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Tumor Deposits as an Adverse Prognostic Indicator in Stage III Colon Cancer

A Multicenter Database Study

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Objective: We explored the oncological impact of tumor deposits (TDs) on colon cancer and proposed optimal modifications to the current staging system.

Background: In the existing American Joint Committee on Cancer colon cancer staging system, TDs are incorporated into the N category as N1c. When lymph node metastases (LNMs) are present, their number is considered to determine nodal stages, such as N1a/b or N2a/b, regardless of TDs.

Methods: 4212 patients with primary colon cancer who underwent surgical resection in the Seoul Colorectal Group (2010–2020) and 93,057 patients from the Surveillance, Epidemiology, and End Results*Stat database (2000–2017) were included in this study. Patients were classified according to the number of metastatic lymph nodes (LNs) (0/1–3/≥4) and the presence of TDs.

Results: TDs were significantly associated with left colon cancer, a higher T category, and vascular/perineural invasion. Patients with TDs had higher recurrence rates (23.1 *vs* 7.5%, $P < 0.001$). The TD-positive patients had notably worse overall survival (OS) and recurrence-free survival rates. The survival outcomes of TD-positive patients without LNM were inferior to those of TD-negative patients with LN1–3 (5-year OS: 78.9 *vs* 87.8%, $P = 0.04$). The survival outcomes of TD-positive patients with LN1–3 were similar to those of TD-negative patients with LN ≥4 (5-year OS: 87.0 *vs* 77.1%, $P = 0.11$). Survival outcomes obtained using the Surveillance, Epidemiology, and End Results *Stat database yielded consistent results.

Conclusions: TDs were associated with poor prognostic factors and had a significant impact on survival outcomes. The incorporation of tumor deposits into nodal classifications beyond the current N1c criteria may improve the staging system and more accurately reflect the recurrence and survival rates among patients with colon cancer. TD-positive in N1a or N1b could be categorized as N2.

Keywords: colon cancer, risk factor, Surveillance, Epidemiology, and End Results database, tumor deposit

INTRODUCTION

Tumor deposits (TDs) refer to focal aggregates of tumor cells in the pericolic or perirectal mesenteric fat, which are distinct from the primary tumor and not associated with a lymph node (LN).[1–3] First described as a vascular invasion by Gabriel et al.[4] in 1935, TDs are currently regarded as a collection of different entities originating from various histological structures, such as venous or perineural invasion and lymph node metastasis (LNM).[5] Previous studies have detected TDs in 20–25% of patients with colon cancer and have reported their association with poor prognosis and reduced survival.[6–8]

The American Joint Committee on Cancer (AJCC) tumor node metastasis (TNM) staging system is essential for predicting prognosis and guiding treatment. In the 5th edition of 1997, TDs were initially described as nodules with a diameter >3 mm that were located in the perirectal or pericolic fat without histological evidence of residual LNs.[9] Tumor nodules with a diameter of <3 mm were classified as discontinuous extensions (specifically T3) under the T category. In the 6th edition

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of 2002, the definition became more ambiguous: metastatic nodules or foci were considered equivalent to regional LNM if the nodules assumed the form and smooth contour of LNs.[10] Nodules with an irregular contour were classified under the T category and coded as either V1 (microscopic venous invasion) or V2 (if grossly evident) because of the likelihood of presenting venous invasion. From the 7th edition in 2010 to the 8th edition in 2017, TDs were recognized as independent prognostic factors and were defined as satellite peritumoral nodules in the pericolorectal adipose tissues of a primary carcinoma without histological evidence of residual LNs. TDs may represent discontinuous spread, venous invasion with extravascular spread (V1/2), or completely substituted LNs (N1/2). Substituted nodes should be counted separately as positive nodes under the N category, whereas discontinuous spread or venous invasion should be classified and counted under the site-specific factor category of TDs. Consequently, when only TDs are present, they can be categorized as N1c.[11] However, if LNM is present, the presence of TDs is disregarded, and only the number of LNMs is considered important for nodal stage (N1a/b or N2a/b) determination.

Over the past decade, several studies have proposed methods to integrate TDs into staging systems.[12–14] Recent studies with post hoc analysis after randomized controlled trials suggested modifications of nodal staging by adding the number of tumor deposits to the number of positive LNM.[8,14–16] The amended nodal stages could reflect the survival outcomes better than the previous AJCC staging system, not ignoring the importance of the prognostic value of tumor deposit. However, there are some controversies regarding whether tumor deposits can be evaluated as having the same value as the lymph node. Because the LNM is the most important prognostic factor for distant metastasis and long-term survival, some critics still remain only for calculating the number of tumor deposits and lymph nodes, weighing the value as 1 by 1.[9,17]In this study, we aimed to investigate the clinical significance and oncologic impact of TDs in colon cancer using a multicenter retrospective database and to clarify oncologic impact of TDs in current AJCC staging system at each N stage for reasonable changes in the staging system.

