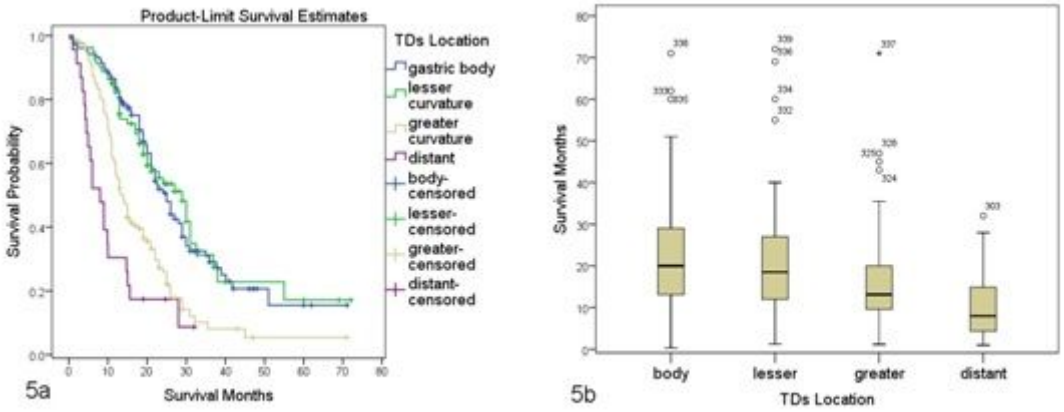

Figure 5

Comparison of prognosis survival between different location withTDs.

