Original Article

The potential role of tumor deposits in the prognosis and TNM staging for colorectal cancer

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Background: Tumor deposits (TDs) can impact proper staging of cancer, which is crucial for discussing prognosis and determining the appropriate treatment plan. Our study aimed to correlate how TDs influence prognosis of resected colorectal cancer (CRC) and how to optimize tumor-node-metastasis (TNM) staging with respect to TDs for clinical decision-making.

Methods: A retrospective analysis was performed on 611 patients with CRC treated in Jiangsu Cancer Hospital from January 1, 2010 to December 31, 2020 among whom 197 had TDs. The influence and distribution characteristics of TDs on the median overall survival (mOS) of patients with CRC were quantitatively and qualitatively analyzed, and the differences in mOS between different subgroups were also analyzed.

Results: Patients with TDs had a shorter mOS (only 60.3±3.9 months) than did patients without TDs. TDs had a more significant association with the survival of M0 patients, and there were significant differences in the prognosis of M0 patients with stage pN0 and pN1c or stage pN0, pN1, and pN2. The combination of lymph node metastases (LNMs) and TDs was associated with mOS. The proportion of rectal cancer, papillary tissue type, and nerve invasion was higher in the TD-positive group, and proportion of metastasis to the brain, spleen, lung, and bone in this groups was also higher. Subgroup analysis showed that the degree of tumor differentiation, the depth of tumor invasion, vascular invasion, nerve invasion, liver metastasis, lung metastasis, bone metastasis, peritoneal metastasis, ovarian metastasis, pelvic and abdominal metastasis, and the number of distant metastases were associated with the prognosis of patients with CRC.

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Conclusions: TDs were closely correlated with the poor prognosis of patients with CRC. Greater attention should be paid to improving the quality of pathological reports in clinical decision-making and the comprehensive assessment of patients' baseline characteristics so that accurate prognosis and corresponding treatment plan can be properly communicated with patients.

Keywords: Colorectal cancer (CRC); tumor deposits (TDs); tumor-node-metastasis staging (TNM staging)

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Introduction

Colorectal cancer (CRC) is the third most prevalent tumor globally and the second leading cause of cancer-related death, and the incidence of CRC ranks the third and fourth in male and female malignant tumors, respectively (1,2).

In 1967, the American Joint Committee on Cancer (AJCC) and the International Alliance Against Cancer (UICC) published the first edition of the tumor-node-metastasis (TNM) classification, which is based on three indicators: tumor (T), regional lymph nodes (N), and metastasis (M) (3-6), to determine the extent of cancer and facilitate prognostication and clinical decision-making (7). The concept of tumor deposits (TDs) was first proposed by Gabriel *et al.* in 1935 (8) and is defined as focal aggregates of adenocarcinoma tissue located in the fat surrounding the colon or rectum that are separated from the primary tumor and are independent of the lymph nodes. This definition is being constantly updated and revised as research continues. In the absence of lymph node metastases (LNMs), positive TDs were classified into the new N1c category as follows: if LNM is present, the TDs are classified strictly as N, while patients who are TD-positive and LNM negative are reclassified to a more advanced stage regardless of pT classification (9,10). The 8th edition of the AJCC TNM staging guide was published in 2017 and did not modify the definitions and classifications of TDs proposed in the 7th edition (11,12). However, this method and its ability to predict patient prognosis remain controversial. Some studies, including several recent meta-analyses, have suggested that considering TDs only in the absence of LNM will lead to the loss of valuable prognostic information and that combining the number of TDs to the number of LNMs may be more relevant to N classification (13-15). The postmortem analysis conducted in the 2020 International Duration Evaluation of Adjuvant Chemotherapy (IDEA) France phase III trial (PRODIGE-GERCOR) corroborates this assertion (16).

The most recent TNM staging method remains insufficient for the classification of patients with both TDs and LNM, and the influence of the number of TDs on the prognosis requires further assessment and discussion.

The purpose of this study was thus to evaluate the association of TDs with the prognosis and TNM

Highlight box

Key findings

- In this study on colorectal cancer (CRC), patients with tumor deposits (TDs) had a shorter median overall survival (mOS) than did patients without TDs. TDs had a more significant association with the survival of patients with M0, among whom there were significant differences in prognosis between those with stage pN0 and pN1c and between those with stage pN0, pN1, and pN2. The combination of lymph node metastases (LNMs) and TDs was associated with mOS. The proportion of rectal cancer, papillary tissue type, and nerve invasion was higher in the TD-positive group, and proportion of metastasis of brain, spleen, lung, and bone in this group was also higher.

What is known and what is new?

- Only in the absence of LNM will TDs lead to the loss of valuable prognostic information, and adding the number of TDs to the number of LNMs may be clinically meaningful for N classification.
- We additionally found that the presence of TD was significantly negatively associated with the prognosis of patients with CRC. The clinical features, pathological types, and number of distant metastases of patients were not only correlated with TDs but were significantly associated with the long-term prognosis of patients.

What is the implication, and what should change now?

- A comprehensive assessment of a patient's basic condition, especially the presence of TDs, is crucial for improving prognosis and extending long-term survival in cancer management.

stage of patients with CRC in the real world through retrospective analysis and to observe and analyze the clinical characteristics, pathological types, and distant metastases of patients with TDs. The correlations of clinical features, pathological types, distant metastases, and staging on long-term prognosis were also examined. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-786/rc)

Methods

Patient screening

In this retrospective clinical study, the data of patients with CRC admitted to The Affiliated Cancer Hospital of Nanjing Medical University (Jiangsu Cancer Hospital) from January 1, 2010 to December 31, 2020 were collected. After screening, a total of 611 patients met the inclusion criteria and were included in the study. The inclusion criteria were as follows: (I) age above 18 years; (II) CRC confirmed by clear cytological or pathological evidence; (III) Easter Cooperative Ontology Group (ECOG) performance status scores of 0–2; (IV) expected survival ≥2 months; and (V) no serious diseases of the heart, liver, kidney, or other important organs. Meanwhile, the exclusion criteria were as follow: (I) death within 30 days after surgery; (II) multiple adenocarcinomas of the colon and rectum; (III) synchronous or heterogeneous multiple primary tumors; (IV) administration of neoadjuvant therapy before surgical treatment; (V) incomplete pathological data; and (VI) lost to follow up during the study period. The final follow-up was completed on December 31, 2020; 39 patients were lost to follow up, and the compliance rate was 94%. The mean evaluation survival time was 73.889±1.239 months, and the median survival time was 81.400±1.580 months [95% confidence interval (CI): 78.303–84.497].

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Institutional Ethics Review Committee of The Affiliated Cancer Hospital of Nanjing Medical University (Jiangsu Cancer Hospital) (No. 2020-037) before the study was initiated. Patients' basic information and personal privacy were protected during the study. This study is a retrospective study, and individual consent was not required.

Data collection

The following data were collected: age, sex, body mass index (BMI), smoking history, diabetes history, date of diagnosis, date of death, date of follow-up, primary tumor location, tumor size, type of remains, histological type, differentiation grade, depth of invasion, venous invasion, vascular invasion, lymph node invasion, number of lymph nodes detected, number of TDs, number of metastases, and site of metastasis.

The 8th edition of the TNM staging system of the UICC and the AJCC was used to stage patients. The presence of 1 and 2–3 regional LNMs was considered N1a and N1b, respectively; when both TDs and regional LNM are present, staging is determined based on the status of the regional LNM, this practice is because LNM usually indicates the extent of disease progression; the presence of TD but no regional LNMs in subserous, mesenteric, nonperitoneally covered tissues around the colon or rectum was considered N1c; meanwhile, the presence of 4–6 and 7 or more regional LNMs was considered N2a and N2b, respectively.

M1 stage was subdivided into M1a (distant metastasis limited to a single organ), M1a (distant metastasis distributed to more than one organ), and M1c (peritoneal metastasis). Tumors originating from the cecum to the sigmoid colon were considered to colon cancer and divided into left or right colon cancers depending on the splenic flexure. Tumors located at the junction of the rectum or rectosigmoid were defined as rectal cancer.

Pathological specimens obtained from surgery or needle biopsy were fixed in formalin, cut into sections with a thickness of 5 mm, and stained with hematoxylin and eosin. At least two pathologists independently assessed the maximum depth of infiltration, pathological types, and number of TDs in the pathological sections, and the third pathologist performed the final diagnosis. If there was a difference in diagnosis, the three pathologists jointly reviewed the slides and arrived at a consensus. Over our study's 10-year period, 21 pathologists participated in the evaluation.

Prognostic evaluation

Patients diagnosed with CRC were reviewed regularly, and tumor evaluation was performed every 1–2 months during

radiotherapy and medical oncology treatment. Tumor evaluation was performed every 3 months for the first 2 years after the end of treatment. Tumor evaluations were performed every 6 months after 2 years of stable disease (SD) before the end of treatment. Tumor evaluation was performed according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, the curative effects were classified as complete response (CR), partial response (PR), SD, and progressive disease (PD). Symptoms were assessed according to changes in symptoms associated with lung cancer. Overall survival (OS) was considered to be the time from the initial diagnosis of CRC to death from any cause, including death from nontumor factors. The receiver operating characteristic (ROC) curve method was used to evaluate the performance of a diagnostic test by plotting the true positive rate (sensitivity) against the false positive rate (1–specificity) across different threshold values. The curve helps to determine the optimal threshold value by analyzing the trade-offs between sensitivity and specificity. Telephone calls or clinical visits were used to follow up patients.

