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Brief Communication

Readjustment of nodal staging by integrating tumor deposits and positive lymph nodes in patients with stage III colon cancer: a population-based analysis

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Abstract: Whether tumor deposits (TDs) should be classified as lymph node metastasis or distant metastasis remains controversial. To address this predicament, we conducted this study to identify the predictive value of TDs on the survival of patients diagnosed with stage III colon cancer (CC). 12,904 eligible patients diagnosed with stage III CC between 2010 and 2015 were extracted from the Surveillance, Epidemiology, and End Results (SEER) database. The best cutoff point of TD quantity was determined based on the difference in survival. Cox proportional hazards model was employed to perform univariate and multivariate analyses. The Kaplan-Meier method and log-rank test were performed to calculate the differences between overall survival (OS). Our results showed that the number of TDs was a significant prognostic factor in patients with stage III CC ($P < 0.0001$). We added the number of TDs to the pN stage and devised a new pN stage, there were no significant differences in the survival of npN, except npN2a ($P > 0.05$). Upon re-staging to the same npN stage, the difference in survival between TDs+ and TDs- disappeared ($P > 0.05$). The median survival times for N2aTDs > 4 and N2bTDs > 4 were 33 and 37 months, respectively, which were significantly shorter than that of N2TDs- (65 months) and represented the worst survival rates among all groups. In conclusion, the number of TDs indicated a poor prognosis for patients with stage III CC. Incorporating TDs into the pN is feasible to predict prognosis.

Keywords: Stage III colon cancer, tumor deposits, lymph node metastasis, new pN staging system, survival

Introduction

The GLOBOCAN 2020 report presents the latest information regarding the global cancer burden. According to the statistics, colorectal cancer (CRC) ranks as the third most common malignancy worldwide among new cancer cases (10.0%). CRC ranks second in mortality among the most frequent malignant neoplasms, after lung cancer (9.4%) [1].

Clinicopathological factors commonly predict the prognosis of patients with CRC. The TNM staging system, proposed by the American Joint Committee on Cancer (AJCC), is the most widely recognized. This system is acknowledged for its sensitivity in identifying patients at risk of recurrence, predicting survival, and guiding clinical decisions. However, it tends to overlook tumor heterogeneity, and differences in the prognosis of patients with similar TNM stages may not be accounted for when relying solely on the staging system. The National Comprehensive Cancer Network (NCCN) identified additional pathological features related to patient survival, including lymphatic vascular infiltration, TDs, and perineural infiltration [2, 3]. Among these histopathological features, only TDs are commonly incorporated into TNM staging; their presence is considered a high-risk factor for postoperative recurrence and metastasis and an essential indicator for postoperative adjuvant chemotherapy [4, 5].

TDs were first described in the fifth edition of the AJCC TNM staging system. TDs with diameters > 3 mm and without regional lymph node metastasis are classified as pN. In contrast, TDs with diameters < 3 mm were classified as T3. The sixth edition of the TNM defined TDs based on contour. A firm and smooth contour is deemed a positive lymph node, whereas irregular TDs remain categorized as T3. The seventh TNM edition defined TDs as discrete cancerous nodules located around the pericolic or perirectal fat or adjacent mesentery, with no features of lymph node tissue. The seventh and eighth editions included TDs without LNM into the N1c stage of CRC. In cases of LNM, the number of TDs is not calculated into the number of positive lymph nodes. Compared with the seventh edition, the eighth edition only excludes tumor lesions related to "identifiable vascular or neural structures", classifying them as vascular or perineural invasion. Nevertheless, the guidelines still do not clarify the classification of patients identified simultaneously with LNM and TDs.

Several previous retrospective analyses and meta-analyses indicated a statistically significant difference in the survival of patients confirmed with or without TDs in lymph node-positive [6-8]. Currently, controversies regarding redefining the relationship between LNM and TDs and whether TDs should be regarded as lymph node metastasis or distant metastasis remain unsolved [9-11]. Therefore, it is crucial to clarify the prognostic role of TDs, particularly in evaluating the prognosis of patients with CRC with LNM and TDs. However, previous studies revealing differences between colon and rectal cancer regarding etiology, embryonic origin, and metastasis model. Additionally, variations in surgical methods and systemic treatment, such as neoadjuvant therapy, concurrent chemoradiotherapy, or chemotherapy, exist between patients with stage III colon cancer (CC) and those with stage III rectal cancer. Therefore, separate studies should be conducted to assess the impact of TDs on the prognoses of patients with CC and those with rectal cancer [12-14]. Our study aimed to determine the predictive value of TDs in patients with CC, combine the number of TDs with the pN stage, and explore the possibility of the inclusion of TDs in the pN stage.

Materials and methods

Patients and data sources

We extracted the data of patients with CC from the Surveillance, Epidemiology, and End Results (SEER) database from January 2010 to December 2015 by applying SEER * stat (version 8.3.9.2). The inclusion criteria were as follows: (I) patients aged 18-80 years; (II) patients received resection at the primary site, and the site codes C18.0 and C18.2-18.7 were used; (III) patients were pathologically confirmed to have colon cancer, with histology codes encompassing adenocarcinoma [8140-8144, 8210-8213, 8220-8221, and 8260-8263], mucinous adenocarcinoma [8480-8481], and signet ring cell carcinoma [8490]; (IV) patients were diagnosed at stage III, according to the TNM stage; (V) patients with complete survival information; (VI) patients with follow-up period > 1 month.

This study excluded patients with missing or incomplete clinical basic, clinicopathological, and therapeutic information (see **Figure 1** in the supplementary file for details). This study was conducted according to the SEER data use agreement, and patient informed consent was not required given the anonymized, de-identified data in the SEER database.

