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RESEARCH

# Prognostic impact and independent significance of tumor deposits in early-stage colon cancer: a population-based cohort study

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## Abstract

**Background** Tumor deposits (TD) are well-established prognostic markers in advanced-stage colorectal cancer (CRC), but their independent significance in early-stage disease remains unclear. Current staging systems do not account for TD in node-negative CRC, despite emerging evidence suggesting a potential impact on survival. This study aimed to assess the prognostic impact of TD in early-stage (T1-T3, N0) colon cancer using a large population-based cohort and advanced statistical methods.

**Methods** A retrospective cohort study was conducted using the SEER database (2010–2021), including 111,106 patients with early-stage (T1–T3) colon cancer, of whom 4055 (3.6%) were TD-positive. To minimize baseline imbalances, propensity score matching (1:3 nearest-neighbor; caliper = 0.2) was applied. Overall survival (OS) and disease-specific survival (DSS) were assessed using the Kaplan–Meier analysis and compared with log-rank tests. Multivariate Cox regression was performed to evaluate the independent prognostic impact of TD status in both unmatched and matched cohorts.

**Results** TD-positive patients demonstrated significantly worse overall survival (OS) and disease-specific survival (DSS) compared to TD-negative patients (log-rank $p < 0.001$). In the unmatched cohort, TD positivity was independently associated with reduced OS (HR: 1.56, 95% CI: 1.48–1.65) and DSS (HR: 2.33, 95% CI: 2.14–2.54; both $p < 0.001$). These associations remained significant after propensity score matching (OS: HR: 1.44, 95% CI: 1.35–1.54; DSS: HR: 2.17, 95% CI: 1.97–2.40; both $p < 0.001$).

**Conclusion** TD is an independent prognostic factor in early-stage colon cancer, warranting closer surveillance and reconsideration of treatment strategies. These findings suggest that TD should be integrated into risk stratification models, challenging current staging paradigms.

**Keywords** Colorectal cancer · Tumor deposits · Prognostic factor · Overall survival

## Introduction

Colorectal cancer is a significant public health concern worldwide, and surgical treatment can improve survival rates. However, certain prognostic factors influencing this success have not yet been fully elucidated. Colorectal cancer (CRC) remains the second leading cause of cancer-related mortality worldwide, accounting for over 900,000 deaths annually. While surgical resection improves survival, the role of specific prognostic factors in early-stage disease remains unclear [1].

In recent years, tumor deposits (TD) have emerged as a significant prognostic indicator. TDs are tumor foci located in the mesenteric soft tissue surrounding the tumor, independent of lymph nodes, and lacking a distinct lymph node structure [2, 3].

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Although the biological nature of TDs remains controversial, they are thought to be associated with lymphatic invasion, perineural spread, or vascular metastatic foci. However, current guidelines and studies primarily focus on the prognostic value of TDs in advanced-stage colorectal cancer [4–6]. The impact of TD on survival in early-stage (T1-T3, N0) colorectal cancer patients has not yet been sufficiently elucidated [2].

Approximately 20% of patients with colon cancer exhibit TDs. Although the presence of TDs has been associated with poorer prognosis in the existing literature, these findings are largely based on stage III and IV patients [4, 5, 7–9].

Although T4 stage and inadequate lymph node sampling (< 12 nodes) are well-established high-risk features, other adverse prognostic indicators include poor histologic differentiation, lymphovascular and perineural invasion, bowel obstruction or perforation, and elevated preoperative carcinoembryonic antigen (CEA) levels. These features are routinely considered in current adjuvant treatment guidelines for stage II colon cancer [10, 11]. But, the prognostic value of tumor deposits (TDs) remains insufficiently characterized. Adjuvant chemotherapy is generally recommended for stage II patients with a high risk of recurrence. However, there is no consensus on which factors predict the benefit of adjuvant chemotherapy. Accurate identification of prognostic and predictive parameters is essential to optimize survival while avoiding overtreatment in patients who would not benefit from additional therapy [10, 11].

Although patients with stage II colon and rectal cancer with TDs have been reported to have a prognosis as poor as that of stage III patients, these findings have not been supported by prospective studies, and the level of evidence remains insufficient [12]. Additionally, the presence or number of TDs has been reported to strongly correlate with poor prognostic pathological factors such as intramural and extramural vascular invasion, perineural invasion, lymphatic invasion, and lymph node metastasis [7, 8, 13]. Therefore, it has been suggested that TD should be considered a prognostic marker in stage II colorectal cancer patients and classified within the "m" stage in existing staging systems [12, 13]. However, stronger prospective studies are needed to clarify the clinical significance of TD.