MATERIALS AND METHODS

Patient Selection

A total of 10,557 prospectively collected patients with primary nonmetastatic colon cancer from the Seoul Colorectal Group (SECOG) database were retrospectively analyzed. These patients underwent curative radical resection between January 2010 and December 2020 at tertiary hospitals. The exclusion criteria were as follows: (1) patients with recurrent colorectal cancer (CRC); (2) patients with hereditary CRC, including familial adenomatous polyposis and hereditary nonpolyposis CRC; (3) patients who underwent local excision; (4) patients with combined synchronous CRC; and (4) patients who underwent palliative resection, received concurrent chemoradiation therapy preoperatively, or had incomplete medical records or follow-up data. Overall, 4212 patients with primary colon cancer were eligible for this study. This study was approved by the institutional review boards of 3 hospitals (approval numbers:2110-162-1266, 2206-765-401). The requirement for informed consent from the patients was waived owing to the retrospective nature of this study.

Histological slides and reports were reviewed to collect the following data: histological grade, invasion depth, number of LNMs, presence of vascular or perineural invasion, presence of TDs, and surgical margins. The maximum diameter of the TDs was measured, and the number of TDs was counted separately for cases in which the deposits were not adjacent. The clinical characteristics and risk factors of the TD-positive patients were analyzed. Recurrence-free survival (RFS) and overall survival (OS) were compared between the TD-negative and TD-positive patients in each pN category. Survival outcomes were compared by dividing patients according to the number of metastatic LNs (0/1–3/≥4) and the presence or absence of TDs. Adjuvant chemotherapy is recommended for all medically fit patients after resection.

The Surveillance, Epidemiology, and End Results Database

The Surveillance, Epidemiology, and End Results (SEER) program is a comprehensive population-based cancer registry that encompasses approximately 26% of the US population across various distinct geographic regions, making it the largest publicly accessible cancer dataset. Since 2004, the SEER registry has been collecting patient data including histological type, diagnostic stage, and TDs. In the present study, the "Incidence—SEER Research Data, 18 Registries, Nov 2019 Sub (2000–2017)" dataset was used for analysis. Anatomical subsites of the proximal and distal colon were classified based on the International Classification of Diseases for Oncology, third edition (ICD-O-3) topography codes. Specifically, the right-sided or proximal colon comprised cancers of the cecum (ICD-O-3 code C18.0), ascending colon (ICD-O-3 code C18.2), hepatic flexure (ICD-O-3 code C18.3), transverse colon (ICD-O-3 code C18.4), and splenic flexure (ICD-O-3 code C18.5), and the left-sided or distal colon consisted of the descending colon (ICD-O-3 code C18.6) and sigmoid colon (ICD-O-3 code C18.7). Additionally, colon cancer included large intestine cancer, not otherwise specified (ICD-O-3 codes C18.8 and C18.9). The derived AJCC TNM (7th edition) stages for the period 2010–2015 were exported. Cancer-specific survival (CSS) was ascertained from SEER records, considering both survival time and vital status. Among 100,524 patients, only T1-T4b patients without distant metastasis were included, and 735 patients without N stage citation and 3188 patients lacking the data of the number of metastasized lymph nodes were excluded. A total of 93,057 patients were analyzed from the SEER registry.

Statistical Analyses

All statistical analyses were performed using SPSS version 27.0 (IBM Corp., Armonk, NY, USA). Clinical and demographic characteristics were analyzed using the χ^2 test for categorical variables. Logistic regression analysis was conducted to identify independent risk factors for TDs, and survival analysis was performed using the Kaplan–Meier method with the log-rank test. Continuous variables are presented as mean ± standard deviation, whereas categorical variables are expressed as the percentage of patients. In multivariate analyses, the clinicopathological characteristics with $P < 0.05$ in univariate analysis were included to determine independent prognostic factors. Statistical significance was set at a P value of <0.05.

RESULTS

Clinicopathological Characteristics of Colon Cancer Patients with TDs

Among the 4212 patients (mean age:63.86 years, male-to-female ratio:56.2:43.8) included in this study, 662 (15.7%) had TDs; the mean number of TDs was 2.15 ± 2.251 (range:1–27). Of the 662 TD-positive patients, 500 (75.5%) were LNM-positive, while 162 (24.5%) were LNM-negative and classified as stage pN1c. The proportion of TDs increased according to the nodal stage: 463 of 1373 N1 colon cancers and 199 of 464 N2 colon cancers (33.7% *vs* 42.9%, $P < 0.001$). Compared with TD-negative patients, a higher proportion of TD-positive patients received postoperative chemotherapy. However, there

TABLE 1.