Variables and outcomes

Our primary endpoint was overall survival (OS), defined as the interval from diagnosis to death or the last follow-up. The primary site of the tumor was defined as the right colon (cecum, ascending colon, hepatic flexure of colon, and transverse colon) and the left colon (splenic flexure of the colon, descending colon, and sigmoid colon). Carcinoembryonic antigen (CEA) was considered negative when its levels were within the normal range and positive when its levels were higher than the normal range.

Statistical analysis

All continuous variables were transformed into categorical variables. We used the χ^2 test or Fisher exact test to compare categorical variables for demographic and clinicopathological characteristics. Univariate and multivariate analyses were performed using Cox proportional hazards models. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were

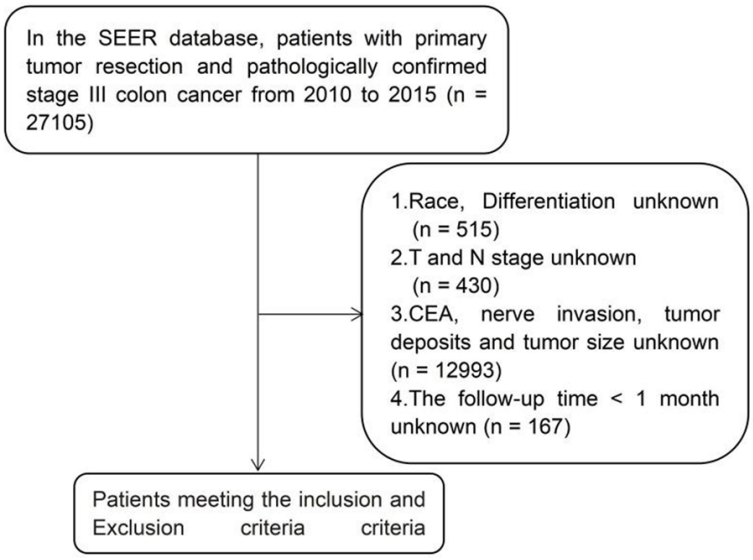

Figure 1. The workflow of the patient selection process.

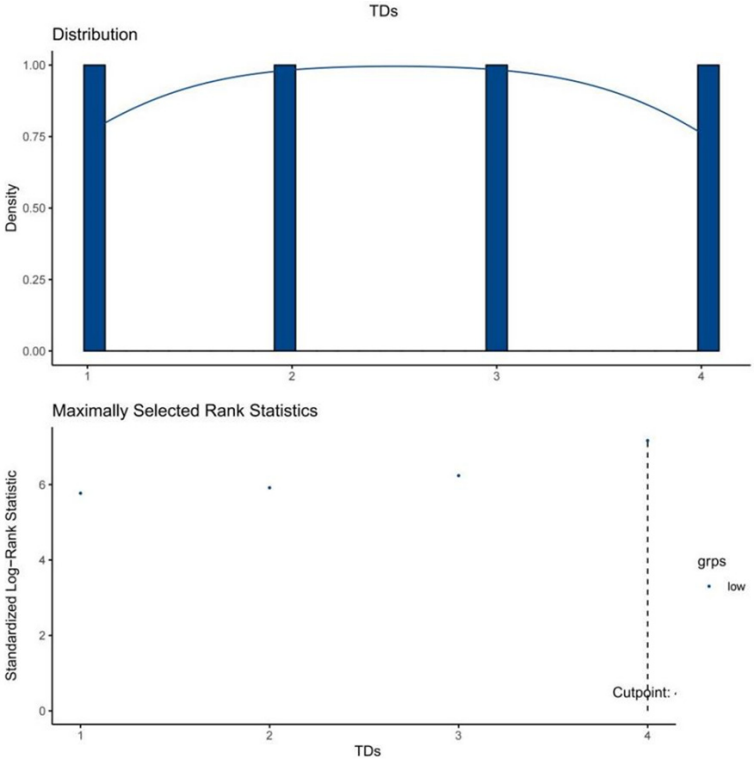

Figure 2. The best cutoff point of tumor deposits quantities.

expressed as numerical values. The Kaplan-Meier method and log-rank test were used to further calculate the difference in OS among groups to determine the independent effect of TD on OS.

All statistical analyses in this study were performed using EmpowerStats 2.0 (R 3.4.3) software and R Statistical Software version 4.1.2 (Vienna, Austria; www.r-project. org). A bilateral *p*-value < 0.05 was considered statistically significant.

Results

Baseline characteristics of patients with stage III colon cancer

A total of 12,904 patients were included in this study. Patients were categorized into three groups according to the best cutoff point: TDs-, TDs ≤ 4, and TDs > 4 (10884, 1766, and 254, respectively; see **Figure 2** in the supplementary file for details).

Table 1 presents the baseline characteristics of patients with stage III CC according to the TDs status. Among the 12904 patients, 2020 (15.65%) were confirmed as TDs+. No significant differences were identified regarding sex, race, age at diagnosis, tumor size, or chemotherapy among the TDs-, TDs ≤ 4, and TDs > 4 groups (P > 0.05).

Regarding the degree of differentiation, moderately differentiated tumors constituted the highest proportion, followed by poorly differentiated tumors. Within the moderately differentiated category, TDs > 4 accounted for 60.63%, lower than TDs- (71.46%) and TDs ≤ 4 (72.76%). Nevertheless, TDs > 4 accounted for 31.50% in the poorly differentiated category, which was significantly higher than the TDs- (19.48%) and TDs ≤ 4 (18.91%).