Statistical analysis

SPSS 23 software (IBM Corp., Armonk, NY, USA) was used for statistical processing, and P<0.05 indicated a statistically significant difference. The Kaplan-Meier method was used for survival analysis, the Cox proportional risk model was used for multivariate analysis, the *t*-test and linear regression equation were used to analyze the mean and correlation of continuous variables, and the chi-square test was used for the comparative analysis of categorical variables, ratios, or constituent ratios.

Results

Basic information

The data of 611 patients with CRC admitted to The Affiliated Cancer Hospital of Nanjing Medical University (Jiangsu Cancer Hospital) from January 1, 2010 to December 31, 2020 were retrospectively collected. There were 418 males (68.41%) and 193 females (31.59%), the ECOG scores were all 0–2, and the patient age ranged from 23 to 96 years old, with an average age of 61.2 years old. There were 145 former smokers, 54 patients with diabetes, 288 patients with rectal cancer, and 204 patients with colon cancer. The portion of patients with ulcerative gross type, tubular papillary histological type, moderately differentiated pathological type, a tumor size less than 5 cm, and tumor infiltration into the subserous membrane was largest. There were 86 patients with nerve invasion, and 63 patients with vascular invasion. Among metastatic sites, lung metastases were the most common (18.00%), followed by bone metastases (10.97%), peritoneal metastases (5.07%), brain metastases (4.58%), adrenal metastases (0.65%), and ovarian metastases (1.15%) (*Table 1*, *Figure 1*). TDs were detected in the pathological specimens of 197 patients, the positive rate was about 32.24%, and the average number of TDs was 2.6. LNMs were observed in the pathological specimens of 208 patients, the average number of LNMs observed was 3.2, the average number of LNMs detected per patient was 8.2, and the average rate of LNMs detected was 27.0%.

TNM staging and association of TDs with prognosis

Overall, the difference in the prognosis between patients with stage I, II, III, and IV disease was significantly different (P=0.03; *Figure 2A*). However, we observed that the OS of stage II patients seemed to be longer than that of stage I patients, even if the difference was not statistically significant, which is inconsistent with previous research results. There was no significant difference in prognosis between patients with stage IIa and IIc disease (P=0.14; *Figure 2B*) (there were no stage IIb patients) or between patients with stage IIIa, IIIb, and IIIc disease (P=0.11; *Figure 2C*). However, among patients with stage IV disease, there were significant and statistically significant differences in prognosis between patients with IVa, IVb, and IVc disease (P<0.001, *Figure 2D*). The overall prognosis of patients with TDs was worse than those without TDs, and the median OS (mOS) was shorter, at only 60.3±3.9 months (P=0.02; *Figure 3A*). Among the 260 patients with M0, the presence or absence of TDs was significantly associated with prognosis (P=0.02; *Figure 3B*); meanwhile, among the 351 patients with M1, the presence or absence of TDs was not associated with prognosis (P=0.84; *Figure 3C*).

Subsequently, we evaluated the differences in OS between patients with different N stages within the M0 and M1 groups. In patients with M0, there was a significant difference in prognosis between the pN0 and pN1c subgroups for any pT category (P=0.04; *Figure 4A*), and there was a significant difference between the pN0, pN1, and pN2 subgroups (P=0.03; *Figure 4B*). However, there was no significant difference in prognosis between the pN1a, pN1b, and pN1c subgroups (P=0.35; *Figure 4C*). When the number and staging of TDs was combined with

Table 1 Baseline and mOS of patients with colorectal cancer

Items	All			
	n (%)	mOS (95% CI) (months)	Standard error	P value
Sex				0.72
Male	418 (68.41)	63.000 (55.909, 70.091)	3.618	
Female	193 (31.59)	61.033 (56.249, 65.818)	2.441	
Age (years)				0.47
<65	361 (59.08)	62.500 (56.728, 68.727)	2.945	
≥65	250 (40.92)	59.633 (54.226, 65.041)	2.759	
BMI (kg/m^2)				0.99
<18.5	30 (4.91)	63.400 (58.688, 68.112)	2.404	
≥18.5, <24	207 (33.88)	56.833 (47.939, 65.727)	4.538	
≥24	152 (24.88)	57.167 (46.740, 67.593)	5.320	
Unknown	222 (36.33)	–	–	
Smoking history				0.90
Negative	466 (76.27)	60.333 (55.855, 64.811)	2.285	
Positive	145 (23.73)	63.433 (55.292, 71.575)	4.154	
Diabetes				0.39
Negative	557 (91.16)	62.500 (58.000, 67.000)	2.296	
Positive	54 (8.84)	56.300 (49.509, 63.091)	3.465	
Tumor location				0.050
Rectum	288 (47.14)	65.167 (61.437, 68.897)	1.903	
Colon	204 (33.39)	56.267 (52.420, 60.113)	1.962	
Others	119 (19.48)	58.033 (50.836, 65.231)	3.672	
General morphology				0.79
Ulcerative type	272 (44.52)	59.200 (53.910, 64.490)	2.699	
Protruded type	62 (10.15)	61.733 (42.864, 80.603)	9.627	
Infiltration type	44 (7.20)	55.633 (45.060, 66.207)	5.395	
Unknown	233 (38.13)	63.933 (58.328, 69.539)	2.860	
Histological type				0.051
Tubular	119 (19.48)	63.433 (55.003, 71.864)	4.301	
Papillary	58 (9.49)	49.400 (29.222, 69.578)	10.295	
Tubular papillary	257 (42.06)	64.067 (58.455, 69.678)	2.863	
Unknown	177 (28.97)	59.667 (53.256, 66.077)	3.271	

Table 1 (*continued*)

Table 1 (*continued*)

Items	All			
	n (%)	mOS (95% CI) (months)	Standard error	P value
Differentiation degree				0.002
Low	48 (7.86)	–	–	
Medium low	89 (14.57)	–	–	
Medium	218 (35.68)	–	–	
Medium high	15 (2.45)	–	–	
High	2 (0.33)	–	–	
Unknown	239 (39.12)	–	–	
Size (cm)				0.91
≤5	269 (44.03)	60.500 (53.091, 67.909)	3.780	
>5	103 (16.86)	61.033 (52.256, 69.811)	4.478	
Unknown	239 (39.12)	–	–	
Depth of invasion				<0.001
Submucosa (T1)	38 (6.22)	54.900 (51.943, 57.857)	1.508	
Muscularis propria (T2)	32 (5.24)	62.500 (50.304, 74.696)	6.222	
Subserosa (T3)	254 (41.57)	56.300 (50.304, 62.296)	3.059	
Splanchnic peritoneum (T4)	64 (10.47)	57.167 (50.308, 64.025)	3.499	
Unknown	223 (36.50)	65.467 (56.454, 74.480)	4.598	
The presence or absence of TDs				0.02
Negative	414 (67.76)	63.400 (58.320, 68.480)	2.592	
Positive	197 (32.24)	60.333 (52.753, 67.914)	3.867	
Nerve invasion				0.004
Negative	525 (85.92)	63.433 (60.067, 66.800)	1.718	
Positive	86 (14.08)	43.433 (30.762, 56.104)	6.465	
Vascular invasion				<0.001
Negative	548 (89.69)	63.933 (59.870, 67.997)	2.073	
Positive	63 (10.31)	40.500 (33.787, 47.213)	3.425	
Liver metastasis				<0.001
Negative	562 (91.98)	63.567 (59.850, 67.283)	1.896	
Positive	49 (8.02)	34.133 (13.847, 54.419)	10.350	
Spleen metastasis				0.33
Negative	586 (95.91)	61.733 (57.354, 66.113)	2.235	
Positive	25 (4.09)	39.833 (6.522, 73.145)	19.996	

Table 1 (*continued*)

Table 1 (*continued*)

Items	All			
	n (%)	mOS (95% CI) (months)	Standard error	P value
Lung metastasis				0.001
Negative	501 (82.00)	63.567 (59.829, 67.304)	1.907	
Positive	110 (18.00)	51.400 (45.737, 57.063)	2.889	
Bone metastasis				0.001
Negative	544 (89.03)	63.433 (59.035, 67.831)	2.244	
Positive	67 (10.97)	51.667 (31.270, 72.063)	10.406	
Peritoneum metastasis				<0.001
Negative	580 (94.93)	63.400 (59.275, 67.525)	2.105	
Positive	31 (5.07)	44.400 (36.910, 51.890)	3.821	
Ovarian metastasis				0.02
Negative	604 (98.85)	62.367 (57.989, 66.745)	2.234	
Positive	7 (1.15)	46.467 (6.316, 86.617)	20.485	
Brain metastasis				0.09
Negative	583 (95.42)	61.733 (57.235, 66.232)	2.295	
Positive	28 (4.58)	40.867 (21.334, 60.400)	9.966	
Abdominal pelvic implantation metastasis				0.007
Negative	587 (96.07)	62.367 (57.949, 66.785)	2.254	
Positive	24 (3.93)	40.467 (19.301, 61.632)	10.799	
Adrenal metastasis				0.002
Negative	607 (99.35)	61.733 (57.291, 66.175)	2.266	
Positive	4 (0.65)	38.300 (0.000, 92.285)	27.543	

mOS, median overall survival; CI, confidence interval; BMI, body mass index; TDs, tumor deposits.

lymph node invasion, 7 patients with M0 were upgraded from stage N1 to stage N2, and the difference in prognosis between the pN0, pN1, and pN2 subgroups after restaging remained significant (P=0.03; *Table 2*); however, there was no significant difference in prognosis between the pN1a and pN1b subgroups with new staging (P=0.46; *Table 2*). The mOS of patients with M0 who had been restaged to N2 stage was nonsignificantly longer than that of those who remained in the pN1 stage and pN2 stage (*Table 3*). The association of the number of LNMs, positive rate of LNMs (number of LNMs/number of detected lymph nodes × 100%), number of TDs, and number of LNMs on patient prognosis was analyzed. The ROC curve was used to determine the critical value (*Table 4*), and the score of LNMs, TDs, and LNM + TDs were all less than 1. Kaplan-Meier survival analysis indicated that a positive rate of LNM greater than 17.143% was no significantly associated with the mOS of patients with M0 (58.867±13.197 *vs.* 67.9±9.274 months; P=0.91).