Clinical Characteristics of Patients with Nonmetastatic Colon Cancer (SECOG data)

Characteristic	TD-negative (n = 3550)	TD-positive (n = 662)	*P* value
Age (years, mean ± SD)	63.92 ± 11.19	63.45 ± 11.15	0.489
≤65	1930 (54.4)	350 (53.0)	
>65	1617 (45.6)	311 (47.0)	
Sex			0.982
Male	1996 (56.2)	372 (56.2)	
Female	1553 (43.8)	275 (43.8)	
BMI	23.89 ± 3.45	23.84 ± 3.27	0.999
≤25	2333 (65.8)	435 (65.8)	
>25	1212 (34.2)	226 (34.2)	
Comorbidity	2319 (65.3)	432 (65.3)	0.973
CEA	7.80 ± 61.89	10.22 ± 42.33	<0.001
≤5 ng/mL	2831 (81.4)	471 (71.5)	
>5 ng/Ml	646 (18.6)	188 (28.5)	
Location			<0.001
Rt colon	1436 (40.5)	201 (30.4)	
Lt colon	2114 (59.5)	461 (69.6)	
Postoperative chemotherapy			<0.001
No	1015 (39.5)	66 (13.0)	
Yes	1552 (60.5)	441 (87.0)	
Chemotherapy regimen (n = 1481)*			0.987
5-FU	192 (20.0)	107 (20.6)	
5-FU + Oxaliplatin	764 (79.5)	410 (78.8)	
5-FU + Irinotecan	2 (0.2)	1 (0.2)	
Others	3 (0.3)	2 (0.4)	

Values are presented as number (%).

*only in stage III.

BMI indicates body mass index; CEA, carcinoembryonic antigen; Lt. colon, left colon; Rt. colon, right colon; SECOG, Seoul colorectal research group.

TABLE 2.

Histopathological Characteristics of Patients With Non-metastatic Colon Cancer (SECOG data)

Characteristic	TD-negative (n = 3550)	TD-positive (n = 662)	*P* value
Histology			<0.001
ADC, WD	356 (10.4)	16 (2.4)	
ADC, MD	2802 (82.1)	574 (87.1)	
ADC, PD	149 (4.4)	44 (6.7)	
Others*	105 (3.1)	25 (3.8)	
T category			<0.001
T1	461 (13.0)	56(0.9)	
T2	522 (14.7)	21 (3.2)	
T3	2146 (60.5)	435 (65.7)	
T4	421 (11.9)	200 (30.2)	
N category			<0.001
N0	2375 (66.9)	0 (0.0)	
N1	910 (25.6)	463 (69.9)	
N2	265 (7.5)	199 (30.1)	
Lymphatic invasion			<0.001
Negative	2257 (76.5)	297 (52.9)	
Positive	694 (23.5)	264 (47.1)	
Vascular invasion			<0.001
Negative	3150 (88.8)	427 (64.6)	
Positive	398 (11.2)	234 (35.4)	
Perineural invasion			<0.001
Negative	2316 (65.3)	201 (30.4)	
Positive	1232 (34.7)	460 (69.6)	

Values are presented as number (%).

*Mucinous, Signet ring cell, Undifferentiated.

ADC indicates adenocarcinoma; MD, moderately-differentiated; PD, poorly-differentiated; SECOG, Seoul colorectal research group; WD, well-differentiated.

was no difference in the chemotherapy regimen according to the presence or absence of TDs in the stage III patients. The main chemotherapy regimen was XELOX (capecitabine, oxaliplatin) or FOLFOX (5-FU, leucovorin, oxaliplatin). The association between the TD status and clinicopathologic findings is shown in Tables 1 and 2.

Risk Factors for TDs

Univariate analysis showed that carcinoembryonic antigen (CEA) level >5 ng/mL, left-sided colon cancer, poorly-differentiated histology, higher T category, N category (odds ratio [OR]: 1.48; 95% confidence interval [CI] = 1.19–1.83), lymphatic invasion (OR: 2.89; 95% CI = 2.40–3.48), vascular invasion (OR: 4.34; 95% CI = 3.59–5.25), and perineural invasion (OR: 4.30; 95% CI = 3.60–5.15) were significant risk factors for TDs ($P < 0.001$; Table 3). In contrast, multivariate analysis indicated that CEA level, histology, and lymphatic invasion were not significant.

Patterns of Tumor Recurrence

During a median follow-up period of 38.70 months (range: 0–114 months), 23.11% of the TD-positive patients and 7.46% of the TD-negative patients experienced local and/or distant tumor recurrence ($P < 0.001$; Table 4). Tumor recurrence encompassed local and distant metastases in 55 and 130 patients, respectively. The frequency of both metastatic patterns significantly increased as the N stage advanced (distant metastasis, $P < 0.001$; local recurrence, $P < 0.001$). Local and distant metastases occurred more frequently in TD-positive patients than in TD-negative patients ($P < 0.001$), with comparable ORs for distant metastasis (OR: 3.59; 95% CI = 2.82–4.58; $P < 0.001$) and local recurrence (OR: 3.53; 95% CI = 2.49–5.01; $P < 0.001$).