Regarding the T stage, the proportion of patients with TDs in stages ≥ T3 was higher

Table 1. Clinicopathological features of patients with stage III colon cancer

	Total (N = 12904)	Tumor deposits (TDs)			*P*-value
		TDs- (n = 10884)	TDs ≤ 4 (n = 1766)	TDs > 4 (n = 254)	
Sex					0.328
Male	6270 (48.59%)	5311 (48.80%)	846 (47.90%)	113 (44.49%)	
Female	6634 (51.41%)	5573 (51.20%)	920 (52.10%)	141 (55.51%)	
Age					0.19
< 65	6725 (52.12%)	5687 (52.25%)	895 (50.68%)	143 (56.30%)	
≥ 65	6179 (47.88%)	5197 (47.75%)	871 (49.32%)	111 (43.70%)	
Race					0.353
White	9550 (74.01%)	8028 (73.76%)	1328 (75.20%)	194 (76.38%)	
AmericanIndian/Alaska Native	116 (0.9%)	97 (0.89%)	15 (0.85%)	4 (1.57%)	
Black	1916 (14.85%)	1620 (14.88%)	265 (15.01%)	31 (12.20%)	
Asian or Pacific Islanders	1322 (10.24%)	1139 (10.46%)	158 (8.95%)	25 (9.84%)	
Primary site					< 0.001
Right colon	7472 (57.9%)	6392 (58.73%)	965 (54.64%)	115 (45.28%)	
Left colon	5432 (42.1%)	4492 (41.27%)	801 (45.36%)	139 (54.72%)	
Pathology					0.002
Adenocarcinoma	11551 (89.51%)	9745 (89.54%)	1595 (90.32%)	211 (83.07%)	
Mucinous adenocarcinoma	1186 (9.19%)	1006 (9.24%)	145 (8.21%)	35 (13.78%)	
Signet ring cell carcinoma	167 (1.29%)	133 (1.22%)	26 (1.47%)	8 (3.15%)	
Degree of differentiation					< 0.001
Well	642 (4.98%)	566 (5.20%)	68 (3.85%)	8 (3.15%)	
Moderately	9217 (71.43%)	7778 (71.46%)	1285 (72.76%)	154 (60.63%)	
Poorly	2534 (19.64%)	2120 (19.48%)	334 (18.91%)	80 (31.50%)	
Undifferentiated	511 (3.96%)	420 (3.86%)	79 (4.47%)	12 (4.72%)	
pT stage					< 0.001
T1	495 (3.84%)	473 (4.35%)	20 (1.13%)	2 (0.79%)	
T2	1229 (9.52%)	1116 (10.25%)	108 (6.12%)	5 (1.97%)	
T3	8450 (65.48%)	7181 (65.98%)	1133 (64.16%)	136 (53.54%)	
T4	2730 (21.16%)	2114 (19.42%)	505 (28.60%)	111 (43.70%)	
pN stage					< 0.001
N1a	4198 (32.53%)	3842 (35.30%)	335 (18.97%)	21 (8.27%)	
N1b	4095 (31.73%)	3625 (33.31%)	422 (23.90%)	48 (18.90%)	
N1c	474 (3.67%)	0 (0.00%)	447 (25.31%)	27 (10.63%)	
N2a	2416 (18.72%)	2048 (18.82%)	309 (17.50%)	59 (23.23%)	
N2b	1721 (13.34%)	1369 (12.58%)	253 (14.33%)	99 (38.98%)	
Tumor size(cm)					0.187
< 5	7264 (56.29%)	6153 (56.53%)	981 (55.55%)	130 (51.18%)	
≥ 5	5640 (43.71%)	4731 (43.47%)	785 (44.45%)	124 (48.82%)	
CEA					< 0.001
Negative	7637 (59.18%)	6526 (59.96%)	984 (55.72%)	127 (50.00%)	
Positive	5267 (40.82%)	4358 (40.04%)	782 (44.28%)	127 (50.00%)	
Nerve invasion					< 0.001
No	10821 (83.86%)	9323 (85.66%)	1343 (76.05%)	155 (61.02%)	
Yes	2083 (16.14%)	1561 (14.34%)	423 (23.95%)	99 (38.98%)	
Chemotherapy					0.644
No/Unknown	2969 (23.01%)	2488 (22.86%)	420 (23.78%)	61 (24.02%)	
Yes	9935 (76.99%)	8396 (77.14%)	1346 (76.22%)	193 (75.98%)	

Table 2. Univariate and multivariate Cox regression analysis of overall survival rate of patients with stage III colon cancer