Among patients with M1, there was no significant difference in prognosis between the pN0 and pN1c subgroups for any pT category (P=0.58; *Figure 4D*); between the pN0, pN1, and pN2 subgroups (P=0.12; *Figure 4E*); or between the pN1a, pN1b, and pN1c subgroups (P=0.36; *Figure 4F*). According to the combination of counting and staging of TDs and lymph node invasion, 20 patients with

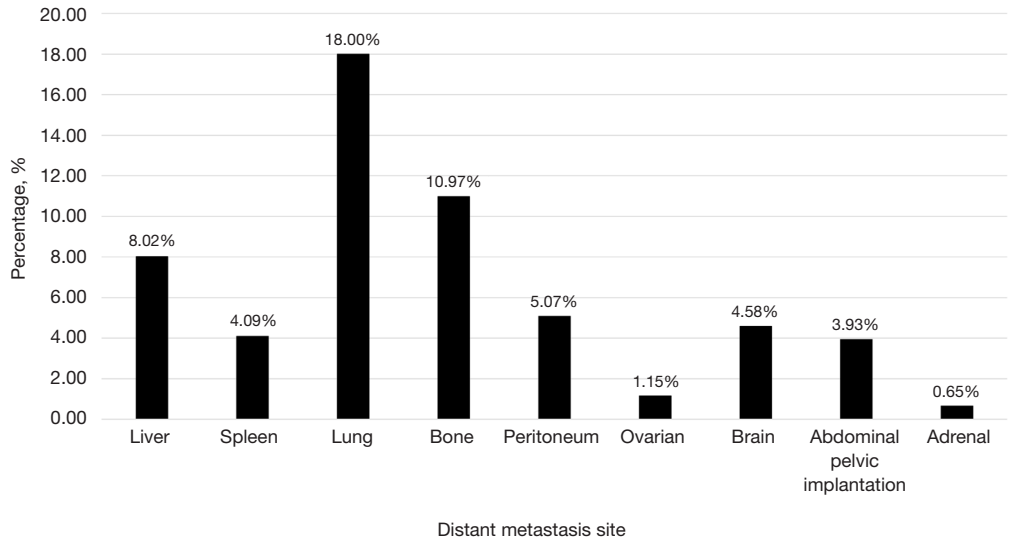

Figure 1 Distant metastasis of patients with colorectal cancer.

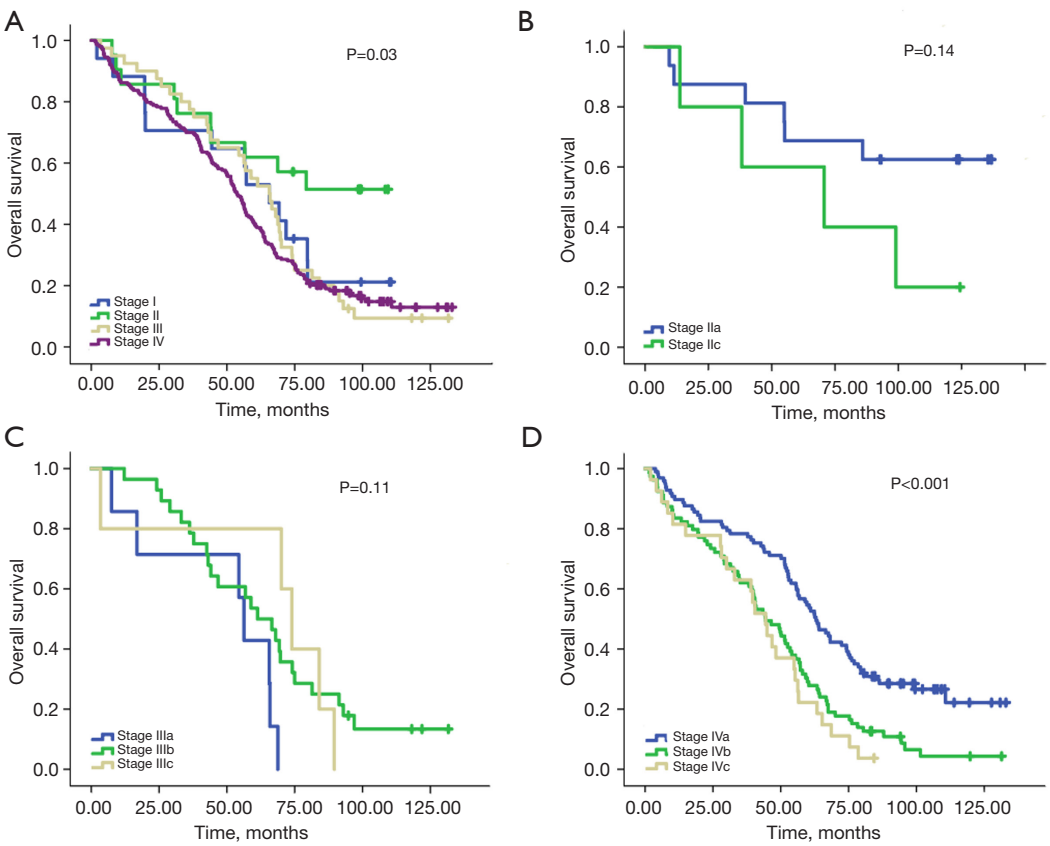

Figure 2 The Kaplan-Meier analysis of patients with colorectal cancer with different stages. Overall survival of different stages (A), stage II (B), stage III (C) and stage IV (D) patients.

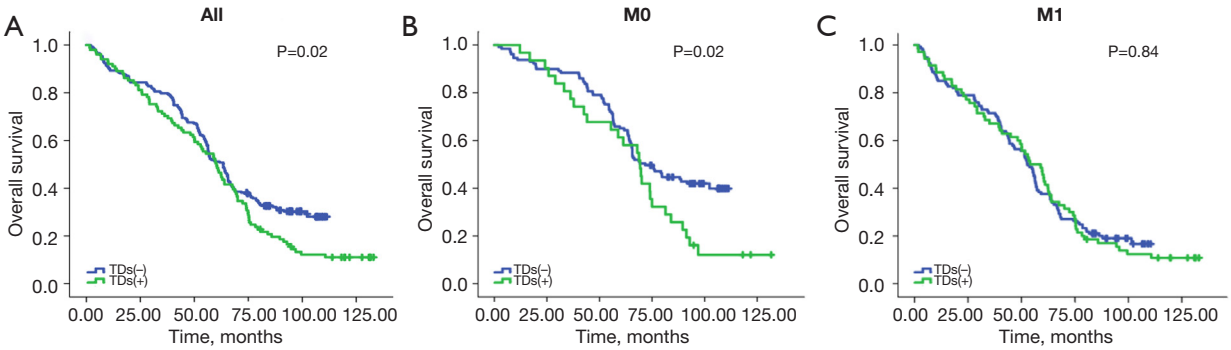

Figure 3 The Kaplan-Meier analysis of patients with colorectal cancer with and without TDs. Overall survival of all patients with TDs and without TDs (A); in M0 patients, the presence or absence of TDs (B); in patients with M1, the presence or absence of TDs (C). TDs, tumor deposits.