Survival Analysis Based on Nodal Status and TDs

The RFS and OS rates of the TD-positive patients were significantly lower than those of the TD-negative patients (5-year RFS: 70.7% *vs* 89.8%, $P < 0.001$; 5-year OS: 78.2% *vs* 90.5%, $P < 0.001$; Fig. 1). In the LN0 group, both RFS and OS rates were inferior among the TD-positive patients (5-year RFS: 76.8% *vs* 93.6%, $P < 0.001$; 5-year OS: 78.9% *vs* 92.0%, $P < 0.001$; Fig. 2). The RFS and OS rates of TD-positive patients with LN0 were inferior to those of TD-negative patients with LN1–3 (5-year RFS: 76.8% *vs* 84.5%, $P = 0.024$; 5-year OS: 78.9% *vs* 87.8%, $P = 0.035$). The RFS and OS rates of TD-positive patients with LN0 were not significantly different from those of TD-negative patients with LN ≥4 (5-year RFS: 76.8% *vs* 74.1%, $P = 0.856$; 5-year OS: 78.9% *vs* 87.0%, $P = 0.571$). TD-positive patients with LN1–3 had markedly lower RFS and OS rates than TD-negative patients with LN1–3 (5-year RFS: 69.3% *vs* 84.5%, $P < 0.001$; 5-year OS: 77.1% *vs* 87.8%, $P < 0.001$). Furthermore, the RFS and OS rates of TD-positive patients with LN1–3 were not different from those of TD-negative patients with LN ≥4 (5-year RFS: 74.1% *vs* 69.3%, $P = 0.177$; 5-year OS: 87.0% *vs* 77.1%, $P = 0.106$). The RFS and OS rates of TD-positive patients with ≥4 LNs were lower than those of TD-negative patients with ≥4 LNs; however, the difference was not statistically significant (5-year RFS: 67.5% *vs* 74.1%, $P = 0.109$; 5-year OS: 79.7% *vs* 87.0%, $P = 0.401$).

Survival Analysis from the SEER Database

Overall, 8320 (8.64%) patients had TDs, among whom 5976 (71.8%) were LNM-positive. The mean number of TDs was 2.81 ± 5.118 (range: 1–81). The association between the TD status and clinicopathological characteristics in the SEER registry is shown in Supplemental Table 1, http://links.lww.com/AOSO/A365. Survival analysis was performed to compare TD-positive and TD-negative patients based on SEER data

TABLE 3.
Risk Factors for TDs

	Univariate Analysis			Multivariate Analysis		
Prognostic Factor	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
Age >65	1.061	0.898–1.253	0.489			
CEA >5 ng/mL	1.749	1.447–2.114	<0.001	0.964	0.743–0.1251	0.784
Location						
Rt colon	1.000					
Lt colon	1.558	1.303–1.863	<0.001	1.438	1.125–1.837	0.004
Histology						
ADC, WD	1.000					
ADC, MD	4.558	2.740–7.582	<0.001	1.615	0.740–3.524	0.229
ADC, PD	6.570	3.594–12.012	<0.001	1.813	0.748–4.397	0.188
T category						
T1	1.000					
T2	3.091	1.237–7.724	0.016	1.755	0.546–5.640	0.345
T3	15.574	6.915–35.077	<0.001	4.063	1.410–11.708	0.009
T4	36.500	16.032–83.102	<0.001	5.4355	1.807–15.871	0.002
N category						
N1	1.000					
N2	1.476	1.190–1.830	<0.001	1.082	0.828–1.413	0.563
Lymphatic invasion	2.891	2.399–3.483	<0.001	0.910	0.722–1.147	0.424
Vascular invasion	4.337	3.585–5.247	<0.001	1.669	1.280–2.175	<0.001
Perineural invasion	4.302	3.595–5.148	<0.001	1.458	1.141–1.864	0.003

Values are presented as number (%).
ADC indicates adenocarcinoma; CEA, carcinoembryonic antigen; Lt. colon, left colon; MD, moderately-differentiated; PD, poorly-differentiated; Rt. colon, right colon; WD, well-differentiated.

TABLE 4.
Recurrence Pattern

Characteristic	**TD-negative (n = 3550)**	**TD-positive (n = 662)**	***P* value**
Recurrence	265 (7.46)	153 (23.11)	<0.001
Site of recurrence			
Local	87 (2.45)	55 (8.31)	<0.001
Distant	215 (6.06)	130 (19.64)	<0.001
Both	66 (1.86)	46 (6.95)	<0.001

Values are presented as number (%).