	Univariate analysis			Multivariate analysis		
	H.R.	95% CI	*P*-value	H.R.	95% CI	*P*-value
Sex						
Male	1					
Female	1.16	1.09, 1.23	< 0.0001	1.32	1.22, 1.43	< 0.0001
Age						
< 65	1					
≥ 65	1.84	1.73, 1.95	< 0.0001	1.90	1.75, 2.06	< 0.0001
Race						
White	1					
American Indian/Alaska Native	0.93	0.67, 1.29	0.6695	0.97	0.63, 1.50	0.9034
Black	1.26	1.16, 1.36	< 0.0001	1.44	1.29, 1.61	< 0.0001
Asian or Pacific Islanders	0.88	0.79, 0.97	0.0137	0.84	0.74, 0.97	0.0141
Primary site						
Right colon	1					
Left colon	0.72	0.68, 0.77	< 0.0001	0.79	0.73, 0.86	< 0.0001
Pathology						
Adenocarcinoma	1					
Mucinous adenocarcinoma	1.21	1.09, 1.33	0.0002	1.08	0.94, 1.23	0.2915
Signet ring cell carcinoma	3.12	2.58, 3.76	< 0.0001	2.46	1.72, 3.52	< 0.0001
Degree of differentiation						
Well	1					
Moderately	1.15	0.99, 1.34	0.072	1.07	0.89, 1.30	0.4765
Poorly	1.69	1.45, 1.99	< 0.0001	1.24	1.01, 1.53	0.0383
Undifferentiated	2.06	1.70, 2.50	< 0.0001	1.39	1.07, 1.82	0.0152
pT stage						
T1	1					
T2	1.26	0.98, 1.62	0.0762	1.15	0.86, 1.53	0.355
T3	2.17	1.74, 2.71	< 0.0001	1.82	1.40, 2.35	< 0.0001
T4	4.06	3.24, 5.09	< 0.0001	3.40	2.60, 4.44	< 0.0001
pN stage						
N1a	1					
N1b	1.31	1.21, 1.42	< 0.0001	1.36	1.23, 1.51	< 0.0001
N1c	1.41	1.19, 1.67	< 0.0001	0.94	0.74, 1.21	0.6483
N2a	1.66	1.52, 1.81	< 0.0001	1.71	1.52, 1.92	< 0.0001
N2b	2.54	2.32, 2.78	< 0.0001	2.62	2.30, 2.98	< 0.0001
Tumor size (cm)						
< 5	1					
≥ 5	1.25	1.18, 1.33	< 0.0001	0.94	0.86, 1.02	0.1221
CEA						
Negative	1					
Positive	1.64	1.55, 1.74	< 0.0001	1.53	1.41, 1.66	< 0.0001
Nerve invasion						
no	1					
yes	1.53	1.42, 1.65	< 0.0001	1.27	1.14, 1.41	< 0.0001
Tumor deposits						
No	1					
≤ 4	1.37	1.26, 1.48	< 0.0001	1.24	1.10, 1.41	0.0007
> 4	2.67	2.28, 3.14	< 0.0001	2.48	1.87, 3.29	< 0.0001

Chemotherapy						
No/Unknown	1					
Yes	0.45	0.42, 0.47	< 0.0001	0.40	0.37, 0.44	< 0.0001

than those without TDs (TDs- vs. TDs ≤ 4 vs. TDs > 4: 85.4% vs. 92.76% vs. 97.24%, P < 0.001). Regarding the N stage, the N1 stage (N1a, N1b, N1c) constituted the primary phase in TDs- and TDs ≤ 4, accounting for 64.26% and 68.17%, respectively. Conversely, the main phase shifted to the N2 stage (N2a, N2b) in cases of TDs > 4, accounting for 62.31% (P < 0.001). As the number of TDs increased, the scale of CEA positivity and nerve invasion gradually increased (CEA positivity: 40.04% vs. 44.28% vs. 50.00%; nerve invasion: 14.34% vs. 23.95% vs. 38.98%).

The median follow-up time in this study was 53.0 months (range 1.0-107.0 months). Overall, 4376 (33.91%, n = 12904) patients died by the final follow-up.

Identification of independent prognostic factors for overall survival in patients with stage III colon cancer

Univariate and multivariate analyses were performed to evaluate the predictive differences in OS among patients with stage III CC (**Table 2**). In addition to the number of TDs, other significant prognostic factors included sex, age, race, primary tumor site, pathological type, histological grade, T stage, N stage, CEA levels, nerve invasion, and chemotherapy.

Differences in overall survival in patients with stage III colon cancer with different lymph node stages and tumor deposits

When ignoring the number of TDs, the 5-year overall survival rate of the N1a stage was 76.48%, constituting the longest survival time. Subsequently, the Kaplan-Meier curves reveal no survival difference between N1b and N1c (69.57% vs. 66.28%), indicating that the survival of patients with TDs and stage II CC is similar to that of patients with stage III CC without LNM. Finally, the 5-year overall survival of the N2a and N2b stages were 63.03% and 50.25% (P < 0.0001) (**Figure 3A**).

Regarding the TDs status, the survival prognosis of the TDs+ was worse than that of the TDs- (P < 0.0001) (**Figure 3B**). We performed further categorization based on the best cutoff point of TDs, and the OS of TDs- was the best, followed by TDs ≤ 4, and TDs > 4 was the worst (P < 0.0001) (**Figure 3C**). The Kaplan-Meier curve showed that the OS of patients with stage III CC was worse with increased TDs.

Survival analysis of varying numbers of tumor deposits in patients with stage III colon cancer

In stage N0, the survival prognosis of TDs ≤ 4 (N0TDs ≤ 4) was better than that of TDs > 4 (N0TDs > 4) (P < 0.05) (**Figure 4C**). Among patients with existing LNM (N1a, N1b, N2a, N2b), those with TDs- (N1-2TDs-) had the longest survival, followed by those with TDs ≤ 4 (N1-2TDs ≤ 4), whereas patients with TDs > 4 (N1-2TDs > 4) had the shortest survival (P < 0.05) (**Figure 4A**, **4B**, **4D**, **4E**).

The Kaplan-Meier curve indicated that the OS of patients with stage III CC decreases gradually with an increasing number of LNMs and TDs, suggesting significant differences in the survival prognosis among different TDs quantities in the same pN stage (**Table 3**).

Restaging according to different lymph node stages and groups of tumor deposits to develop a new pN stage

The 1-year, 3-year, and 5-year survival rates for patients with stage III CC when integrating the pN stages with the TDs groups are shown in **Table 3**. After interpreting the aforementioned survival, we performed restaging when similar survival prognoses were observed (**Table 4**).