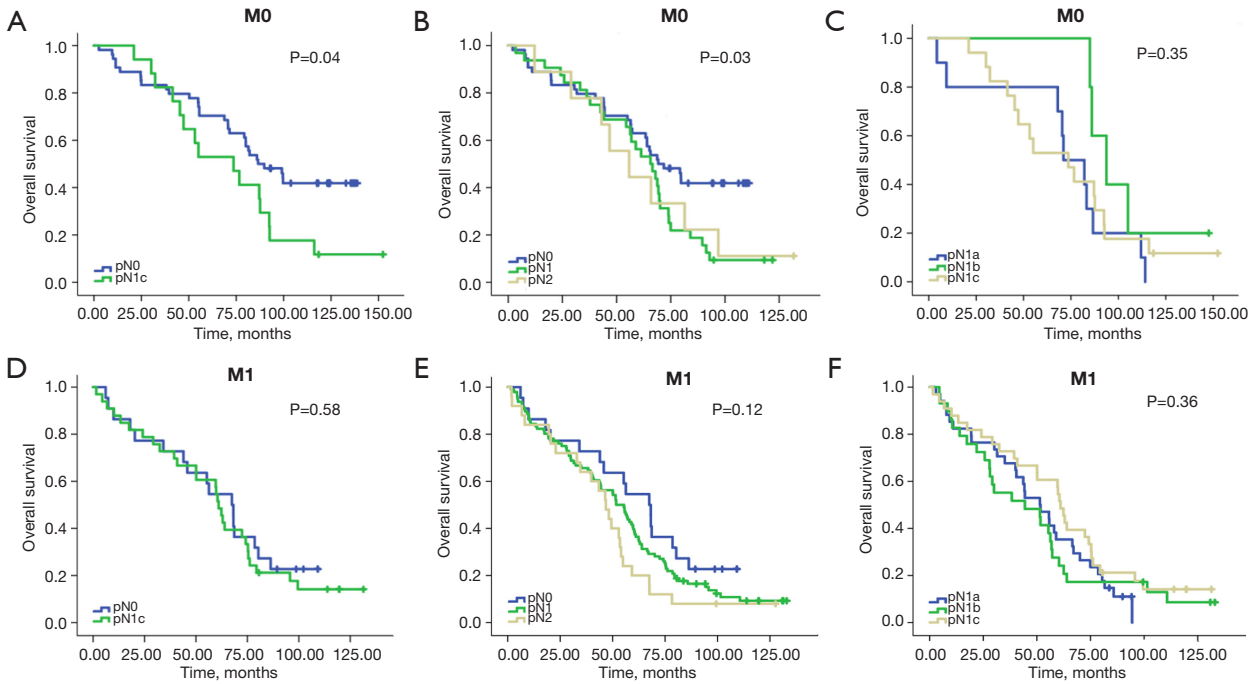

Figure 4 The Kaplan-Meier analysis of patients with colorectal cancer with different N stages. In M0 patients, overall survival between pN0 and pN1c patients in any pT category (A); overall survival among patients in the pN0, pN1, and pN2 categories (B); overall survival among patients in pN1a, pN1b, and pN1c subclasses (C). In M1 patients, overall survival between pN0 and pN1c patients in any pT category (D); overall survival among patients in the pN0, pN1, and pN2 categories (E); overall survival among patients in pN1a, pN1b, and pN1c subclasses (F).

M1 were upgraded from stage N1 to stage N2, and there was no significant difference in prognosis between the pN0, pN1, and pN2 subgroups after restaging (P=0.16; *Table 2*). Moreover, LNM greater than 17.143% was not significantly associated with the mOS of patients with M0 (58.867±13.197 *vs.* 67.9±9.274 months; P=0.91). Among the patients with M1, there was no significant difference in prognosis between the pN0 and pN1c subgroups for any pT category (P=0.58; *Figure 4D*); between the pN0, pN1, and pN2 subgroups (P=0.12; *Figure 4E*); or between the

Table 2 The mOS of colorectal cancer patients with different N stage divided by initial/new TNM category

Items	Initial TNM stage[†]			New TNM stage[‡]		
	mOS (95% CI) (months)	Standard error	P value	mOS (95% CI) (months)	Standard error	P value
M0						
pN0	69.200 (52.522, 85.878)	8.509	0.03	71.800 (57.288, 86.312)	7.404	0.03
pN1	65.633 (53.021, 78.245)	6.435		58.867 (47.664, 70.069)	5.715	
pN2	55.800 (29.309, 82.291)	13.516		65.867 (40.387, 91.347)	13.000	
pN1a	56.833 (42.371, 71.295)	7.379	0.35	65.633 (53.577, 77.690)	6.151	0.46
pN1b	74.967 (61.726, 88.207)	6.755		58.867 (38.654, 79.079)	10.312	
pN1c	58.867 (33.679, 84.055)	12.851		–	–	
M1						
pN0	67.467 (52.643, 82.291)	7.563	0.12	67.467 (51.983, 82.950)	7.900	0.16
pN1	51.667 (45.201, 58.132)	3.299		55.633 (49.592, 61.675)	3.082	
pN2	46.767 (38.987, 54.546)	3.969		46.467 (34.855, 58.078)	5.924	
pN1a	51.400 (35.067, 67.733)	8.333	0.36	55.633 (38.951, 72.315)	8.511	0.48
pN1b	44.400 (6.718, 82.082)	19.226		56.267 (49.621, 62.912)	3.391	
pN1c	61.033 (57.244, 64.822)	1.933		55.633 (49.592, 61.675)	3.082	

[†], initial TNM stage: classified according to AJCC Cancer Staging Manual 8th Edition Criteria by counting TDs and LNM separately; [‡], new TNM stage: classified according to AJCC Cancer Staging Manual 8th Edition Criteria after counting TDs as LNM. mOS, median overall survival; TNM, tumor-node-metastasis; CI, confidence interval; AJCC, American Joint Committee on Cancer; TDs, tumor deposits; LNM, lymph node metastasis.

Table 3 The mOS comparison of colorectal cancer patients between initial N stage and new N stage classified after counting TDs as LNM

Items	mOS (95% CI) (months)	Standard error	P value[†]
M0			
New pN2[‡]	74.967 (59.142, 90.792)	8.074	–
Initial pN1[§]	61.300 (46.938, 75.662)	7.327	0.16
Initial pN2[§]	55.800 (29.309, 82.291)	13.516	0.90
M1			
New pN2	35.033 (19.840, 50.227)	7.752	–
Initial pN1	55.633 (49.511, 61.756)	3.124	0.045
Initial pN2	46.767 (38.987, 54.546)	3.969	0.70

[†], obtained by comparing mOS of new pN2 and initial pN1/initial pN2; [‡], upgrade to N2 according to AJCC Cancer Staging Manual 8th Edition Criteria after counting TDs as LNM; [§], keep the original N1/N2 stage according to AJCC Cancer Staging Manual 8th Edition Criteria after counting TDs as LNM. mOS, median overall survival; TDs, tumor deposits; LNM, lymph node metastasis; CI, confidence interval; AJCC, American Joint Committee on Cancer.

Table 4 The ROC curve of continuous variable about LNM and TDs of colorectal cancer patients

Items	Cut-off	AUC	Youden index	Sensitivity	Specificity
M0					
LNM[†]	0.500	0.623	0.249	0.324	0.925
LNM%[‡]	17.143%	0.511	0.174	0.424	0.750
TDs[§]	0.500	0.594	0.181	0.250	0.931
LNM + TDs	0.500	0.615	0.210	0.691	0.519
M1					
LNM	0.500	0.592	0.196	0.640	0.556
LNM%	8.013%	0.587	0.249	0.649	0.600
TDs	0.500	0.556	0.099	0.341	0.758
LNM + TDs	1.500	0.656	0.282	0.504	0.778

[†], the number of LNM; [‡], the number of positive LNM/the number of lymph nodes detected × 100%; [§], the number of TDs. ROC, receiver operating characteristic; LNM, lymph node metastasis; TDs, tumor deposits; AUC, area under the curve.

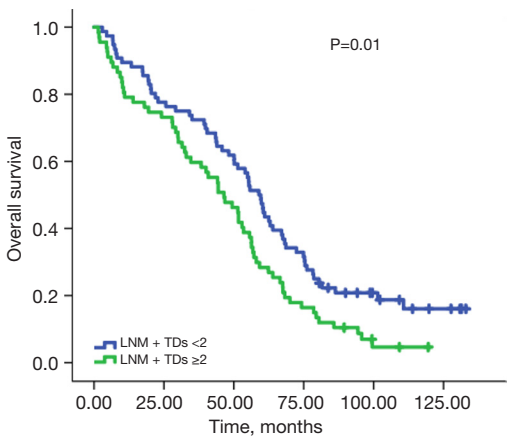

Figure 5 The Kaplan-Meier analysis of M1 patients with colorectal cancer with and without an LNM + TDs count ≥2. LNM, lymph node metastasis; TDs, tumor deposits.

pN1a, pN1b, and pN1c subgroups (P=0.36; *Figure 4F*). According to the combination of counting and staging of TDs and lymph node invasion, 20 patients with M1 were upgraded from stage N1 to stage N2, and there was no significant difference in the prognosis between the pN0, pN1, and pN2 subgroups (P=0.16, *Table 2*) or between the pN1a and pN1b subgroups after restaging (P=0.48; *Table 2*). Among the patients with M1, the mOS of those restaged to pN2 was nonsignificantly shorter than that of those who had remained in the pN1 stage and pN2 stage (*Table 3*). According to ROC curve and Kaplan-Meier survival analysis (*Table 4*), when the positive rate of LNM was greater than 8.013%, the mOS of M1 patients was shorter, but this did not represent a significant association (61.033±1.933 *vs.* 446.767±5.042 months; P=0.07); however, the mOS was significantly shorter when the number of LNM + TDs was greater than 2 (P=0.01; *Figure 5*).