(median survival:44.00 months; range, 0–95 months). The 5-year CSS rates for TD-positive and TD-negative patients were 54.8% and 82.7%, respectively ($P < 0.001$; Fig. 3). In the LN0 group, CSS rates were lower in the TD-positive patients than in the TD-negative patients (5-year CSS: 88.1% *vs* 68.3%, $P < 0.001$; Fig. 3). Notably, TD-positive patients with LN0 exhibited worse survival than patients with LN1-3 (5-year CSS:76.0% *vs* 68.3%, $P < 0.001$). In the LN1-3 group, TD-positive patients had lower survival rates than TD-negative patients (5-year CSS: 59.9% *vs* 75.7%, $P < 0.001$). No significant difference in survival was observed between TD-positive patients with LN1-3 and TD-negative patients with LN ≥4 (5-year CSS: 59.9% *vs* 58.3%, $P = 0.116$). The CSS rates of TD-positive patients with LN ≥4 were lower than those of TD-negative patients with LN ≥4 (5-year CSS: 40.5% *vs* 58.3%, $P < 0.001$).

DISCUSSION

This retrospective multicenter study revealed that the oncologic outcomes of TD-positive patients were inferior to those of TD-negative patients and that patients with TDs in the N1 category exhibited the same risk of recurrence as patients in the N2 category. In this study, TDs were detected in 15.7% (662/4,212) of stage I–III colon cancer patients in the Korean SECOG database and in 8.94% (8320/93,057) of patients in the US SEER database. The difference might be due to the fact that the experienced pathologists in the tertiary hospitals in SECOG tried more efforts to detect TDs after the importance of TDs in the AJCC 7th edition in 2010. TDs were more frequently observed in patients with elevated CEA levels, left-sided colon cancer, aggressive tumor histology, and advanced T- and N-stages. In addition, the presence of TDs is associated with lymphatic, vascular, and perineural invasions.

Since the 2000s, TDs have been detected in approximately 20% (range: 4.9–41.8%) of patients with stage I–IV colon or rectal cancer,[18] with an increasing number of studies highlighting the adverse prognostic impact of TDs in CRC. Furthermore, some studies have focused on considering TDs independently from LNMs because of potential differences in the survival impact between these 2 forms of discontinuous spread.[8,19] A meta-analysis of TDs reported hazard ratios of 2.2 (1.6–3.0) for disease-free survival, 3.3 (2.2–4.7) for disease-specific survival, and 2.9 (2.2–3.8) for OS.[18] An analysis of CRC data pooled from the SEER database demonstrated that TD was associated with lower 3-year OS in multivariate models. A phase III trial involving colon cancer patients who received adjuvant chemotherapy (IDEA, International Duration Evaluation of Adjuvant Chemotherapy, France) further showed that the risk of recurrence or death was significantly higher in patients with TDs, irrespective of LNM substrates.[17] Our findings indicate that TDs are an independent prognostic factor associated with a higher T category, along with vascular invasion and the number of LNMs in patients with CRC. The RFS and OS of the TD-positive patients were significantly poorer than those of the TD-negative patients. We also conducted a survival analysis using the SEER database, a large dataset from multiple institutions that produced similar outcomes.

We further analyzed the survival outcomes by stratifying the presence of TDs according to the number of metastatic LNs. Our findings indicated that both RFS and OS of TD-positive patients were worse under each N category, suggesting that N1c should not be overlooked when N1a/b is present and that it may be associated with a more aggressive prognosis. Even N1a/b TD-positive cases can be upstaged to N2. Dividing the N2 category into TD-negative and TD-positive subgroups for prognostic value or proposing a more aggressive N category (e.g., N3) may prove beneficial.

To validate our findings, we conducted a similar analysis using SEER data and observed a strikingly comparable