Despite the aforementioned evidence, studies on TDs have methodological limitations. These include (i) the analysis of colon and rectal cancer as a single entity; (ii) small sample sizes; (iii) a low number of lymph nodes removed, raising concerns about adequate staging and surgical quality; and (iv) a lack of stratification or adjustment for postoperative chemotherapy use [7, 8, 12, 13].

The question, "Do these foci truly have significance in early-stage colorectal cancer patients?," necessitates a reconsideration of both surgical practice and treatment strategies. Therefore, this study was designed to evaluate the prognostic impact of tumor deposit (TD) positivity on overall survival (OS) and disease-specific survival (DSS) in patients with early-stage colon cancer using a large population-based cohort and robust statistical methods.

## Materials and methods

### Data source and study population

This retrospective cohort study utilized data from the Surveillance, Epidemiology, and End Results (SEER) 17 Registries database for the period 2010–2021. SEER is a comprehensive cancer registry system that provides extensive epidemiological data on cancer incidence, treatment, and survival outcomes across diverse geographic regions in the USA. In this study, early-stage colon cancer was defined as T1–T3 disease with no regional lymph node metastasis (N0) based on AJCC criteria. However, due to occasional inconsistencies in SEER coding—such as cases recorded as N0 despite the presence of tumor deposits (TD) or cases classified as N1c without corresponding TD coding—reclassification was undertaken. Specifically, patients with N0 staging but TD positivity were recoded as N1c, and those labeled as N1c were assumed to be TD-positive regardless of TD field status, in alignment with AJCC TNM staging definitions. This approach ensured internal consistency within the dataset and accounted for potential misclassification. The primary objective of the study was to evaluate the prognostic impact of TD positivity on survival outcomes in early-stage colon cancer.

The study population was initially defined by identifying 431,633 patients with colorectal cancer recorded in the SEER 17 Registries database from 2010 to 2021. Patients were excluded if they had tumors located in the rectum or appendix ($n = 113{,}927$), unknown tumor deposit status ($n = 88{,}129$), Tis, Tx, or T4 stage tumors ($n = 53{,}242$), nodal classifications other than N0 or N1c (including N1 NOS, N1a, N1b, N2, and NX; $n = 61{,}484$), or AJCC Stage 4 disease ($n = 3{,}745$). After applying standard exclusion criteria, a total of 111,106 colon cancer patients remained eligible for analysis. Following reclassification, 4055 patients were categorized as TD-positive (T1–T3, N1c), and 107,051 patients as TD-negative (T1–T3, N0). After 1:3 nearest-neighbor propensity score matching, 14,810 patients were retained for the final matched cohort, including 3712 TD-positive and 11,098 TD-negative individuals (Fig. 1).

To investigate the prognostic relevance of TD in early-stage colon cancer, a comprehensive analysis was performed of demographic, clinicopathological, and survival-related variables. Demographic characteristics included age (< 65 vs. ≥ 65 years), sex (female vs. male), race (White, Black, Other), and marital status (married vs.

