



Tumor deposit indicates worse prognosis than metastatic lymph node in gastric cancer: a propensity score matching study

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Background: The prognostic value of tumor deposit (TD) in gastric cancer is controversial. This study aims to investigate the prognostic value of TD.

Methods: The consecutive patients diagnosed with gastric cancer from October 2007 to October 2012 were selected. The patients were divided by whether they suffered TD into two groups. The basic data were comparable between the two groups after propensity score matching (PSM), then survival analysis [overall survival (OS) and cancer-specific survival (CSS)] was applied in two groups. After that, all the patients were divided by pN staging and survival analysis were applied in each subgroup. At last, all patients were divided into TD group, pN1 stage group, pN2 stage group, pN3a, and pN3b stage group, OS and CSS were compared between them. Multivariable competing risk analyses tested association of TD with OS and CSS, before and after PSM.

Results: Eight hundred and three patients were concluded. After PSM, 137 patients with TD and 274 patients without TD were selected, the 5-year OS and CSS rates of patients with TD were significantly worse than patients without TD (OS: 19.7% *vs.* 42.0%, $P < 0.001$; CSS: 22.6% *vs.* 45.6%, $P < 0.001$). In all patients' survival analysis, the 5-year OS and CSS rates of TD group were comparable with pN3a group (OS: 19.7% *vs.* 25.3%, $P = 0.221$, CSS: 22.6% *vs.* 30.1%, $P = 0.092$) and pN3b group (OS: 19.7% *vs.* 19.6% $P = 0.349$, CSS: 22.6% *vs.* 23.5%, $P = 0.452$). Meanwhile, on multivariable cox regression analyses, the presence of TD significantly reduces the OS and CSS of patients in gastric cancer.

Conclusions: TD has a marked impact on the prognosis of gastric cancer. Even patients with TD had the same prognosis with pN3 stage.

Keywords: Tumor deposit (TD); gastric cancer; prognosis; TNM staging

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Introduction

The concept of TD was proposed by scientist Gabriel as early as 1935. He discovered and reported the tumor-like nodular masses besides the colorectal tumor and in the fat tissue of mesocolon and mesorectum (1). With

the deepening of research, the conclusion that TD is a poor prognosis for colorectal cancer has been confirmed eventually (2-4) and was finally included in the N1c stage in colorectal cancer separately in the 7th edition of the TNM staging (5). Puppa *et al.* reported that TD not only existed

in colorectal cancer but also other solid malignant tumors such as gastric cancer, cholangiocarcinoma, and pancreatic cancer (6). However, the prognostic value of TD in gastric cancer is controversial. In the 8th edition of TNM staging, TD tend to be considered as metastatic lymph nodes (7), while there is some studies that indicate that TD should be regarded as serosal invasion (8,9). This study aims to invest the value of TD in the prognosis of gastric cancer through propensity score matching (PSM).

Methods

Data source

A prospective retrospective database was applied by this study, including the consecutive gastric cancer patients with curative resection from October 2007 to October 2012 in Sun Yat-sen Memorial Hospital. There is no intentional inclusion or exclusion. All patients diagnosed with gastric cancer at in our institution were registered with the follow-up data, including survival state, causes of death, and the follow-up times. Follow up data were recorded through telephone, email, and outpatient.

Patients diagnosed with gastric cancer from October 2007 to October 2012 were selected along with their clinicopathological data, including sex, age, method of therapy, tumor deposits (TDs), lymphatic nodes, depth of invasion, differentiated degree, the follow-up date, overall survival (OS), and cancer-specific prognosis. All the selected patients are performed curative tumor resection with lymph node dissection, but not including gastric cancer resection and combined metastatic organ resection. Patients with malignancies other than gastric adenocarcinoma, or recurrent gastric cancer, or gastric stump cancer, or accepted neoadjuvant chemotherapy, patients with the number of LN detection less than 15 were excluded. Finally, a total of 803 patients were included. According to the 8th edition of TNM staging in gastric cancer (10), only when center of tumor is 2 cm away from the gastroesophageal junction, the tumor should be including in TNM staging for gastric cancer.