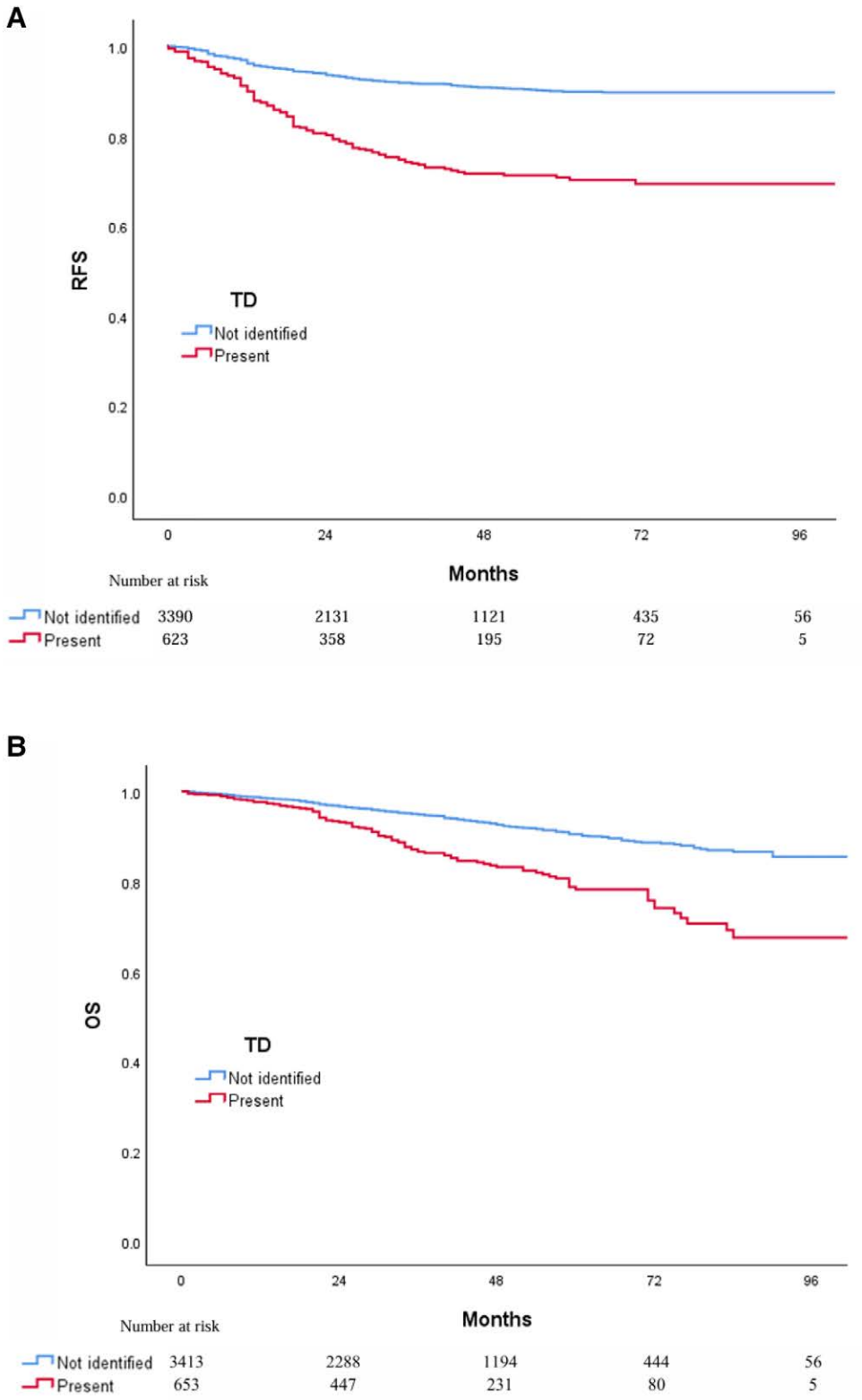

FIGURE 1. Kaplan–Meier curves for (A) recurrence-free and (B) overall survival according to the presence of TDs (SECOG data). OS indicates overall survival; RFS, recurrence-free survival; SECOG, Seoul colorectal research group.

survival curve between TD-positive patients with LN1–3 and TD-negative patients with LN≥4. Other studies on patients with stage III colon cancer using data pooled from the National Cancer Database and SEER registry reported that the coexistence of TDs and LN metastases conferred an additive risk.[20,21] The presence of both factors was significantly correlated with worse survival outcomes than the presence of each risk factor alone. Recent post hoc analyses following randomized controlled trials have proposed modifications to nodal staging by adding the number of TDs to the number of positive LNMs.[13–16] These amended nodal stages may better reflect survival outcomes than the previous AJCC staging