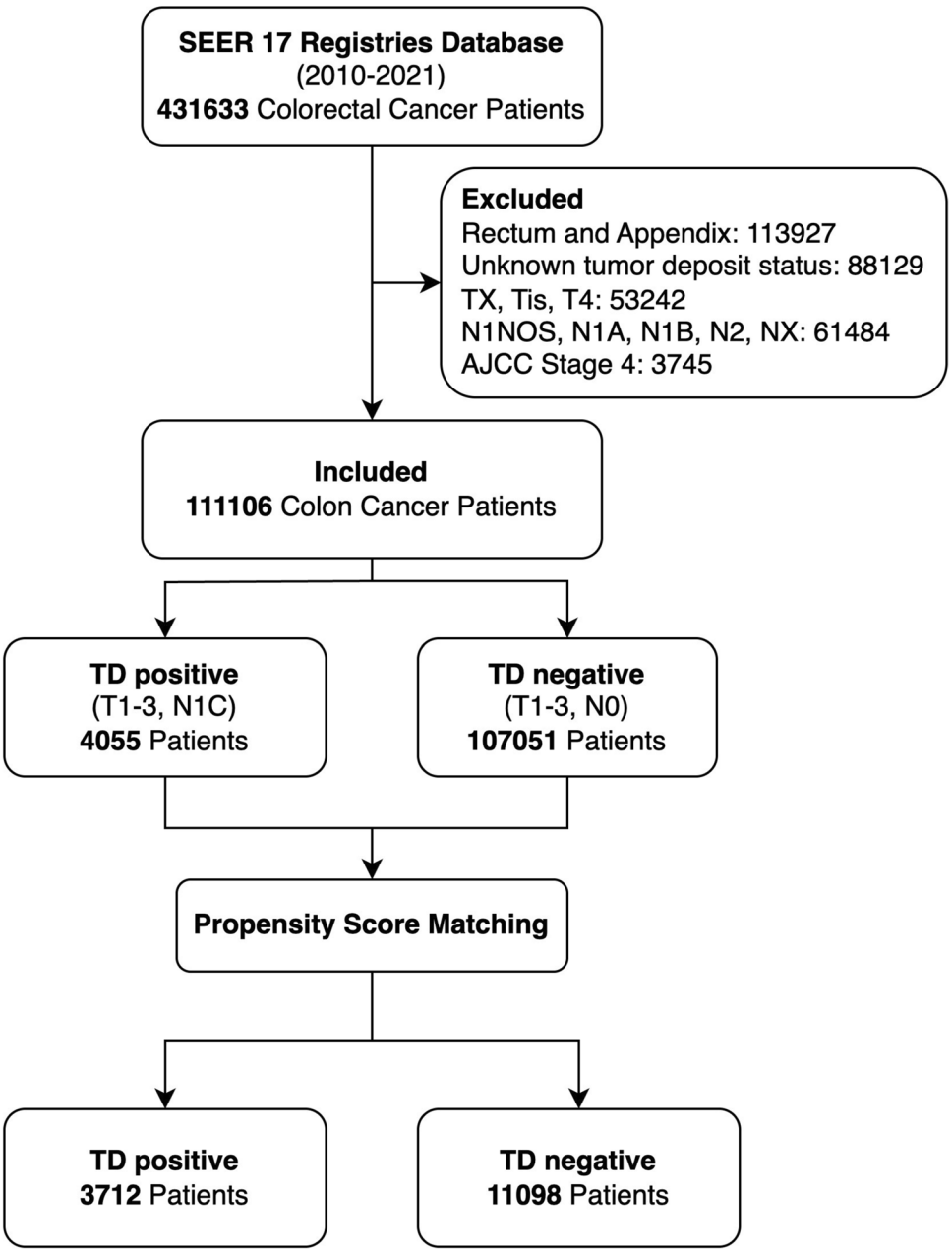


**Fig. 1** Flowchart of the study population

unmarried). Tumor-related features encompassed tumor location (right vs. left colon, or unknown), histological subtype (adenocarcinoma, mucinous, or other), tumor grade (Grade 1: well-differentiated; Grade 2: moderately differentiated; Grade 3/4: poorly differentiated or anaplastic), and T stage (T1, T2, T3). Additional clinical variables included serum carcinoembryonic antigen (CEA) level (positive vs. negative) and receipt of chemotherapy (yes vs. no). As this study utilized de-identified data from the SEER database, which is publicly available and maintains patient anonymity, ethical approval and informed consent were not required.

## Statistical analysis

All statistical analyses were conducted using R software (version 4.4.2) and IBM SPSS Statistics for Mac, Version 29.0.1.0. Categorical variables were expressed as frequencies and percentages, and comparisons between groups were performed using the Pearson chi-square test. To address confounding and reduce baseline differences between tumor deposit-positive and -negative groups, propensity score matching (PSM) was performed using a 1:3 nearest-neighbor matching algorithm with a caliper value of 0.2. Matching was based on logistic regression including variables such as sex, age, marital status, race, tumor

location, grade, T stage, and chemotherapy. Covariate balance was assessed post-matching by calculating standardized mean differences (SMD), with SMD $<0.1$ indicating adequate balance. Following PSM, survival analyses were conducted separately for overall survival (OS) and disease-specific survival (DSS). Kaplan–Meier curves were constructed to estimate survival probabilities, and differences between groups were evaluated using the log-rank test. To identify factors associated with OS and DSS, univariate and multivariate Cox proportional hazards regression analyses were performed. Univariate models were fitted for each variable individually. All covariates were subsequently included in the multivariate model regardless of univariate significance. Hazard ratios (HR) with 95% confidence intervals (CI) and *p*-values were reported. Forest plots were generated to visually display the independent predictors of OS and DSS based on multivariate Cox regression models. A two-sided *p*-value $<0.05$ was considered statistically significant for all analyses.

## Results

A total of 111,106 patients with early-stage (T1–T3) colon cancer were included in the study, comprising 4055 tumor deposit (TD)-positive and 107,051 TD-negative cases. While sex distribution was similar between the two groups ($p = 0.150$), TD-positive patients were slightly more likely to be under 65 years of age (38.9% vs. 35.5%, $p < 0.001$) and less likely to be married (51.3% vs. 53.4%, $p = 0.002$). Racial distribution also differed significantly, with a lower proportion of White patients (76.1% vs. 79.9%) and a higher proportion of Black (12.1% vs. 10.5%) and Other races (11.3% vs. 8.9%) in the TD-positive group ($p < 0.001$) (Table 1).