Definition of TD

TD was defined that discrete foci of tumor found in the perigastric fat or adjacent ligament away from the primary tumor, without evidence of residual lymph node tissue but within the lymph drainage area of the primary tumor.

The examination for TD was dependent on two pathology professors at Sun Yat-sen Memorial Hospital by a double-blind method, and if there is a disagreement between them, the third pathology professor will diagnose it. The depth of invasion and lymphatic nodes metastasis were classified by 8th edition of TNM staging system.

Statistical analysis

First, descriptive statistics were used to describe the participants' clinicopathologic characteristics and other baseline variables. Median (range) values were used to describe continuous variables, and Ratio was used to describe categorical variables. Mann-Whitney U test (for nonparametric distribution), and chi-square tests or Fisher exact test (for categorical variables) were used to assess differences between TD-group and non-TD-group before and after PSM.

To estimate propensity score, logistic regression analysis was performed using nearest neighbor matching. The ratio for matching was 1:2 using a caliper of width equals to 0.2 of the standard deviation of the logit of the propensity score.

Survival analysis was performed using the Kaplan-Meier method with log-rank analysis to compare survival functions between groups. Multivariable cox regression analysis was applied to consider the association between TD and prognosis. Patients who died from other cause or still were alive were treated CSS. Survival rates between groups at 60 months were reported.

Statistical significance was considered at $P < 0.05$. All analyses were performed using the R language version 3.4.2.

Results

Patient's clinicopathologic characteristics before and after propensity score match

The 803 patients were concluded; there were 137 patients with TD and 666 patients without TD; their characteristics were recorded in *Table 1*. Overall, TD was found in 137 patients (20.6%), and there are 666 patients without TD; There was no significant difference in gender, age, tumor location, and chemotherapy rates between TD and non-TD patients (all P value > 0.05). However, patients with TD were more likely in high level pT stage (pT4a: 44.5% *vs.*

Table 1 Clinicopathologic demographics of included patients before and after Propensity Score Matching

Variables	Before PSM				After PSM			
	Total (N=803)	Non-TD (N=666)	TD (N=137)	P value	Total (N=411)	Non-TD (N=274)	TD (N=137)	P value
Gender, n (%)				0.819				0.626
Male	543 (67.6)	452 (67.9)	91 (66.4)		281 (68.3)	190 (69.3)	91 (66.4)	
Female	260 (32.4)	214 (32.1)	46 (33.6)		130 (31.7)	84 (30.7)	46 (33.6)	
Age, median (IQR)	57 [49–66]	57 [50–66]	58 [48–68]	0.811	59 [49–68]	59 [49–67]	58 [48–68]	0.660
Tumor location, n (%)				0.414				0.361
Lower	363 (45.2)	299 (44.9)	64 (46.7)		185 (45.0)	121 (44.2)	64 (46.7)	
Middle	199 (24.8)	161 (24.2)	38 (27.7)		103 (25.1)	65 (23.7)	38 (27.7)	
Upper	241 (30.0)	206 (30.9)	35 (25.6)		123 (29.9)	88 (32.1)	35 (25.6)	
Differentiated degree, n (%)				<0.001				0.268
High	512 (63.7)	464 (69.7)	48 (35.0)		161 (39.2)	113 (41.2)	48 (35.0)	
Low	291 (36.3)	202 (30.3)	89 (65.0)		250 (60.8)	161 (58.8)	89 (65.0)	
pT stage, n (%)				<0.001				0.163
pT1	112 (13.9)	107 (16.0)	5 (3.6)		9 (2.1)	4 (1.5)	5 (3.6)	
pT2	100 (12.5)	85 (12.8)	15 (10.9)		41 (10.0)	26 (9.5)	15 (10.9)	
pT3	187 (23.3)	164 (24.6)	23 (16.8)		82 (20.0)	59 (21.5)	23 (16.8)	
pT4a	294 (36.6)	233 (35.0)	61 (44.5)		200 (48.7)	139 (50.7)	61 (44.5)	
pT4b	110 (13.7)	77 (11.6)	33 (24.1)		79 (19.2)	46 (16.8)	33 (24.2)	
pN stage, n (%)				<0.001				0.371
pN0	310 (38.6)	294 (44.1)	16 (11.7)		53 (12.9)	37 (13.5)	16 (11.7)	
pN1	143 (17.8)	132 (19.8)	11 (8.0)		34 (8.3)	23 (8.4)	11 (8.0)	
pN2	147 (18.3)	106 (15.9)	41 (29.9)		135 (32.8)	94 (34.3)	41 (29.9)	
pN3a	115 (14.3)	83 (12.5)	32 (23.4)		102 (24.8)	70 (25.5)	32 (23.4)	
pN3b	88 (11.0)	51 (7.7)	37 (27.0)		87 (21.2)	50 (18.3)	37 (27.0)	
Chemotherapy, n (%)				0.712				0.093
Yes	484 (60.3)	399 (59.9)	85 (62.0)		279 (67.9)	194 (70.8)	85 (62.0)	
No	319 (39.7)	267 (40.1)	52 (38.0)		132 (32.1)	80 (29.2)	52 (38.0)	
Tumor size, n (%)				<0.001				0.343
<5 cm	451 (56.2)	395 (59.3)	56 (40.9)		183 (44.5)	127 (46.4)	56 (40.9)	
≥5 cm	352 (43.8)	271 (40.7)	81 (59.1)		228 (55.5)	147 (53.6)	81 (59.1)	