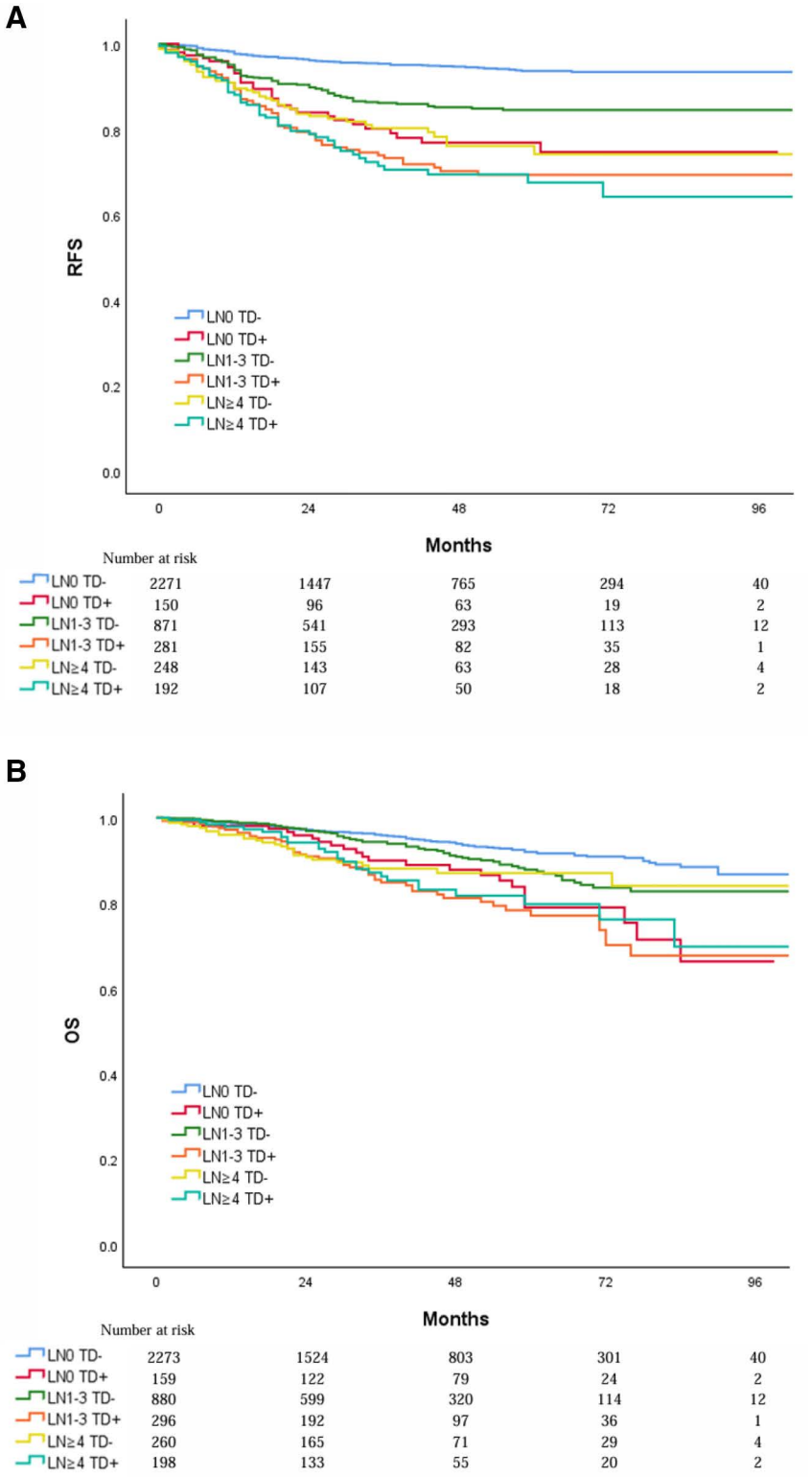

FIGURE 2. Kaplan–Meier curves for (A) recurrence-free (B) overall survival according to the number of LNM (LN 0/1–3/≥4) and the presence of TDs (SECOG data). OS indicates overall survival; RFS, recurrence-free survival; SECOG, Seoul colorectal research group.

system, without disregarding the prognostic value of TDs. Nonetheless, there is an ongoing debate regarding whether TDs should be considered equivalent to LNs in terms of their prognostic value. Given that LNM is the most crucial prognostic factor for distant metastasis and long-term survival, some critics maintain an interest in solely counting the number of TDs and LNs and assigning equal weights to both factors.[17]

Accurate staging of colon cancer is essential for predicting prognosis and determining appropriate treatment plans. Our findings indicate that upstaging the N category for TD-positive patients can more accurately reflect the prognostic value of the current AJCC TNM staging system and may assist in the selection of intensive adjuvant chemotherapy. Recent efforts have been made to reduce the use of systemic chemotherapy in low-risk stage III colon cancer. The IDEA study confirmed that the