The 1-year, 3-year, and 5-year OS rates in N1aTDs- were 94.80%, 85.46%, and 77.56%, respectively, representing the best survival prognoses among all groups. The Kaplan-Meier curve demonstrated that N0TDs ≤ 4, N1aTDs ≤ 4, and N1bTDs- had similar OS (P = 0.079) (**Figure 5A**). The 1-year, 3-year, and 5-year OS rates in N0TDs > 4 were 88.89%, 51.85%, and 41.48%, respectively. The 1-year, 3-year, and 5-year OS rates in N1bTDs ≤ 4 were 91.93%, 73.55%, and 58.90%, slightly lower than those

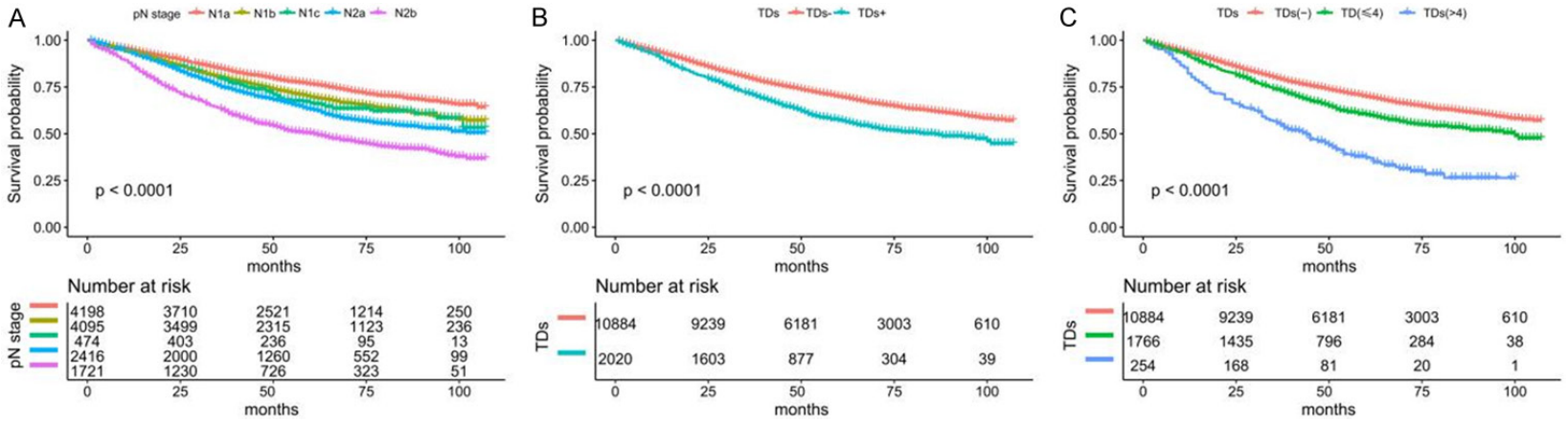

Figure 3. Survival prognosis of lymph node stage and tumor deposits in patients with stage III colon cancer. A. The overall survival (OS) of patients with different pN stages. B. The OS of patients with TDs and without TDs. C. The OS of patients with TDs-, TDs ≤ 4, and TDs > 4.