TD, tumor deposit; PSM, propensity score matching; IQR, interquartile range.

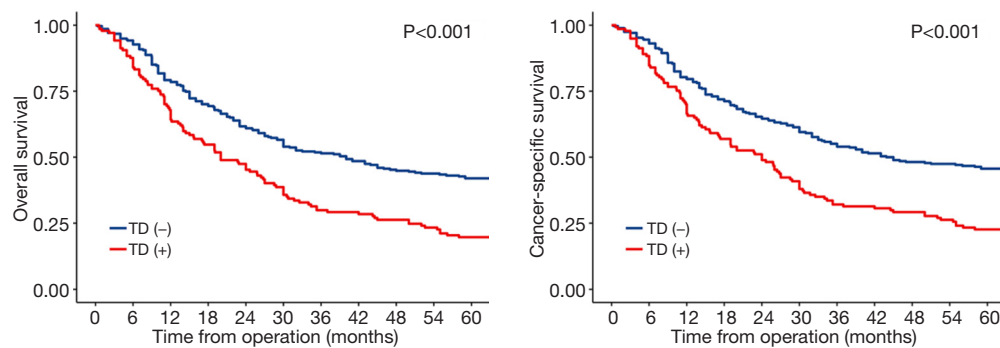


Figure 1 OS and CSS between TD and non-TD group in the matched cohort. OS, overall survival; CSS, cancer-specific survival; TD, tumor deposit.

35.0%; pT4b: 24.2% vs. 11.6%), pN stage (pN3a: 23.4% vs. 12.5%; pN3b: 27.0% vs. 7.7%), poor differentiated degree (65.0% vs. 30.3%) and tumor size (≥ 5 cm: 59.1% vs. 40.7%) compared to patients without TD.

After a propensity score match of 1:2, 137 patients with TD and 274 patients without TD were obtained, and there was no significant difference in between the two groups considering gender, age, tumor location, differentiated degree, pT stage, pN stage, chemotherapy, and tumor size (Table 1).

Survival analysis in the matched cohort

Long term outcomes were performed between the selected patients, the median follow-up period for OS was 80 (95% CI, 70–88) months in the TD group and 75 (95% CI, 71–76) months in the non-TD group. The median follow-up period for CSS was 40 (95% CI, 33–47) months in the TD group and 67 (95% CI, 66–68) months in the non-TD. The 5-year OS rates of TD group and non-TD group were 19.7% (95% CI, 14.1–27.6%) and 42.0% (95% CI, 36.5–48.2%), the 5-year cancer-specific survival (CSS) rates of TD group and non-TD group were 22.6% (95% CI, 16.6–30.8%) and 45.6% (95% CI, 40.1–51.9%) (Figure 1). Both OS and CSS of patients with TD were both significantly worse than patients without TD ($P < 0.001$, $P < 0.001$). Multivariable Cox regression analyses in matched cohort also showed that TD was associated with poor OS and CSS (Tables 2 and 3, $P < 0.001$).