Tumor location varied notably, with left-sided tumors more common among TD-positive patients (51.4% vs. 40.2%) and right-sided tumors more common among TD-negative patients (58.3% vs. 46.8%, $p < 0.001$).

**Table 1** Patient characteristics

| | | Tumor deposit | | *p* |
|---|---|---|---|---|
| | | Positive | Negative | |
| Sex | Female | 1963 (48.4) | 53,054 (49.6) | 0.150 |
| | Male | 2092 (51.6) | 53,997 (50.4) | |
| Age | < 65 | 1577 (38.9) | 38,033 (35.5) | < 0.001 |
| | ≥ 65 | 2478 (61.1) | 69,018 (64.5) | |
| Marital status | Married | 2081 (51.3) | 57,173 (53.4) | 0.002 |
| | Unmarried | 1786 (44) | 44,330 (41.4) | |
| | Unknown | 188 (4.6) | 5548 (5.2) | |
| Race | White | 3084 (76.1) | 85,507 (79.9) | < 0.001 |
| | Black | 489 (12.1) | 11,279 (10.5) | |
| | Other | 458 (11.3) | 9547 (8.9) | |
| | Unknown | 24 (0.6) | 718 (0.7) | |
| Site | Right colon | 1897 (46.8) | 62,414 (58.3) | < 0.001 |
| | Left colon | 2084 (51.4) | 42,998 (40.2) | |
| | Large intestine, nos | 74 (1.8) | 1639 (1.5) | |
| CEA | Negative | 1443 (35.6) | 43,530 (40.7) | < 0.001 |
| | Positive | 1116 (27.5) | 18,663 (17.4) | |
| | Unknown | 1496 (36.9) | 44,858 (41.9) | |
| Grade | 1 | 277 (6.8) | 12,718 (11.9) | < 0.001 |
| | 2 | 2991 (73.8) | 78,597 (73.4) | |
| | 3/4 | 706 (17.4) | 11,952 (11.2) | |
| | Unknown | 81 (2) | 3784 (3.5) | |
| Histology | Adenocarcinoma, nos | 3401 (83.9) | 76,805 (71.7) | 0.166 |
| | Musinöz adenocarcinoma | 266 (6.6) | 7246 (6.8) | |
| | Others | 388 (9.6) | 23,000 (21.5) | |
| T Stage | T1 | 186 (4.6) | 26,640 (24.9) | < 0.001 |
| | T2 | 360 (8.9) | 24,402 (22.8) | |
| | T3 | 3509 (86.5) | 56,009 (52.3) | |
| Chemotherapy | Yes | 1986 (49) | 7914 (7.4) | < 0.001 |
| | No | 2069 (51) | 99,137 (92.6) | |

TD-positive patients also showed higher rates of positive carcinoembryonic antigen (CEA) levels (27.5% vs. 17.4%, $p < 0.001$), and a greater frequency of poorly differentiated tumors (Grade 3/4: 17.4% vs. 11.2%, $p < 0.001$) (Table 1). Advanced T stage was more prevalent in the TD-positive group, with 86.5% having T3 tumors compared to 52.3% in the TD-negative group ($p < 0.001$). Additionally, chemotherapy administration was substantially higher among TD-positive patients (49.0% vs. 7.4%, $p < 0.001$) (Table 1).

Survival analysis revealed significant differences in both overall survival (OS) and disease-specific survival (DSS) between TD-positive and TD-negative patients. In the full cohort, the 5-year OS rate was 62.5% for TD-positive patients versus 74.4% for TD-negative patients, while the 10-year OS rates were 45.3% and 53.9%, respectively (log-rank $p < 0.001$). For DSS, the 5-year survival rate was 78.4% in TD-positive patients compared to 92.5% in TD-negative patients, with corresponding 10-year rates of 71.0% and 89.1%, respectively (log-rank $p < 0.001$) (Fig. 2).

To reduce potential confounding and baseline imbalances, propensity score matching (PSM) was performed. Following 1:3 matching, the survival advantage of TD-negative patients remained evident. In the matched cohort, the 5-year OS rate was 62.8% for TD-positive patients and 73.4% for TD-negative patients, while the 10-year OS rates were 45.5% and 53.2%, respectively (log-rank $p < 0.001$). For DSS, the 5-year survival was 78.3% in the TD-positive group and 89.3% in the TD-negative group, and the 10-year DSS rates were 70.8% and 83.9%, respectively (log-rank $p < 0.001$) (Fig. 3).