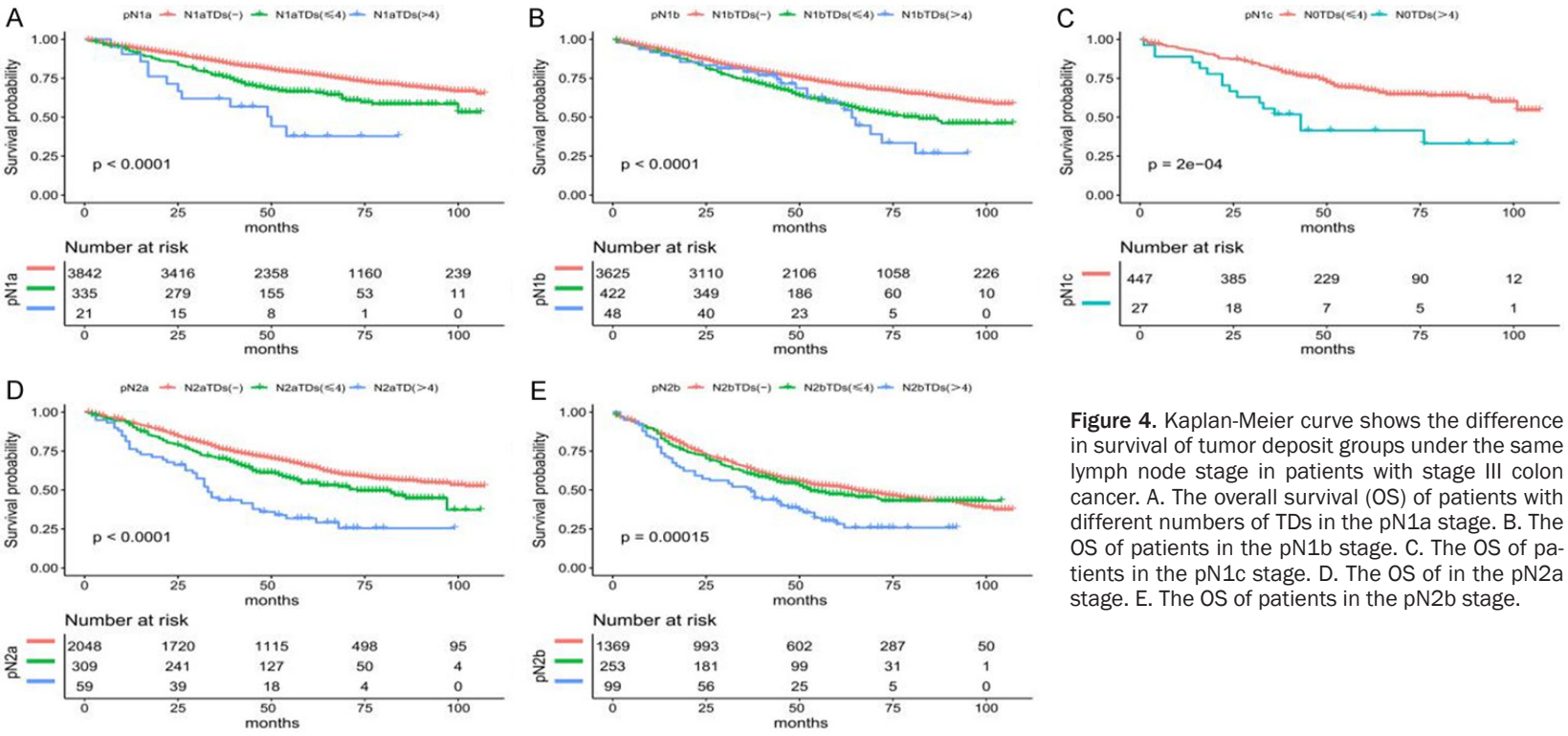

Figure 4. Kaplan-Meier curve shows the difference in survival of tumor deposit groups under the same lymph node stage in patients with stage III colon cancer. A. The overall survival (OS) of patients with different numbers of TDs in the pN1a stage. B. The OS of patients in the pN1b stage. C. The OS of patients in the pN1c stage. D. The OS of in the pN2a stage. E. The OS of patients in the pN2b stage.

Table 3. 1-, 3-, and 5-year overall survival rate and median survival time after reorganization according to tumor deposits and lymph node stage

III stage	1-year survival (%)	3-year survival (%)	5-year survival (%)	mOS (months)
pN0				
N0TDs ≤ 4	93.46	80.93	67.77	NA (101, NA)
N0TDs > 4	88.89	51.85	41.48	43 (26, NA)
pN1a				
N1aTDs-	94.80	85.46	77.56	NA
N1aTDs ≤ 4	92.47	76.83	66.39	NA (100, NA)
N1aTDs > 4	90.48	61.90	37.83	50 (25, NA)
pN1b				
N1bTDs-	93.83	80.87	70.89	NA
N1bTDs ≤ 4	91.93	73.55	58.90	82 (66, NA)
N1bTDs > 4	91.67	79.05	59.08	64 (52, NA)
pN2a				
N2aTDs-	93.63	76.48	65.17	NA (102, NA)
N2aTDs ≤ 4	91.87	70.09	54.42	73 (58, NA)
N2aTDs > 4	76.27	43.49	31.81	33 (29, 51)
pN2b				
N2bTDs-	86.88	64.25	52.24	65 (58, 73)
N2bTDs ≤ 4	86.12	60.59	47.30	53 (44, NA)
N2bTDs > 4	77.62	51.07	28.16	37 (24, 47)

Table 4. Re-staging consists of tumor deposits and lymph node staging

The new pathology lymph node staging (npN)	
N1a	N1aTDs-
N1b	N0TDs ≤ 4, N1aTDs ≤ 4, N1bTDs-
N1c	N0TDs > 4
N2a	N1bTDs ≤ 4, N2aTDs-
N2b	N2aTDs ≤ 4, N2bTDs-
N2c	N1aTDs > 4, N1bTDs > 4, N2bTDs ≤ 4
clinical metastasis	N2aTDs > 4, N2bTDs > 4

of N2aTDs- (93.63%, 76.48%, and 65.17%). The Kaplan-Meier survival curve indicated a statistically significant survival difference (P = 0.014) (**Figure 5B**). No significant difference was observed between N2aTDs ≤ 4 and N2bTDs- (P = 0.11) (**Figure 5C**) or among N1aTDs > 4, N1bTDs > 4, and N2bTDs ≤ 4 (P = 0.61) (**Figure 5D**). The median overall survival rates (mOS) of N2aTDs > 4 and N2bTDs > 4 were 33 and 37 months, respectively, constituting the shortest rates among all groups (P = 0.93) (**Figure 5E**).

After the re-staging, we compared the TDs- and TDs+ in the new pathology lymph node stage. We found no significant difference in survival between the TDs- and the TDs+ in npN1b and npN2b (P = 0.058 and P = 0.11) (**Figure 6A**, **6C**). The survival of TDs+ was slightly lower than that of TDs- in the npN2a stage (P = 0.014) (**Figure 6B**).

Discussion

In this study, we investigated the predictive value of TDs and their relationship with LNM in stage III CC using the SEER database. Our findings demonstrated that TDs independently influenced the survival of patients with stage III CC, based on rigorous univariate and multivariate Cox regression analysis. Notably, N1c showed slightly worse survival than N1a and overlaps with N1b, supporting the classification of patients with stage II CC without LNM but with TDs+ as stage III, as advocated by Belt, Al Sahaf et al. [15-18]. Their conclusions also highlight the presence of TDs as a predictor of poorer survival.