Distribution of TDs

The chi-square test was used to compare the clinical data of the two subgroups of patients with and without TDs (*Table 5*). In the subgroup with TDs, the proportion of patients younger than 65 years old and a BMI ≥24 kg/m^2 was higher, but there was no significant difference between the two subgroups in terms of gender, smoking history, or diabetes. Analysis of the pathological data of the two groups indicated that the proportion of patients with tumors originating from the rectum in the TD-positive group was higher than that in TD-negative group, reaching 52.79%; the proportions of patients with gross tumor types of ulceration and bulge in the TD-negative group were 50.24% and 12.56%, respectively, and were higher than those in the TD-positive group (*Figure 6A*). The most common histological type in both the TD-positive and TD-negative groups was tubular papillary. In addition, the proportion of patients with the papillary histological type in the TD-positive group was 25.38%, while that in TD-negative group was 25.12% (*Figure 6B*). There were also differences in tumor size between the two groups.

Table 5 The characteristics of colorectal cancer patients with TDs or not

Items	TD−, n (%)	TD+, n (%)	P value
Sex			0.68
Male	281 (67.87)	137 (69.54)	
Female	133 (32.13)	60 (30.46)	
Age (years)			0.002
<65	227 (54.83)	134 (68.02)	
≥65	187 (45.17)	63 (31.98)	
BMI (kg/m^2)			<0.001
<18.5	21 (5.07)	9 (4.57)	
≥18.5, <24	147 (35.51)	60 (30.46)	
≥24	107 (25.85)	90 (45.69)	
Unknown	139 (33.57)	38 (19.29)	
Smoking history			0.88
Negative	315 (76.09)	151 (76.65)	
Positive	99 (23.91)	46 (23.35)	
Diabetes			0.47
Negative	375 (90.58)	182 (92.39)	
Positive	39 (9.42)	15 (7.61)	
Tumor location			0.01
Rectum	184 (44.44)	104 (52.79)	
Colon	136 (32.85)	68 (34.52)	
Others	94 (22.71)	25 (12.69)	
General morphology			0.005
Ulcerative type	208 (50.24)	64 (32.49)	
Protruded type	52 (12.56)	10 (5.08)	
Infiltration type	25 (6.04)	19 (9.64)	
Unknown	129 (31.16)	104 (52.79)	
Histological type			<0.001
Tubular	104 (25.12)	15 (7.61)	
Papillary	8 (1.93)	50 (25.38)	
Tubular papillary	176 (42.51)	81 (41.12)	
Unknown	126 (30.43)	51 (25.89)	

Table 5 (*continued*)

Table 5 (*continued*)

Items	TD−, n (%)	TD+, n (%)	P value
Differentiation degree			<0.001
Low	29 (7.00)	19 (9.64)	
Medium low	84 (20.29)	5 (2.54)	
Medium	210 (50.72)	8 (4.06)	
Medium high	15 (3.62)	0 (0.00)	
High	2 (0.48)	0 (0.00)	
Unknown	74 (17.87)	165 (83.76)	
Size (cm)			<0.001
≤5	149 (35.99)	120 (60.91)	
>5	59 (14.25)	44 (22.34)	
Unknown	206 (49.76)	33 (16.75)	
Depth of invasion			<0.001
Submucosa	37 (8.94)	1 (0.51)	
Muscularis propria	22 (5.31)	10 (5.08)	
Subserosa	100 (24.15)	154 (78.17)	
Splanchnic peritoneum	32 (7.73)	32 (16.24)	
Unknown	223 (53.86)	0 (0.00)	
Nerve invasion			<0.001
Negative	370 (89.37)	155 (78.68)	
Positive	44 (10.63)	42 (21.32)	
Vascular invasion			0.29
Negative	375 (90.58)	173 (87.82)	
Positive	39 (9.42)	24 (12.18)	
cM category			<0.001
cM0	214 (51.69)	46 (23.35)	
cM1a	101 (24.40)	65 (32.99)	
cM1b	66 (15.94)	71 (36.04)	
cM1c	33 (7.97)	15 (7.61)	
TNM category			<0.001
I	29 (7.00)	0 (0.00)	
II	40 (9.66)	0 (0.00)	
III	15 (3.62)	44 (22.34)	
IV	200 (48.31)	151 (76.65)	
Unknown	130 (31.40)	2 (1.02)	

Table 5 (*continued*)

Table 5 (*continued*)

Items	TD−, n (%)	TD+, n (%)	P value
Liver metastasis			<0.001
Negative	368 (88.89)	194 (98.48)	
Positive	46 (11.11)	3 (1.52)	
Spleen metastasis			<0.001
Negative	409 (98.79)	177 (89.85)	
Positive	5 (1.21)	20 (10.15)	
Lung metastasis			<0.001
Negative	381 (92.03)	120 (60.91)	
Positive	33 (7.97)	77 (39.09)	
Bone metastasis			<0.001
Negative	411 (99.28)	133 (67.51)	
Positive	3 (0.72)	64 (32.49)	
Peritoneum metastasis			0.24
Negative	396 (95.65)	184 (93.40)	
Positive	18 (4.35)	13 (6.60)	
Ovarian metastasis			0.07
Negative	407 (98.31)	197 (100.00)	
Positive	7 (1.69)	0 (0.00)	
Brain metastasis			<0.001
Negative	409 (98.79)	174 (88.32)	
Positive	5 (1.21)	23 (11.68)	
Abdominal pelvic implantation metastasis			0.01
Negative	392 (94.69)	195 (98.98)	
Positive	22 (5.31)	2 (1.02)	
Adrenal metastasis			0.31
Negative	410 (99.03)	197 (100.00)	
Positive	4 (0.97)	0 (0.00)	

TDs, tumor deposits; BMI, body mass index; TNM, tumor-node-metastasis.

The proportion of patients with tumor neural invasion in the TD-positive group was higher than that in the TD-negative group, but there was no significant difference in the proportion of tumor invasion of blood vessels between the two groups. In addition, the proportion of splenic, lung, bone, and brain metastases was higher in the TD-positive group, while the proportion of liver and pelvic abdominal metastases was higher in TD-negative group. However, there was no significant difference in the proportion of peritoneal, ovarian, or adrenal metastases between the two groups (*Figure 6C*).

Prognostic analysis of the other subgroups

The site of the primary tumor, the grade of tumor

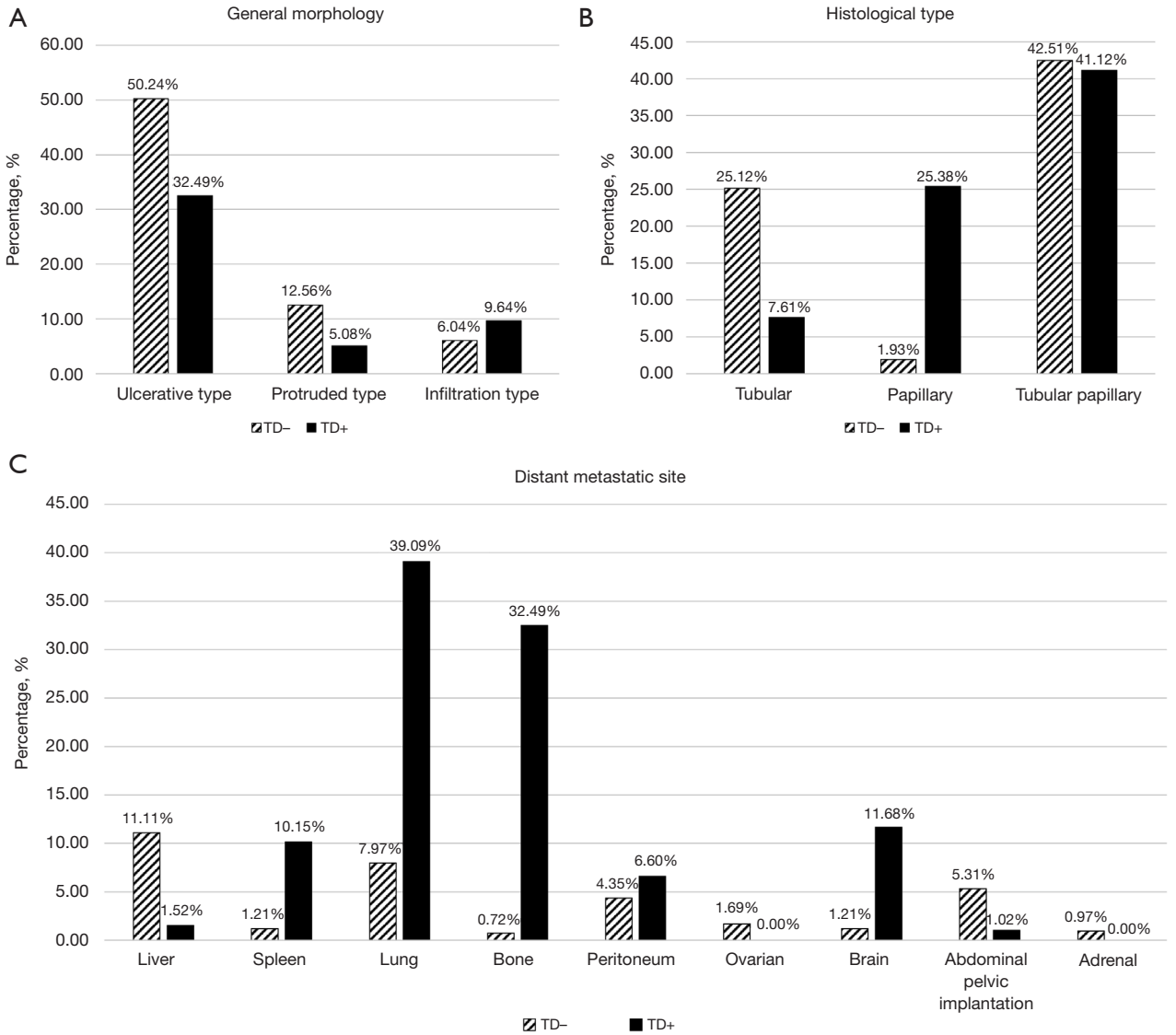

Figure 6 The proportions of (A) general morphology, (B) histological type, and (C) distant metastatic site of patients with colorectal cancer with and without TDs. TDs, tumor deposits.