In the unmatched cohort, TD positivity was significantly associated with worse OS in both univariate (HR: 1.47, 95% CI: 1.40–1.55) and multivariate analyses (HR: 1.56, 95% CI: 1.48–1.65; both $p < 0.001$). Other independent predictors of decreased OS included male sex, older age (≥ 65), unmarried status, Black race, mucinous

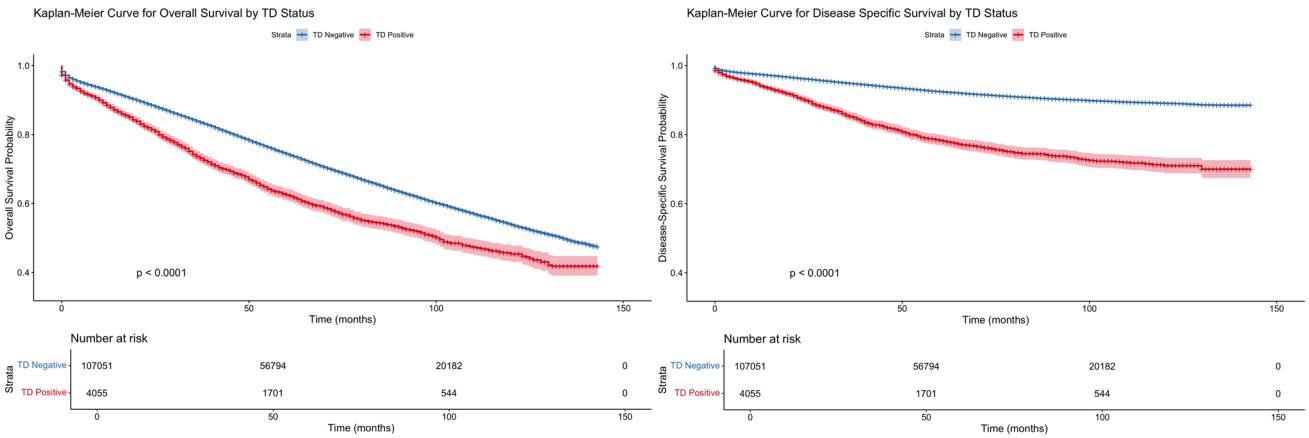


**Fig. 2** KM curves for OS and DSS in the unmatched cohort

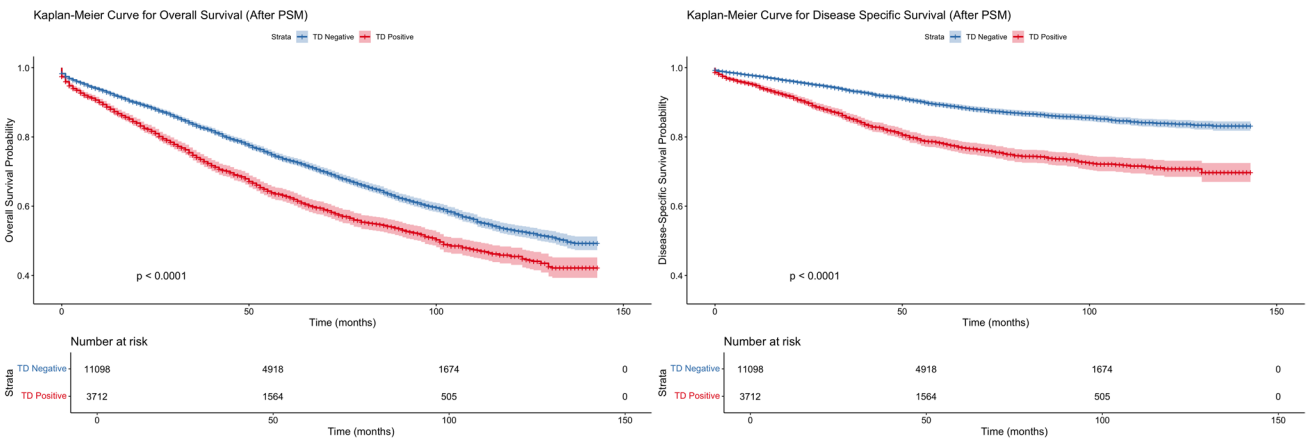


**Fig. 3** KM curves for OS and DSS after PSM

**Table 2** Cox regression analysis for overall survival

| Variable | Category | Univariate | | Multivariate | |
|---|---|---|---|---|---|
| | | HR (95% CI) | *p* | HR (95% CI), | *p* |
| Tumor deposit | Positive vs negative | 1.47 (1.40–1.55) | < 0.001 | 1.56 (1.48–1.65) | < 0.001 |
| Sex | Male vs female | 1.10 (1.07–1.12) | < 0.001 | 1.34 (1.31–1.37) | < 0.001 |
| Age | ≥ 65 vs < 65 | 3.72 (3.61–3.83) | < 0.001 | 3.54 (3.42–3.65) | < 0.001 |
| Marital status | Unmarried vs married | 1.60 (1.57–1.64) | < 0.001 | 1.57 (1.53–1.60) | < 0.001 |
| Race | Black vs White | 0.95 (0.92–0.98) | 0.004 | 1.05 (1.01–1.09) | 0.022 |
| | Other vs White | 0.69 (0.66–0.72) | < 0.001 | 0.77 (0.73–0.80) | < 0.001 |
| Tumor location | Left vs right | 0.76 (0.74–0.78) | < 0.001 | 0.98 (0.96–1.01) | 0.130 |
| Tumor grade | Grade 2 vs 1 | 1.12 (1.08–1.16) | < 0.001 | 1.14 (1.08–1.19) | < 0.001 |
| | Grade 3 vs 1 | 1.37 (1.31–1.43) | < 0.001 | 1.02 (0.98–1.06) | 0.286 |
| Histology | Mucinous vs Adeno | 1.18 (1.14–1.23) | < 0.001 | 1.09 (1.05–1.14) | < 0.001 |
| | Other vs Adeno | 0.78 (0.76–0.80) | < 0.001 | 0.99 (0.96–1.02) | 0.459 |
| T stage | T2 vs T1 | 1.32 (1.28–1.37) | < 0.001 | 1.17 (1.12–1.21) | < 0.001 |
| | T3 vs T1 | 1.68 (1.63–1.73) | < 0.001 | 1.49 (1.44–1.55) | < 0.001 |
| Chemotherapy | No vs yes | 1.50 (1.43–1.56) | < 0.001 | 1.42 (1.35–1.49) | < 0.001 |

histology, advanced T stage, and lack of chemotherapy (Table 2).

After propensity score matching, TD positivity remained significantly associated with worse OS (HR: 1.44, 95% CI: 1.35–1.54, $p < 0.001$). Older age, unmarried status, and lack of chemotherapy continued to be independent predictors. Tumor grade and T stage were not significantly associated with OS in the matched cohort (Table 3) (Fig. 4).