Our study determined the optimal cutoff point for TDs and found that the number of TDs independently predicted prognosis in patients with stage III CC. By combining the pN stage and TDs, we observed that increasing TDs at the same pN stage corresponded to a worse prognosis in stage III CC. These findings are consistent with those of Bai et al. [19], who identified a cutoff point of 1 and 5 for TDs. Patients with TDs ≥ 5 had the worst survival, followed by those in the TDs 2-4 groups, whereas patients with TDs = 1 demonstrated a better prognosis.

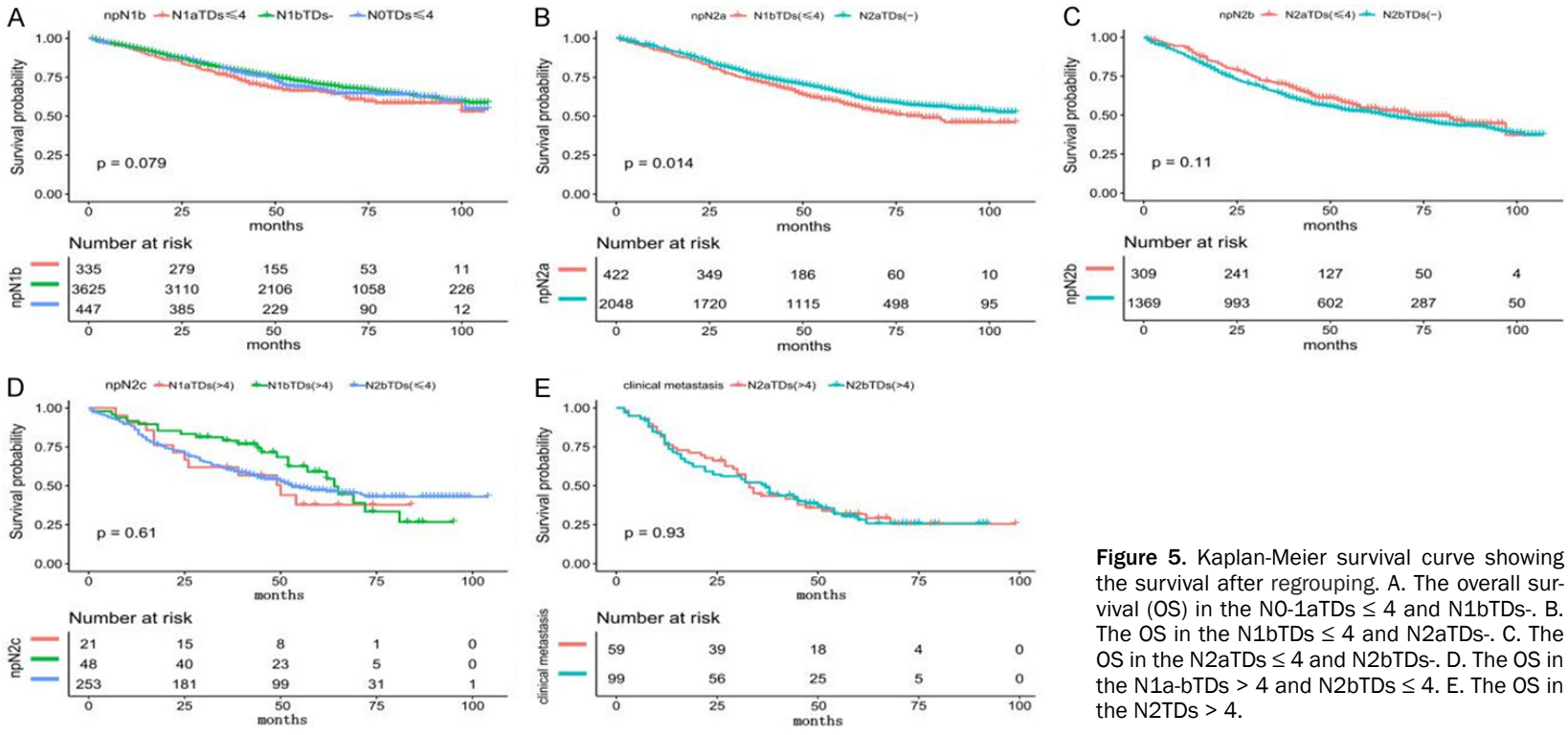

Figure 5. Kaplan-Meier survival curve showing the survival after regrouping. A. The overall survival (OS) in the N0-1aTDs ≤ 4 and N1bTDs-. B. The OS in the N1bTDs ≤ 4 and N2aTDs-. C. The OS in the N2aTDs ≤ 4 and N2bTDs-. D. The OS in the N1a-bTDs > 4 and N2bTDs ≤ 4. E. The OS in the N2TDs > 4.