differentiation, and the depth of tumor invasion were all associated with the long-term prognosis of patients (*Table 1*). Tumor vascular invasion (P<0.001; *Figure 7A*), tumor neural invasion (P=0.004; *Figure 7B*), and distant metastasis were significantly associated with a worse mOS. Patients with liver, lung, bone, peritoneal, ovarian, peritoneal, and adrenal metastases had a significantly shorter mOS, while the presence or absence of spleen and brain metastases was not significantly associated with mOS (*Figure 8*). In the subgroup analysis of patients with M0 and M1, we found that histological type and degree of differentiation of the tumor were significantly associated with the mOS of patients with M0; meanwhile, tumor invasion of blood vessels and presence of hepatic, peritoneal, and adrenal metastases were significantly associated with a shorter mOS in patients with M1 (*Table 6*).

Discussion

Tumor staging is an important tool for clinical decision-making, particularly for selecting treatment plans and predicting long-term survival. The UICC/AJCC TNM

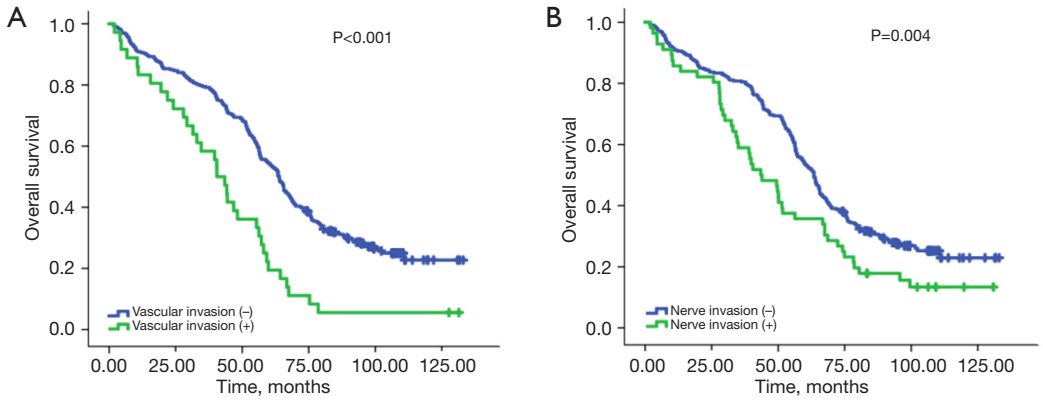

Figure 7 The Kaplan-Meier analysis of patients with colorectal cancer with and without (A) vascular invasion or (B) neural invasion.

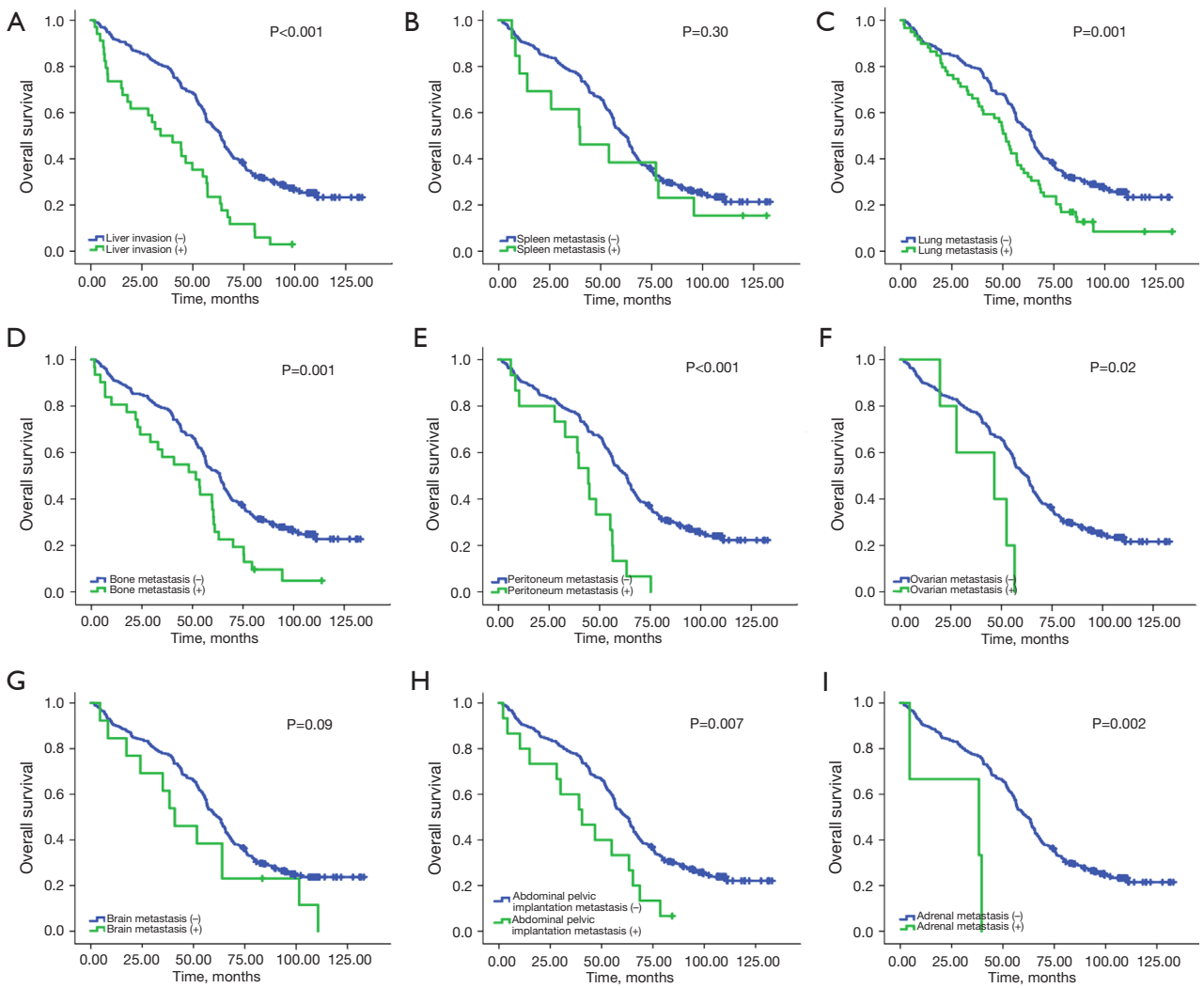

Figure 8 The Kaplan-Meier analysis of patients with colorectal cancer with different metastatic sites. Overall survival curve for patients with or without (A) liver metastasis, (B) spleen metastasis, (C) lung metastasis, (D) bone metastasis, (E) peritoneum metastasis, (F) ovarian metastasis, (G) brain metastasis, (H) abdominal pelvic implantation metastasis, (I) adrenal metastasis.