In the unmatched cohort, TD positivity was strongly associated with reduced DSS, with a hazard ratio of 2.91 in univariate analysis and 2.33 in multivariate analysis (both $p < 0.001$). Additional independent predictors of worse DSS included male sex, older age, unmarried status, Black race, and advanced T stage. Mucinous histology and tumor grade also showed significant associations in the adjusted model (Table 4).

Following propensity score matching, TD positivity remained an independent risk factor for DSS (HR: 2.17, 95% CI: 1.97–2.40, $p < 0.001$). Age ≥ 65, unmarried status, and chemotherapy were also associated with survival outcomes, while tumor grade, T stage, and tumor location were not significant in the matched cohort (Table 5) (Fig. 4).

## Discussion

The prognostic significance of TD in CRC has been well established in advanced-stage disease, where their presence is associated with worse survival outcomes. However, their role in early-stage CRC remains controversial due to a paucity of studies specifically addressing this subset of patients. While TD has been included in staging systems, its prognostic impact in the absence of lymph node involvement

**Table 3** Cox regression analysis for overall survival after PSM

| Variable | Category | Univariate | | Multivariate | |
|---|---|---|---|---|---|
| | | HR (95% CI) | *p* | HR (95% CI) | *p* |
| Tumor deposit | Positive vs negative | 1.43 (1.34–1.52) | < 0.001 | 1.44 (1.35–1.54) | < 0.001 |
| Sex | Male vs female | 1.14 (1.07–1.21) | < 0.001 | 1.33 (1.25–1.42) | < 0.001 |
| Age | ≥ 65 vs < 65 | 3.07 (2.85–3.30) | < 0.001 | 2.64 (2.44–2.85) | < 0.001 |
| Marital status | Unmarried vs married | 1.48 (1.40–1.57) | < 0.001 | 1.47 (1.38–1.56) | < 0.001 |
| Race | Black vs White | 1.07 (0.98–1.17) | 0.128 | 1.13 (1.03–1.23) | 0.010 |
| | Other vs White | 0.73 (0.66–0.82) | < 0.001 | 0.78 (0.70–0.88) | < 0.001 |
| Tumor location | Left vs right | 0.80 (0.75–0.85) | < 0.001 | 1.00 (0.94–1.07) | 0.951 |
| Tumor grade | Grade 2 vs Grade 1 | 1.00 (0.89–1.12) | 0.933 | 0.99 (0.88–1.12) | 0.883 |
| | Grade 3 vs Grade 1 | 1.09 (0.96–1.24) | 0.208 | 1.03 (0.91–1.18) | 0.615 |
| T stage | T2 vs T1 | 0.97 (0.79–1.18) | 0.736 | 0.92 (0.75–1.12) | 0.393 |
| | T3 vs T1 | 1.13 (0.96–1.34) | 0.147 | 1.08 (0.92–1.28) | 0.343 |
| Chemotherapy | Yes vs no | 2.21 (2.08–2.35) | < 0.001 | 1.68 (1.58–1.79) | < 0.001 |