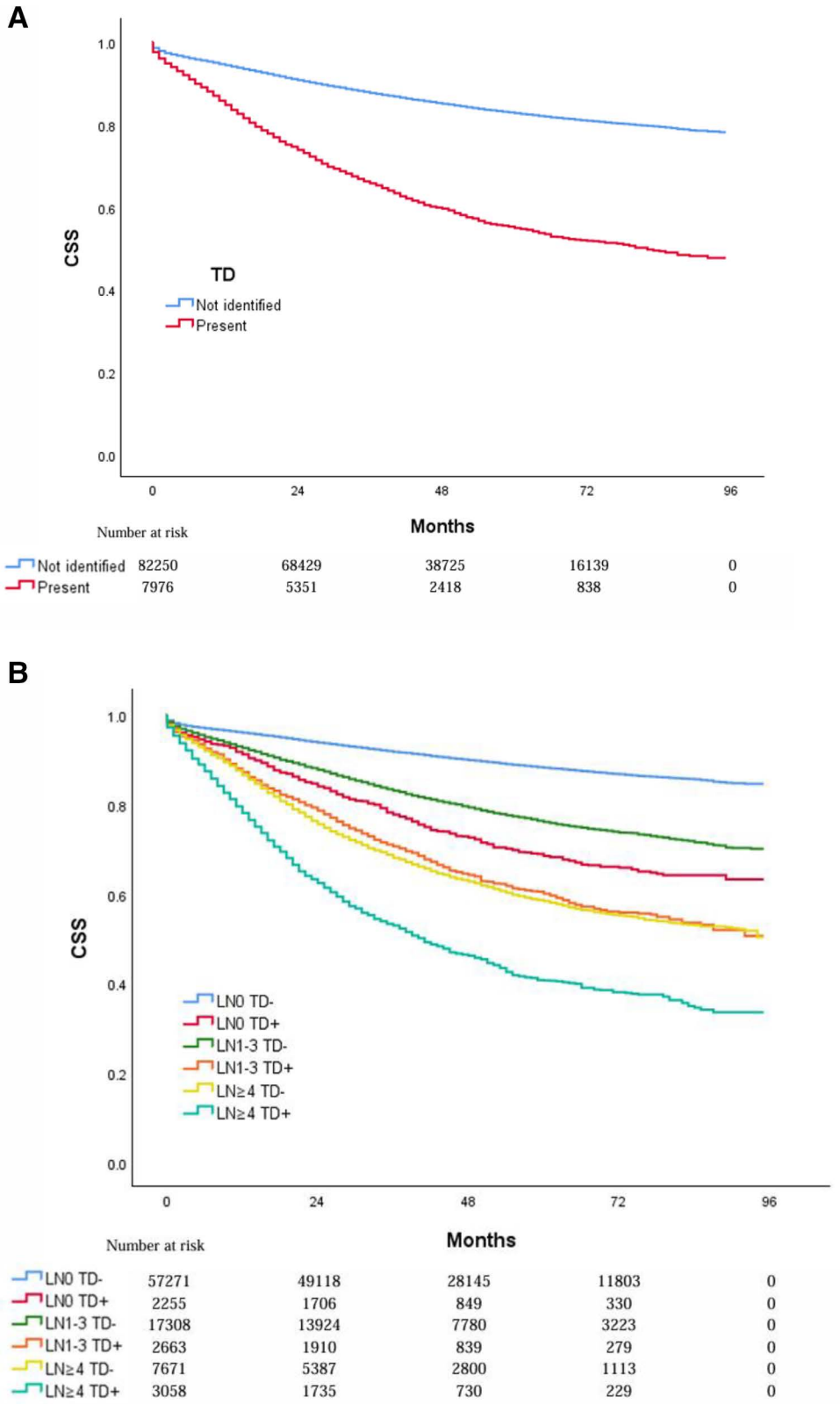

FIGURE 3. Kaplan–Meier curves for CSS according to (A) the presence of TDs and (B) the number of LNM (LN 0/1–3/≥4) and the presence of TDs (SEER data). CSS indicates cancer-specific survival.

3-month CAPOX (capecitabine, oxaliplatin) therapy for T1–3 and N1 cancers was not inferior to the 6-month therapy.[22] Similarly, the KCSG (Korean Cancer Study Group) CO09-07 study suggested that adding 3 months of oxaliplatin to 6 months of capecitabine could serve as an alternative adjuvant treatment for stage III CRC.[23] Nevertheless, caution is warranted when selecting patients for reduced conventional systemic chemotherapy because TDs may represent worse prognostic factors. Further research is required to determine whether chemotherapy reduction is feasible in patients with TD-positive stage III disease.

Our study has several limitations. First, the retrospective nature of this study may have introduced potential bias in the results. However, the baseline characteristics of the hospitals were comparable, suggesting that patient selection bias was within acceptable limits. Second, TD detection can inherently lead to inter-observer variability. In this multicenter study, size and shape were not considered as factors influencing TD identification, in accordance with the College of American Pathologists Cancer Protocol. Finally, owing to insufficient data, this study could not establish whether TD-positive colon cancer patients should receive different management strategies, specifically adjuvant chemotherapy. Nevertheless, the survival rates suggest that TD-positive and advanced-stage patients may benefit from more intensive treatment regimens. Despite these limitations, we posit that TDs have considerable potential as a prognostic marker. The strength of this study was to investigate the impact of TDs in the categories of LN metastasis, N1a, N1b, and N2, separately. The poor prognosis in the presence of TD with LN metastasis should not be ignored and should be followed with adjuvant treatment. Therefore, the presence of TDs should be considered when reclassifying patients into higher-stage categories.

CONCLUSIONS

Tumor deposits are established as adverse prognostic indicators, signifying heightened malignancy within nodal classification strata. Incorporating TDs into the TNM staging system could enhance its accuracy in reflecting patient outcomes, including recurrence and survival rates. Our findings suggest that retaining the N1c category is crucial for a high risk of poor prognosis and that prioritizing TD-positive cases to upstage within N classifications is warranted, especially in the case of TD-positive N1a or N1b to N2 category.

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