Table 2 Multivariable cox regression analysis of OS in the matched cohort

Variables	HR	95% CI lower	95% CI upper	P value
Gender (male vs. female)	0.911	0.689	1.205	0.514
Age	0.996	0.986	1.007	0.484
Tumor location				
Lower	Ref	Ref	Ref	Ref
Middle	0.932	0.678	1.281	0.662
Upper	1.159	0.864	1.555	0.325
Tumor size (≥ 5 vs. < 5 cm)	1.257	0.970	1.629	0.084
Differentiated (high vs. low)	1.613	1.230	2.115	<0.001
Chemotherapy	0.091	0.065	0.126	<0.001
pT stage				
pT1 stage	Ref	Ref	Ref	Ref
pT2 stage	0.617	0.216	1.763	0.368
pT3 stage	1.442	0.554	3.755	0.453
pT4a stage	1.857	0.739	4.664	0.188
pT4b stage	2.813	1.090	7.257	0.032
pN stage				
pN0 stage	Ref	Ref	Ref	Ref
pN1 stage	5.920	2.710	12.933	<0.001
pN2 stage	5.323	2.752	10.296	<0.001
pN3a stage	8.524	4.378	16.597	<0.001
pN3b stage	7.999	4.030	15.877	<0.001
TD	1.594	1.224	2.077	<0.001

OS, overall survival; HR, hazard ratio; CI, confidence interval; TD, tumor deposit.

Table 3 Multivariable cox regression analysis of CSS in the matched cohort

Variables	HR	95% CI lower	95% CI upper	P value
Gender (male vs. female)	1.036	0.779	1.378	0.81
Age	0.998	0.987	1.008	0.68
Tumor location				
Lower	Ref	Ref	Ref	Ref
Middle	0.997	0.719	1.382	0.984
Upper	1.113	0.824	1.503	0.484
Tumor size (≥ 5 vs. < 5 cm)	1.458	1.117	1.903	0.006
Differentiated (high vs. low)	1.743	1.314	2.312	< 0.001
Chemotherapy	0.117	0.086	0.161	< 0.001
pT stage				
pT1	Ref	Ref	Ref	Ref
pT2	0.600	0.209	1.718	0.341
pT3	1.494	0.567	3.936	0.417
pT4a	1.684	0.667	4.255	0.27
pT4b	3.020	1.162	7.850	0.023
pN stage				
pN0	Ref	Ref	Ref	Ref
pN1	7.308	3.267	16.349	< 0.001
pN2	5.415	2.740	10.703	< 0.001
pN3a	8.693	4.371	17.288	< 0.001
pN3b	7.546	3.738	15.234	< 0.001
TD	1.677	1.279	2.201	< 0.001

CSS, cancer-specific survival; HR, hazard ratio; CI, confidence interval; TD, tumor deposit.