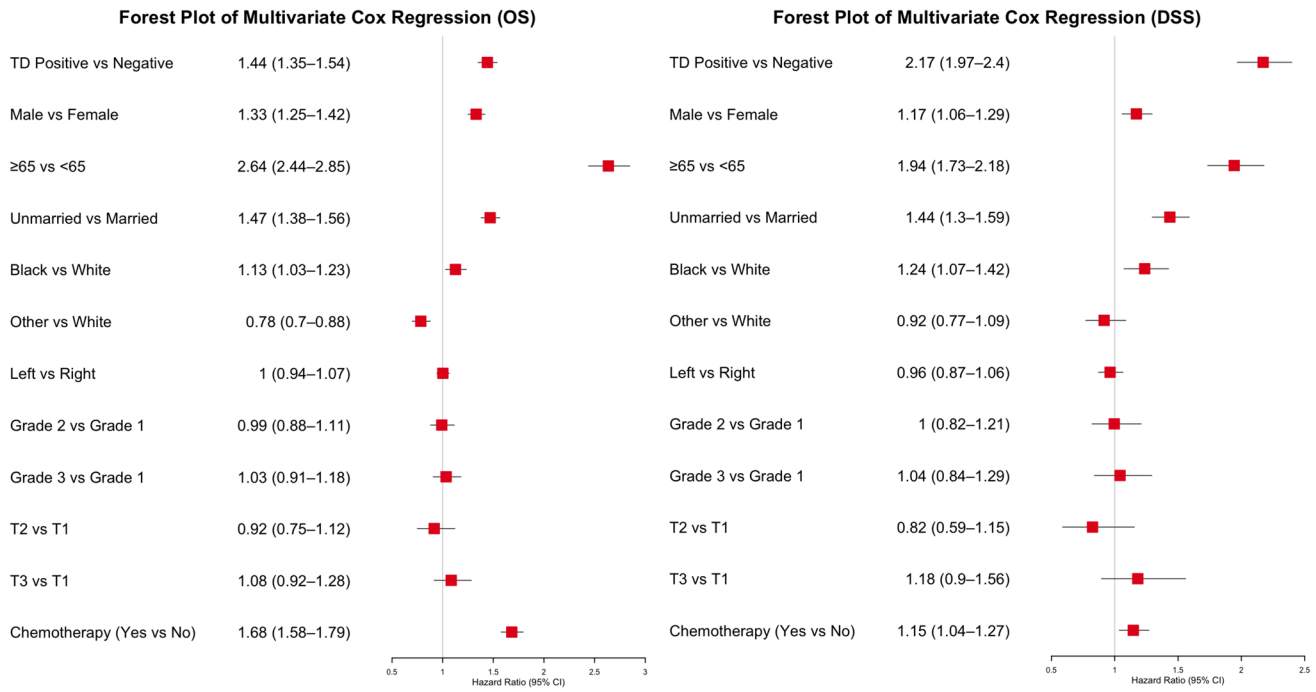


**Fig. 4** Forest plots of multivariate Cox regression for OS and DSS after PSM

**Table 4** Cox regression analysis for disease-specific survival

| Variable | Category | Univariate | | Multivariate | |
|---|---|---|---|---|---|
| | | HR (95% CI) | *p*-value | HR (95% CI) | *p*-value |
| Tumor deposit | Positive vs negative | 2.91 (2.70–3.15) | < 0.001 | 2.33 (2.14–2.54) | < 0.001 |
| Sex | Male vs female | 1.05 (1.00–1.10) | 0.033 | 1.21 (1.16–1.27) | < 0.001 |
| Age | ≥ 65 vs < 65 | 2.26 (2.14–2.38) | < 0.001 | 2.24 (2.11–2.37) | < 0.001 |
| Marital status | Unmarried vs married | 1.58 (1.51–1.65) | < 0.001 | 1.49 (1.42–1.57) | < 0.001 |
| Race | Black vs White | 1.17 (1.10–1.25) | < 0.001 | 1.23 (1.15–1.32) | < 0.001 |
| | Other vs White | 0.83 (0.77–0.91) | < 0.001 | 0.90 (0.82–0.98) | 0.013 |
| Tumor location | Left vs right | 0.91 (0.87–0.95) | < 0.001 | 1.09 (1.04–1.15) | < 0.001 |
| Tumor grade | Grade 2 vs 1 | 1.32 (1.22–1.43) | < 0.001 | 1.08 (0.99–1.17) | 0.081 |
| | Grade 3 vs 1 | 1.71 (1.56–1.88) | < 0.001 | 1.20 (1.09–1.32) | < 0.001 |
| Histology | Mucinous vs Adeno | 1.12 (1.03–1.21) | 0.006 | 1.06 (0.98–1.16) | 0.168 |
| | Other vs Adeno | 0.62 (0.59–0.66) | < 0.001 | 0.98 (0.92–1.05) | 0.552 |
| T stage | T2 vs T1 | 1.35 (1.24–1.47) | < 0.001 | 1.24 (1.13–1.37) | < 0.001 |
| | T3 vs T1 | 2.90 (2.72–3.10) | < 0.001 | 2.51 (2.32–2.73) | < 0.001 |
| Chemotherapy | No vs yes | 0.72 (0.67–0.77) | < 0.001 | 0.98 (0.90–1.05) | 0.518 |