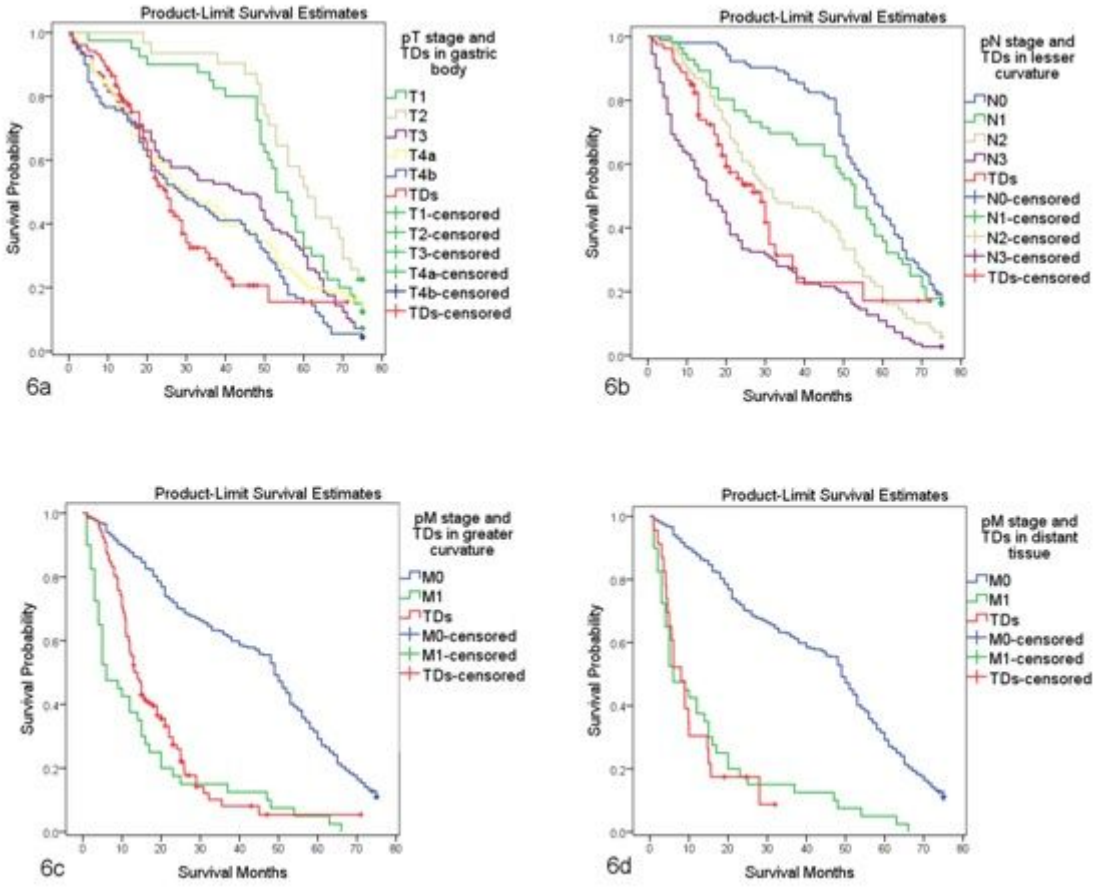

Figure 6

Comparison of survival curves between patients with TDs'different location and those without TDs in pT, pN, pMstage category. a, the K-M curves of TDs located ingastric body compared to pT stage without TDs. b, the K-M curves of TDs located in lesser curvature compared to pN stage without TDs. c, the K-M curves of TDs located in greater curvature compared to pM stage without TDs. d, the K-M curves of TDs located in distant tissue compared to pM stage without TDs.

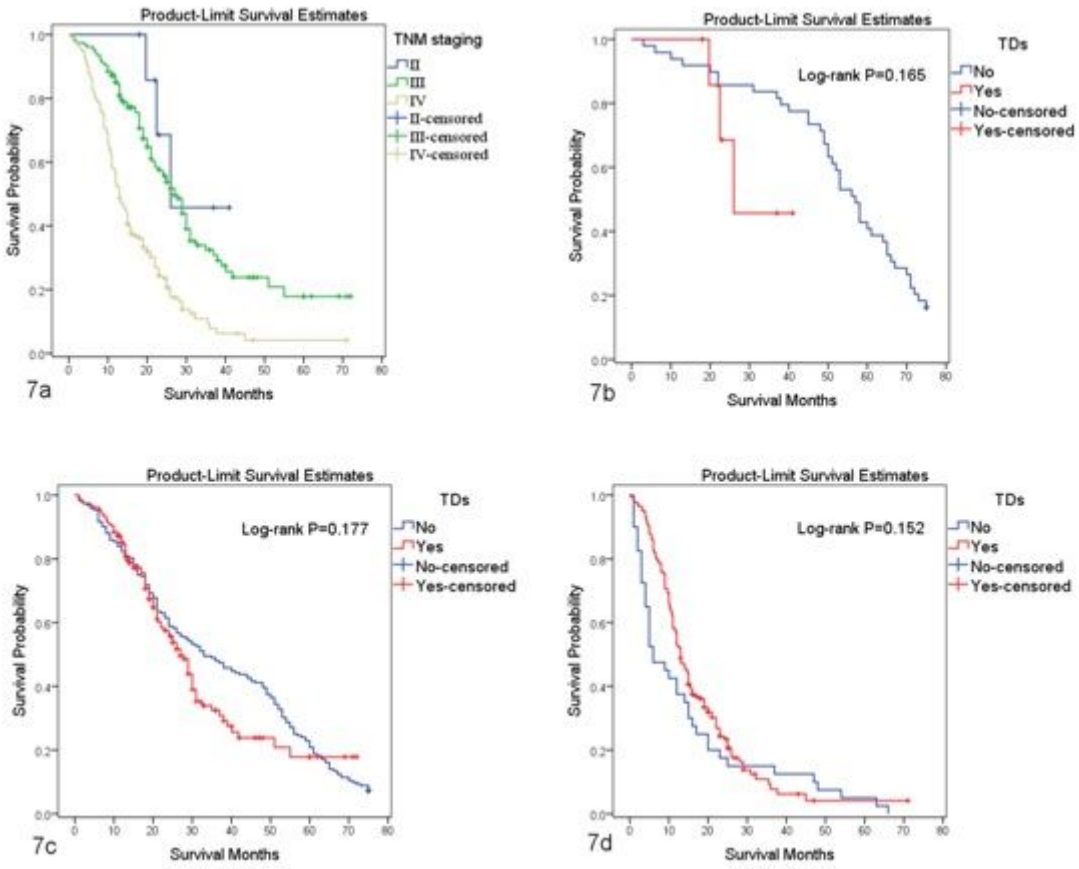

Figure 7

The survival curvesof new TNM staging incorporating TDs. a, the new TNM staging survival curve among patients withTDsof gastric cancer. b, stage II survival curve among postoperative patients with and withoutTDs. c, stage III survival curveamong patients with and withoutTDs. d, stage IV survival curve among patients with and withoutTDs.