Survival analysis in all patients

Finally, we try to compare the relationship between the value of TD and lymph node metastasis. We subdivided the patients without TD into 5 categories according to 8th edition of TNM staging: pN0, pN1, pN2, pN3a, pN3b group. The long term outcomes were recorded in *Figure 2*, the median follow-up time for OS in pN0, pN1, pN2, pN3a and pN3b groups were 77 (95% CI, 74–78) months, 75 (95% CI, 74–78) months, 73 (95% CI, 70–78) months, 71 (95% CI, 65–79) months, 67 (95% CI, 63–70) months, respectively. the median follow-up time for CSS in pN0, pN1, pN2, pN3a and pN3b groups were 67 (95% CI, 66–68) months, 66 (95% CI, 65–67) months, 69 (95% CI, 67–70) months, 66 (95% CI, 63–69) months, 62 (95% CI, 61–65) months, respectively. The 5-year OS rates of TD, pN0, pN1, pN2, pN3a, pN3b group were 19.7% (95% CI, 14.1–27.6%), 83.3% (95% CI, 79.2–87.7%), 63.6% (95% CI, 55.9–72.4%), 48.1% (95% CI, 35.9–58.6%), 25.3% (95% CI, 17.5–36.6%), 19.6% (95% CI, 11.2–34.2%); the 5-year CSS rates of TD, pN0, pN1, pN2, pN3a, pN3b group were 22.6% (95% CI, 16.6–30.8%), 86.7% (95% CI, 82.9–90.7%), 68.2% (95% CI, 60.7–76.6%), 51.9% (95% CI, 43.2–62.3%), 30.1% (95% CI, 21.7–41.8%), 23.5% (95% CI, 14.3–38.6%). Interestingly, the 5-year OS and CSS rates of TD group were comparable with pN3a group (OS: 19.7% vs. 25.3%, $P=0.221$, CSS: 22.6% vs. 30.1%, $P=0.092$) and pN3b group (OS: 19.7% vs. 19.6%, $P=0.349$, CSS: 22.6% vs. 23.5%, $P=0.452$). Multivariable cox regression analyses in all patients also showed that TD was again associated with poor OS and CSS (*Tables 4 and 5*, $P<0.001$).

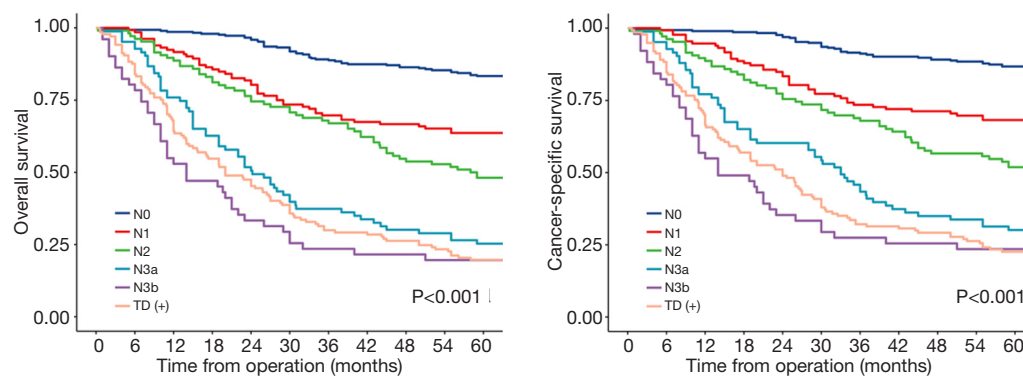


Figure 2 OS and CSS in all patients. OS, overall survival; CSS, cancer-specific survival.

Table 4 Multivariable cox regression analyses of OS in all patients

Variables	HR	95% CI lower	95% CI upper	P value
Gender (male vs. female)	0.923	0.727	1.170	0.508
Age	0.999	0.990	1.008	0.775
Tumor location				
Lower	Ref	Ref	Ref	Ref
Middle	1.050	0.798	1.382	0.725
Upper	1.224	0.959	1.562	0.105
Tumor size (≥5 vs. <5 cm)	1.269	1.016	1.585	0.036
Differentiated (high vs. low)	1.427	1.131	1.800	0.003
Chemotherapy	0.103	0.077	0.138	<0.001
pT stage				
pT1	Ref	Ref	Ref	Ref
pT2	1.962	0.971	3.965	0.06
pT3	5.270	2.733	10.163	<0.001
pT4a	6.288	3.265	12.110	<0.001
pT4b	9.972	5.017	19.818	<0.001
pN stage				
pN0	Ref	Ref	Ref	Ref
pN1	5.862	3.732	9.207	<0.001
pN2	6.401	4.169	9.827	<0.001
pN3a	11.117	7.244	17.060	<0.001
pN3b	10.010	6.346	15.792	<0.001
TD	1.697	1.314	2.191	<0.001

OS, overall survival; HR, hazard ratio; CI, confidence interval; TD, tumor deposit.