Table 6 Subgroup analysis of factors that may influence the mOS of colorectal cancer patients

Items	M0				M1			
	n (%)	mOS (95% CI) (months)	Standard error	P value	n (%)	mOS (95% CI) (months)	Standard error	P value
Sex				0.93				0.43
Male	114 (71.25)	68.733 (60.449, 77.018)	4.227		133 (65.52)	52.933 (48.011, 57.856)	2.511	
Female	46 (28.75)	74.100 (61.619, 86.581)	6.368		70 (34.48)	55.767 (49.891, 61.643)	2.998	
Age (years)				0.40				0.55
<65	88 (55.00)	74.100 (57.486, 90.714)	8.476		124 (61.08)	54.033 (48.161, 59.905)	2.996	
≥65	72 (45.00)	66.567 (61.785, 71.348)	2.440		79 (38.92)	52.933 (43.643, 62.224)	4.740	
BMI (kg/m^2)				0.40				0.67
<18.5	7 (4.38)	65.633 (59.902, 71.365)	2.924		11 (5.42)	63.367 (45.564, 81.169)	9.083	
≥18.5, <24	54 (33.75)	66.567 (53.829, 79.305)	6.499		60 (29.56)	48.200 (37.446, 58.954)	5.487	
≥24	36 (22.50)	88.833 (–)	–		51 (25.12)	51.400 (41.904, 60.896)	4.845	
Unknown	63 (39.38)	–	–		81 (39.90)	–	–	
Smoking history				0.28				0.16
Negative	123 (76.88)	67.967 (60.693, 75.240)	3.711		156 (76.85)	55.400 (51.932, 58.868)	1.769	
Positive	37 (23.13)	84.033 (61.525, 106.542)	11.484		47 (23.15)	39.967 (25.592, 54.341)	7.334	
Diabetes				0.79				0.29
Negative	148 (92.50)	69.300 (62.878, 75.722)	3.276		183 (90.15)	54.033 (50.312, 57.755)	1.899	
Positive	12 (7.50)	56.833 (0.000, 118.789)	31.610		20 (9.85)	43.933 (36.191, 51.676)	3.950	
Tumor location				0.14				0.04
Rectum	84 (52.50)	68.800 (54.820, 82.780)	7.133		97 (47.78)	59.800 (52.463, 67.137)	3.743	
Colon	42 (26.25)	74.967 (–)	–		71 (34.98)	51.400 (43.541, 59.259)	4.010	
Others	34 (21.25)	65.400 (63.114, 67.686)	1.166		41 (20.20)	46.767 (30.164, 63.370)	8.741	
General morphology				0.13				0.92
Ulcerative type	59 (36.88)	79.733 (–)	–		99 (48.77)	53.467 (47.676, 59.258)	2.955	
Protruded type	15 (9.38)	–	–		18 (8.87)	50.133 (39.877, 60.389)	5.233	
Infiltration type	13 (8.13)	69.200 (27.365, 111.035)	21.345		14 (6.90)	52.633 (44.139, 61.128)	4.334	
Unknown	73 (45.63)	66.567 (62.567, 70.567)	2.041		72 (35.47)	56.300 (49.682, 62.918)	3.376	
Histological type				0.02				0.06
Tubular	37 (23.13)	–	–		37 (18.23)	43.933 (31.062, 56.805)	6.567	
Papillary	8 (5.00)	33.167 (7.850, 58.483)	12.916		23 (11.33)	50.100 (33.196, 67.004)	8.624	
Tubular papillary	63 (39.38)	75.800 (51.830, 99.770)	12.229		82 (40.39)	59.633 (52.445, 66.821)	3.667	
Unknown	52 (32.50)	67.967 (62.627, 73.306)	2.724		61 (30.05)	52.533 (38.466, 66.600)	7.177	

Table 6 (*continued*)

Table 6 (*continued*)

Items	M0				M1			
	n (%)	mOS (95% CI) (months)	Standard error	P value	n (%)	mOS (95% CI) (months)	Standard error	P value
Differentiation degree				0.06				0.26
Low	6 (3.75)	–	–		26 (12.81)	43.433 (26.527, 60.340)	8.626	
Medium low	19 (11.88)	–	–		32 (15.76)	44.200 (33.806, 54.594)	5.303	
Medium	74 (46.25)	–	–		68 (33.50)	56.833 (47.574, 66.093)	4.724	
Medium high	7 (4.38)	–	–		0 (0.00)	–	–	
High	1 (0.63)	–	–		0 (0.00)	–	–	
Unknown	53 (33.13)	–	–		77 (37.93)	53.733 (46.918, 60.549)	3.477	
Size (cm)				0.37				0.74
≤5	79 (49.38)	68.800 (58.814, 78.786)	5.095		84 (41.38)	54.033 (44.842, 63.225)	4.690	
>5	25 (15.63)	75.800 (61.520, 90.080)	7.286		37 (18.23)	53.467 (47.190, 59.743)	3.202	
Unknown	56 (35.00)	–	–		82 (40.39)	–	–	
Depth of invasion				<0.001				0.63
Submucosa	19 (11.88)	54.533 (37.328, 71.739)	8.778		7 (3.45)	56.767 (51.976, 61.557)	2.444	
Muscularis propria	9 (5.63)	65.633 (51.998, 79.268)	6.957		7 (3.45)	55.300 (30.921, 76.679)	12.438	
Subserosa	47 (29.38)	67.967 (53.950, 81.983)	7.151		87 (42.86)	54.033 (45.807, 62.260)	4.197	
Splanchnic peritoneum	13 (8.13)	70.067 (49.673, 90.461)	10.405		28 (13.79)	51.667 (38.184, 65.149)	6.879	
Unknown	72 (45.00)	–	–		74 (36.45)	52.533 (47.370, 57.697)	2.634	
The presence or absence of TDs				0.02				0.84
Negative	129 (80.63)	71.800 (61.489, 82.111)	5.261		133 (65.52)	52.767 (47.844, 57.689)	2.511	
Positive	31 (19.38)	69.300 (59.738, 78.862)	4.879		70 (34.48)	54.033 (43.579, 64.487)	5.334	
Nerve invasion				–				0.39
Negative	160 (100.00)	69.300 (62.618, 75.982)	3.409		147 (72.41)	56.267 (52.649, 59.884)	1.846	
Positive	0 (0.00)	–	–		56 (27.59)	43.433 (30.762, 56.104)	6.465	
Vascular invasion				–				0.005
Negative	160 (100.00)	69.300 (62.618, 75.982)	3.409		167 (82.27)	55.767 (50.552, 60.981)	2.661	
Positive	0 (0.00)	–	–		36 (17.73)	40.500 (33.787, 47.213)	3.425	
pN category				0.005				0.008
pN0	54 (33.75)	69.200 (52.522, 85.878)	8.509		22 (10.84)	67.467 (52.643, 82.291)	7.563	
pN1a	10 (6.25)	56.833 (42.371, 71.295)	7.379		34 (16.75)	51.400 (35.067, 67.733)	8.333	
pN1b	5 (3.13)	74.967 (61.726, 88.207)	6.755		29 (14.29)	44.400 (6.718, 82.082)	19.226	
pN1c	17 (10.63)	58.867 (33.679, 84.055)	12.851		33 (16.26)	61.033 (57.244, 64.822)	1.933	
pN2a	8 (5.00)	46.733 (15.134, 78.333)	16.122		13 (6.40)	54.033 (47.575, 60.492)	3.295	

Table 6 (*continued*)

Table 6 (*continued*)

Items	M0				M1			
	n (%)	mOS (95% CI) (months)	Standard error	P value	n (%)	mOS (95% CI) (months)	Standard error	P value
pN2b	1 (0.63)	55.800 (–)	–		12 (5.91)	32.967 (13.050, 52.883)	10.161	
Unknown	65 (40.63)	91.800 (61.603, 121.997)	15.407		60 (29.56)	56.300 (50.480, 62.120)	2.969	
N category				0.03				0.12
N0	54 (33.75)	69.200 (52.522, 85.878)	8.509		22 (10.84)	67.467 (52.643, 82.291)	7.563	
N1	32 (20.00)	65.633 (53.021, 78.245)	6.435		96 (47.29)	51.667 (45.201, 58.132)	3.299	
N2	9 (5.63)	55.800 (29.309, 82.291)	13.516		25 (12.32)	46.767 (38.987, 54.546)	3.969	
Liver metastasis				–				0.001
Negative	160 (100.00)	69.300 (62.618, 75.982)	3.409		169 (83.25)	55.767 (50.846, 60.688)	2.511	
Positive	0 (0.00)	–	–		34 (16.75)	34.133 (13.847, 54.419)	10.350	
Spleen metastasis				–				0.98
Negative	160 (100.00)	69.300 (62.618, 75.982)	3.409		190 (93.60)	53.733 (50.109, 57.358)	1.849	
Positive	0 (0.00)	–	–		13 (6.40)	39.833 (6.522, 73.145)	16.996	
Lung metastasis				–				0.27
Negative	160 (100.00)	69.300 (62.618, 75.982)	3.409		144 (70.94)	55.400 (50.721, 60.079)	2.387	
Positive	0 (0.00)	–	–		59 (29.06)	51.400 (45.737, 57.063)	2.889	
Bone metastasis				–				0.09
Negative	160 (100.00)	69.300 (62.618, 75.982)	3.409		172 (84.73)	54.900 (51.068, 58.732)	1.955	
Positive	0 (0.00)	–	–		31 (15.27)	51.667 (31.270, 72.063)	10.406	
Peritoneum metastasis				–				0.009
Negative	160 (100.00)	69.300 (62.618, 75.982)	3.409		188 (92.61)	54.900 (50.677, 59.123)	2.155	
Positive	0 (0.00)	–	–		15 (7.39)	44.400 (36.910, 51.890)	3.821	
Ovarian metastasis				–				0.10
Negative	160 (100.00)	69.300 (62.618, 75.982)	3.409		198 (97.54)	54.033 (50.287, 57.780)	1.911	
Positive	0 (0.00)	–	–		5 (2.46)	46.467 (6.316, 86.617)	20.485	
Brain metastasis				–				0.51
Negative	160 (100.00)	69.300 (62.618, 75.982)	3.409		190 (93.60)	54.033 (50.409, 57.658)	1.849	
Positive	0 (0.00)	–	–		13 (6.40)	40.867 (21.334, 60.400)	9.966	
Abdominal pelvic implantation metastasis				–				0.12
Negative	160 (100.00)	69.300 (62.618, 75.982)	3.409		188 (92.61)	54.033 (50.405, 57.661)	1.851	
Positive	0 (0.00)	–	–		15 (7.39)	40.467 (19.301, 61.632)	10.799	
Adrenal metastasis				–				0.02
Negative	160 (100.00)	69.300 (62.618, 75.982)	3.409		200 (98.52)	54.033 (50.338, 57.729)	1.886	
Positive	0 (0.00)	–	–		3 (1.48)	38.300 (0.000, 92.285)	27.543	

mOS, median overall survival; CI, confidence interval; BMI, body mass index; TDs, tumor deposits.