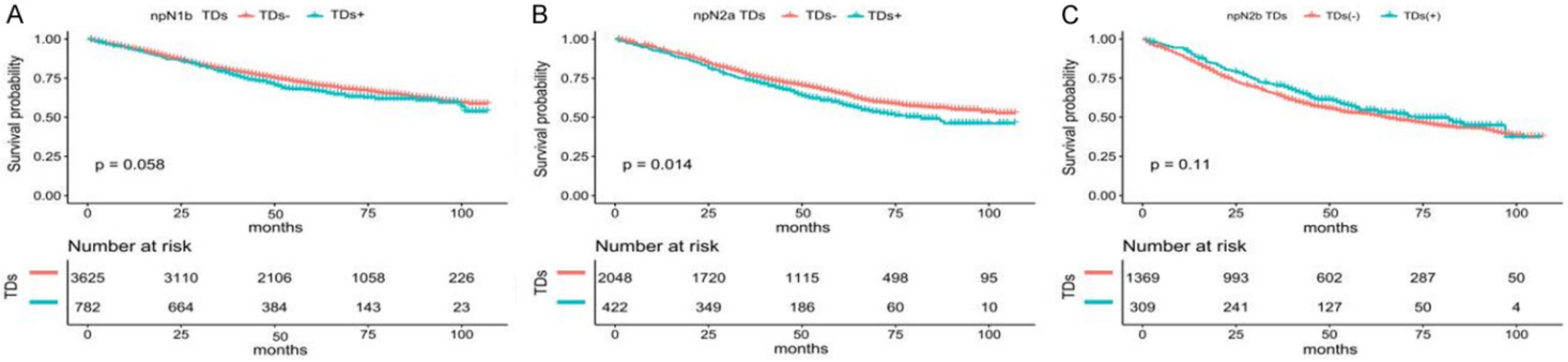

Figure 6. Difference in survival of tumor deposits after re-staging. A. The overall survival (OS) of patients with TDs and without TDs in the npN1b stage. B. The OS of patients with TDs and without TDs in the npN2a stage. C. The OS of patients with TDs and without TDs in the npN2b stage.

A previous study [20] determined that the presence of TDs was an independent adverse prognostic factor in patients with CRC. However, their findings showed that the number of TDs had no association with OS. Another study [21] analyzed 146 patients with simultaneous CRC and liver metastases who underwent R0 resection. This study found a significant correlation between TDs and shorter disease-free survival (DFS). However, the patients in the aforementioned study were in the TNM stage IV or had liver metastasis, which could mask the impact of TDs owing to adverse factors associated with distant metastasis, rendering the number of TDs irrelevant to survival prognosis.

Post-hoc analysis of two phase 3 clinical trials [22, 23] revealed a linear and negative correlation between the number of TDs and DFS and OS. Upon combining the TDs and LNM, some patients were restaged from the pN1 stage to the pN2 stage. No differences in DFS were observed between patients re-staged to npN2 and those originally staged to pN2. Song and Pei et al's. [24, 25] conclusion aligned with this post-hoc analysis, suggesting that integrating TDs into LNM to form the npN stage has a higher prediction ability than the pN stage. Importantly, Song's research found no significant prognosis difference between TDs+ and TDs- in the same npN stage. The findings of Li [26] and Ueno [27] also support that incorporating the number of TDs into the number of LNM can enhance prognosis accuracy. However, Liu [20] and the results of our study indicate that the number of TDs and the number of LNMs do not have a one-to-one correspondence. Consequently, our study first grouped TDs based on the impact on survival in patients with stage III CC before combining them with pN staging. We proposed an adjustment of pN staging following the seventh edition of the TNM guidelines. After regrouping TDs and LNM, all the npN stages did not significantly differ in OS, except for npN2a. Survival of TDs- was equal to that of TDs+ in the same npN stage. Therefore, we believe it is feasible to include TDs in the LNM approach.

Tong [28] analyzed 1541 patients with stage I-IV CRC using subgroup analysis and found that the 5-year OS of T3N2bM0TD+ was significantly lower than that of T3N2bM0TD- (7.8% vs. 46.9%; P = 0.012), which was similar to that of stage IV (7.8% vs. 9.9%; P = 0.730). Furthermore, the 5-year OS of T4N2bM0 was 0%, with or without TDs. Lino-Silva [10] found that the average OS of patients complicated with TDs+ in stage I-III was 69.3 months, which was different from that of stage III (110.5 months), stage II (135.7 months), and stage I (114.9 months) and similar to that of stage IV (64.6 months), and recommended to treat these patients as clinical IV-TD+.

Chemotherapy combined with targeted therapy has significantly improved the survival of patients with advanced CRC, and the mOS increased from 13 to nearly 30 months. Among patients with advanced CRC where surgery is feasible, those treated with surgery and systemic treatment can achieve a 5-year OS of 25-55%, with a mOS of 31-64.7 months [29-34]. Importantly, the OS of N2aTDs > 4 and N2bTDs > 4 was significantly lower than that of N2TDs-; the 5-year OS was 31.81% and 28.16%, with mOS of 33 and 37 months, respectively. Compared with simply adding the number of TDs to LNM in other research, our study initially grouped the TDs before combining them with the pN stage. This approach revealed that patients with N2TDs > 4 had a worse prognosis than those with distant metastasis. Therefore, we propose the classification of clinical metastasis when N2TDs > 4, and more active treatments are recommended to improve the survival of patients at this stage.

Our study had notable strengths. First, we used SEER data, which offers a large sample of evidence-based medicine, reduces potential biases arising from limited sample sizes, and enhances clinical value. Second, our study improves the accuracy of prognostic evaluation in patients with stage III colon cancer by incorporating the number of TDs into LNM. Notably, our findings demonstrated that patients with N2TDs > 4 exhibited the worst prognosis, suggesting its potential classification as clinically distant metastasis.

However, our study also had limitations. First, this was a retrospective study, and inherent selection biases may exist in the inclusion process, exclusion criteria, and variable screening. Second, the SEER database lacks key factors affecting survival outcomes, such as surgical approach, treatment regimens, and genetic mutations. Finally, the small sample size of

patients in the TDs > 4 groups (n = 254) may introduce bias in the analysis of survival prognosis. Future studies should incorporate multicenter data to further validate our conclusions.

In summary, the number of TDs had predictive value for the prognosis of patients with stage III CC, and the presence and number of TDs should be considered to guide treatment decisions. Finally, it is feasible to include TDs in the LNM. We propose the classification of clinical metastasis when the staging diagnosis is N2TDs > 4.

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Disclosure of conflict of interest

None.

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