Table 5 Multivariable cox regression analyses of CSS in all patients

Variables	HR	95% CI lower	95% CI upper	P value
Gender (male vs. female)	0.885	0.690	1.135	0.337
Age	1.001	0.991	1.010	0.873
Tumor location				
Lower	Ref	Ref	Ref	Ref
Middle	1.032	0.773	1.377	0.832
Upper	1.210	0.938	1.560	0.143
Tumor size (≥5 vs. <5 cm)	1.427	1.133	1.798	0.003
Differentiated (high vs. low)	1.571	1.228	2.010	<0.001
Chemotherapy	0.149	0.114	0.195	<0.001
pT stage				
pT1	Ref	Ref	Ref	Ref
pT2	1.527	0.723	3.224	0.267
pT3	3.971	1.994	7.909	<0.001
pT4a	4.251	2.154	8.388	<0.001
pT4b	6.831	3.360	13.891	<0.001
pN stage				
pN0	Ref	Ref	Ref	Ref
pN1	4.617	2.915	7.312	<0.001
pN2	5.765	3.733	8.904	<0.001
pN3a	9.735	6.296	15.053	<0.001
pN3b	8.861	5.570	14.096	<0.001
TD	1.905	1.470	2.469	<0.001

CSS, cancer-specific survival; HR, hazard ratio; CI, confidence interval; TD, tumor deposit.

Discussion

With the advances made in medicine, more attention is paid to the examination of the pathology of specimens after curative surgery of gastric cancer. In the pathological examination, an increasing number of lymph nodes, vascular invasion, nerve infiltration, and TDs were discovered and reported (11). Many studies had reported TD indicated worse prognosis in a variety of malignancies (12-14). However, the significance of TD in gastric cancer is still controversial.

To analyze the effect of TD on the prognosis of gastric cancer, we used PSM analysis. This analysis method considers and eliminates potential factors that may have an impact on the outcomes, widely applied to multicenter cohort researches (15). In our study, we recorded the baseline data included age, tumor size, differentiated degree, gender, pT stage, pN stage and tumor location, chemotherapy, and there exist difference in these baseline data between TD group and non-TD group, which may affect the survival outcomes independently. After PSM, the quality of analysis has improved significantly with the

elimination of the difference in baseline data.

There were a few of study focused on TD in gastric cancer. Lee *et al.* conducted a retrospective analysis of 653 patients with gastric cancer and found TDs in 23.9% of all patients, and regression analysis revealed that TDs were positively associated with synchronous gastric cancer metastases ($P < 0.01$). The sensitivity of TD for predicting synchronous metastasis was 83.6%, while its specificity was 82.3%. In their study, multivariate analyses showed that TD is an independent risk factor that affects prognosis. Meanwhile, patients with TD suffered poor prognosis than patients without TD under neoadjuvant chemotherapy. Besides, patients with TD showed worse prognosis in pN1, pN2, pN3 subgroup, respectively. It significantly suggested that the worse survivals of patients with TD (16). Sun *et al.* investigated the effect of TD on TNM staging in gastric cancer, through studied 2,998 patients diagnosed gastric adenocarcinoma who underwent radical gastrectomy (8). There were 534 patients (17.8%) observed with TD, survival analysis indicated that there is no statistical difference between the prognosis of patients with TD in pT1-4a stage and that of patients without TD but in pT4a stage, pointing that gastric cancer with TD should be treated as a T4a disease. This was the first time to propose that TD is affected by the TNM staging of gastric cancer. However, the patient's group of their studies were associated 30 years, diagnostic and therapeutic approaches of gastric cancer have changed dramatically in these periods. Besides, in their study, some esophagogastric junction cancer patients included should be defined as esophageal carcinoma according to 8th edition of TNM staging, which may influence the quality of their study. Anup *et al.* analyzed 1,250 patients undergoing radical gastrectomy for gastric cancer and TD was founded in 132 (10.5%) patients (9). They also found that patients with TD obtained significantly poor survival outcomes than patients without TD in pT1-pT3 stage, but similar survival outcomes to patients without TD in pT4 stage, which proved that TDs were likely to be treated as the symbol of advanced gastric cancer.