staging system has served as a guideline since 1977. Its clinical value has been widely recognized by the international community and has included the continuous refinement of macroscopic staging based on anatomical pathology and the combination of microscopic factors such as gene mutations and biomarkers. The treatment of CRC also depends strongly on tumor stage, and with the proliferation of therapeutic options and the increased likelihood of treatment for metastatic CRC (mCRC) (17-19), detailed and accurate tumor staging has become one of the main criteria for selecting treatment. The 5th edition of TNM staging, published by UICC/AJCC in 1997, included the concept of TDs for the first time. It classified TDs according to the size according to the "3-mm rule": TDs with a diameter greater than or equal to 3 mm are classified as LNM in the N category, while TDs with a diameter less than 3 mm are classified as T (20). This classification lacked public working validation and was removed from the 6th edition of the AJCC TNM staging guide (21). In this 6th edition, the guidelines emphasize the contours of TDs and classifies the smooth contours of metastatic nodes around the colon or rectum into the N category, which, however, was not supported by subsequent clinical evidence in practice (22,23). The 7th edition of TNM staging, developed in 2010, removed the contour rule. It redefined TDs as isolated neoplasms that surround the colon, rectum, or mesocolic fat and that are distant from the primary tumor site, located in the regional lymph nodes of the primary tumor, with no residual lymphoid tissue, the most recent 8th edition of UICC/AJCC TNM guidelines regarding CRC staging remains problematic. In particular, the role of TDs in CRC staging has been controversial since the introduction of the new pN1c classification in the 7th edition of the AJCC TNM staging system.

In this real-world study, the positive rate of TDs was 32.24%, which was slightly higher than that of previous reports (13,24), but this also illustrates the necessity and importance of evaluating the role of TDs in staging and long-term prognosis. Moreover, presence of TDs was significantly associated with the prognosis of patients with CRC; in particular, for those with M0 and no distant metastasis, the presence of TDs was associated with poor prognosis. This negative association was more pronounced in patients with M0 and no LNM. In contrast, in patients with M1 and distant metastasis or LNM, the presence of TDs was not associated with a poorer prognosis. This suggests that more attention should be paid to the effect of TDs in the clinical treatment of patients with stage TxN0M0 CRC. In addition, there was no significant difference in prognosis between the pN1a, pN1b, and pN1c subgroups among either the patients with M0 or M1. This indicates that adjuvant chemotherapy similar to that for other N classification disease can be considered for patients with pN1c and that the pN1c classification with TDs should be used as a selection criterion only if LNM is absent. This is in line with the conclusions of a previous retrospective study (25), a clinical trial (16), and the current AJCC TNM staging system. In addition, the presence of TDs was significantly associated with prognosis, but the relationship between the number of TDs and prognosis remains unclear (14). In this study, TDs combined with LNMs to perform N classification and to analyze the prognosis of different stages. On the one hand, after reclassification, the prognosis of new pN0, pN1, and pN2 subgroups in the pM0 category was significantly different, which was consistent with the results of a previous study (26). On the other hand, when the number of TD was integrated into the LNM count and TNM reclassification performed, there was no significant difference in the prognosis of patients with pN1 to pN2 compared with those who remained as pN1 or pN2. Although the prognosis of patients with TDs among those with M1 was worse, because patients are already metastatic, and the difference was not significant. This is inconsistent with the results of previous studies, which showed that patients who achieved pN2 after restaging with TDs and LNMs combined together had a worse prognosis than did those who remained with pN1 or pN2 after restaging. This suggests that the number of TDs should be combined with that of LNMs and that reclassification is helpful for the selection of the best treatment plan and the prediction of long-term survival. This may be related to the limitations of this study in the small number of participants, lack of standardization, and the incompletely defined pathology of TD, which illustrates the importance of high-quality, standardized pathology reporting in the treatment of malignancies, including CRC (16,27,28).

In analyzing whether the presence and number of TDs were correlated with other clinical and pathological features, previous studies have reported that TDs are significantly correlated with tumor spread to other regions and that the incidence of TDs is higher in the presence of tumor neural invasion or partial nodular transfer (15,24). Furthermore, the number of TDs has been significantly correlated with vascular invasion, neural invasion, and partial nodular transfer (29,30). In this study, when the medical records of the TD-negative and TD-positive

groups were analyzed, it was also found that neural invasion was closely related to partial nodular transfer, while a correlation of vascular invasion with increased frequency of TDs was not found. Papillary tissue type, poor pathological differentiation, and deep invasion of the primary tumor may also be related to the high incidence of TDs, but this needs to be further examined and verified to clarify the mechanism at the cellular and biochemical levels. The correlation between TDs and some pathological features and its potential clinical significance illustrate the need to improve the skill of pathologists and ensure the quality of pathological reports. In addition, this study found that the presence of TDs may also be related to the metabolic status of patients and thus indirectly associated with prognosis; moreover, the proportion of overweight people with BMI $\geq$24 kg/m^2 in the TD-positive group was much higher than that in the TD-negative group. Obesity has long been recognized as a risk factor for the onset of CRC (31,32), and poor weight management leading to excessive weight gain and loss can lead to CRC recurrence and a poor prognosis (33). In order to assist in antitumor treatment and prevent tumor recurrence in patients with CRC, a comprehensive weight management process that includes a healthy diet and moderate exercise should be advocated.

Other factors that associated with the prognosis of CRC were examined via subgroup analysis, and among the pathological features, the depth of invasion and the degree of differentiation of the primary tumor were found to be significantly associated with the prognosis of patients, while the size, gross type, and histological type of the primary tumor did not demonstrate a significant association. This is consistent with the current TNM staging T classification that employs the depth of invasion rather than the size of the primary tumor as the classification standard. Neurovascular invasion maybe associated with disease recurrence and poor long-term prognosis (24), although vascular invasion and neural invasion demonstrated different degrees of correlation with TDs in this study, they nonetheless shorten the long-term survival of patients and associated with the final outcome of patients. These factors are not clearly used as a separate standard for TNM classification in the current AJCC staging system but should be seriously considered in clinical work. Distant metastasis is an important indicator of M classification in TNM staging, and the long-term survival of patients with distant metastasis is significantly shortened. Among metastatic types, liver metastasis, lung metastasis, bone metastasis, peritoneal metastasis, ovarian metastasis, pelvic and abdominal cavity metastasis, and adrenal gland metastasis may have a negative impact on the prognosis of patients. Therefore, regular systemic imaging examination and early detection and intervention of distant metastases are essential to improving patient prognosis.

In addition, when analyzing the survival data of the enrolled patients, we observed that stage II patients seemed to have better survival compared to stage I patients. We believe the following factors have influenced the results of the analysis: first, the small number (stage I: 29, stage II: 40) and enrollment period was early (from January 1, 2010 to December 31, 2020) which were indeed a limitation of this study, if more patients were enrolled for further research, the results may be different. Second, more stage II patients received subsequent adjuvant therapy, which may improve patient survival. Third, the Chinese Society of Clinical Oncology (CSCO) guidelines indicate that high-risk factors affecting stage II CRC patients include: T4, poor histological differentiation [high grade, excluding microsatellite instability-high (MSI-H)], vascular invasion, nerve invasion, preoperative bowel obstruction or tumor perforation, positive or unclear resection margins, insufficient resection margin safety distance, and fewer than 12 lymph nodes sampled. However, a review of the enrolled patient data found that many stage II patients in this study did not present these high-risk factors. For stage II patients, they are classified into high-risk, intermediate-risk, and low-risk categories [with low-risk referring to MSI-H or deficient mismatch repair (dMMR)]. Except for the low-risk group, all other patients are recommended to receive adjuvant chemotherapy, which is also a factor influencing patient survival.

Conclusions

This study retrospectively analyzed the medical records of 611 patients with CRC in the real world, which indicated that the presence of TD has a significant negative effect on the prognosis of patients with CRC. We found there to be no significant difference between the pN1c and pN1 subgroups, and thus for these patients, adjuvant chemotherapy similar to that for other N classification diseases can be considered. The clinical significance of reclassifying TDs numbers by combining them with LNM count is controversial. The clinical features, pathological types, and distant metastases of patients were not only correlated with TDs but were also significantly associated with their long-term prognosis. Comprehensive assessment of patients' basic conditions before treatment, high-quality

standardized pathology reports, and whole-course health management during treatment are essential to improving prognosis and prolonging the long-term survival of patients with cancer.

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Footnote

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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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Institutional Ethics Review Committee of The Affiliated Cancer Hospital of Nanjing Medical University (Jiangsu Cancer Hospital) (No. 2020-037) before the study was initiated. This study is a retrospective study, and individual consent was not required.

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