Whether the TD should be incorporated in pN or should be considered in TNM staging in gastric cancer is controversial. To answer this question, we analyze the prognosis between patients with TD and patients without TD in pN0, pN1, pN2, pN3 stage, respectively. The results all showed the appearance of TD made for a worse prognosis on patients with gastric cancer; even the prognosis of patients with TD was comparable to patients with pN3 stage. Interestingly, there are 5 (3.6%) cases with TD in pT1 stage and 15 (10.9%) case with TD in pT2 stage. In Hye Seung Lee's study, only 2 cases of pT1 stage and 4 cases of

pT2 stages were found to have TD, accounting for only 0.9% of the total number of cases (16). These finds support the opinion that TD may be a manifestation of advanced gastric cancer.

At present, the formation mechanism of TD is not yet clear, and many hypotheses about the formation mechanism were continuously put forward, but no consensus has been reached between these various hypotheses. In 1935, when Gabriel reported on the discovery of TD, it was thought to be the result of the dissemination of cancer cells along blood vessels. In recent years, some scholars suggested that TD may be an intermediate state of metastasis: On the path of lymphatic vessels between two lymph nodes, tumor cells grow up and form TD (17). Also, some scholars believed that TD is externally capsule invaded from the metastatic lymph nodes; the tumor cells invaded the vascular nerve bundles, and then grow into TD. TD also may be a peritoneal metastasis (18). However, it could not explain that patients with TD but have no lymphatic nodes metastasis. Sun *et al.* compared the prognosis between patients with TD and peritoneal metastasis, and found that the 5-year OS rate of patients with peritoneal metastasis is only 7.4%, patients with TD had better prognosis than peritoneal metastasis ($P < 0.005$) (8); On the other hand, peritoneal metastatic nodules are multiple and closely arranged, but the TD is scattered and larger than peritoneal metastatic nodules, it also can be irregular.

Interestingly, there are quite several patients with TD but have no peritoneal metastasis. Therefore, it is not likely to treat TD as a peritoneal metastasis. The appearance of TD is associated with vascular infiltration, neural infiltration, and lymphatic infiltration (19). In other words, the present of TD showed that the tumors had already metastasized through multiple pathways such as blood vessels, nerves, and lymph vessels. This also explains why TD could significantly affect the prognosis of gastric cancer, even comparable to patients in pN3 stage.

In the 5th edition of TNM staging system for colon and rectal cancer, TDs > 3 mm in diameter in the pericolic and perirectal fat without any lymphatic evidence was treated as a metastasis lymph node (20). After that, in the 6th edition TNM stages of colon and rectal cancer, a TD has the form and contour like a lymph node was treated as a metastasis lymph node (21). However, with more studies on the important prognostic value of TD reported after that (2-4). Finally, AJCC considers that TD should not be treated as a metastatic lymph node, but be included in pN1c stage, this change also supported by many studies later (22-25). In the opinion of the 8th edition of TNM staging system (7),

a TD was thought as a metastatic lymph node in gastric cancer. However, recording to the results of our study, the conclusion may not agree that. At first, many studies and our study all had proved TD was an independent prognostic factor. Secondly, the OS and CSS of patients with TD were comparable to patients in pN3 stage. Finally, TD is defined to have no evidence of lymphatic node. Therefore, we thought it could not fully reflect the prognostic value of a TD as a metastasis lymph node in gastric cancer, instead of that, TD should be considered as a classification separately, like the status of TD in 7th edition of TNM staging system for colon and rectal cancer.

The first limitation of this study is the shortage of PSM that we could not match the unrecorded factors which may affect the outcomes. Secondly, the study is a retrospective analysis and therefore, has the related weakness from it. At last, we did not analyze the correlation between number of TD and prognosis. Larger sample studies are needed to confirm this conclusion further.

Conclusions

TD has a marked impact on the prognosis of gastric cancer, even patients with TD had the same prognosis with patients in pN3 stage. Considering these results, we think a TD may not simply be treated as a metastatic lymph node, but it should be staged for independence.

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Footnote

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

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were following the ethical standards of the institutional and national research committee and with the 1964 Helsinki

declaration and its later amendments or comparable ethical standards. This study also has been approved by the ethics committee of Sun Yat-sen Memorial Hospital (ID: SYSEC-KY-KS-2018-039).

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