(T1–T3, N0) has not been clearly delineated. Existing prognostic models have primarily focused on traditional factors such as TNM stage, lymph node involvement, vascular invasion, and preoperative CEA levels [14], often overlooking the potential impact of TD in early-stage disease. Given its well-documented adverse effect in advanced CRC, it is plausible that TD may also influence prognosis in early-stage cases [14].

Our findings demonstrate that TD is an independent prognostic factor in early-stage CRC, significantly influencing both OS and DSS. These results align with previous studies showing the negative impact of TD in advanced CRC while expanding this evidence to early-stage disease. In contrast to traditional prognostic markers, TD appears to confer an increased risk of recurrence and mortality even in the absence of lymph node metastasis. This suggests that TD should be integrated into future risk assessment models and may warrant closer follow-up strategies in affected patients. Furthermore, our results highlight the potential need for refinements in current staging systems, as TD-positive

**Table 5** Cox regression analysis for disease specific survival after PSM

| Variable | Category | Univariate | | Multivariate | |
|---|---|---|---|---|---|
| | | HR (95% CI) | *p* | HR (95% CI) | *p* |
| Tumor deposit | Positive vs negative | 2.12 (1.92–2.34) | < 0.001 | 2.17 (1.97–2.40) | < 0.001 |
| Sex | Male vs female | 1.02 (0.93–1.13) | 0.640 | 1.17 (1.06–1.30) | 0.002 |
| Age | ≥ 65 vs < 65 | 2.03 (1.82–2.26) | < 0.001 | 1.94 (1.73–2.18) | < 0.001 |
| Marital status | Unmarried vs married | 1.44 (1.30–1.58) | < 0.001 | 1.44 (1.30–1.59) | < 0.001 |
| Race | Black vs White | 1.22 (1.06–1.41) | 0.0048 | 1.24 (1.07–1.43) | 0.003 |
| | Other vs White | 0.89 (0.75–1.05) | 0.162 | 0.92 (0.77–1.09) | 0.316 |
| Tumor location | Left vs right | 0.83 (0.75–0.91) | < 0.001 | 0.96 (0.87–1.07) | 0.466 |
| Tumor grade | Grade 2 vs Grade 1 | 1.03 (0.85–1.25) | 0.743 | 1.00 (0.82–1.21) | 0.970 |
| | Grade 3 vs Grade 1 | 1.13 (0.91–1.40) | 0.263 | 1.04 (0.84–1.29) | 0.709 |
| T stage | T2 vs T1 | 0.90 (0.64–1.26) | 0.526 | 0.82 (0.59–1.16) | 0.261 |
| | T3 vs T1 | 1.21 (0.92–1.59) | 0.181 | 1.18 (0.90–1.56) | 0.238 |
| Chemotherapy | Yes vs no | 1.43 (1.29–1.57) | < 0.001 | 1.15 (1.04–1.27) | 0.008 |

early-stage CRC patients may exhibit outcomes more comparable to those with node-positive disease rather than truly node-negative cases.

Most previous studies on TD have focused on advanced-stage colorectal cancer, consistently demonstrating their association with poor prognosis and reduced survival rates. Several large-scale studies have reported that TDs correlate with worse outcomes in stage III and IV CRC, often being considered an extension of nodal or vascular invasion rather than an independent prognostic entity [15].

For instance, studies by Ma et al. and Zheng et al. have shown that in stage III CRC, the presence of TDs is associated with a significantly higher hazard ratio for recurrence and cancer-specific mortality. Our findings align with these earlier studies but extend the current knowledge by confirming the prognostic significance of TD even in early-stage CRC. Notably, the inclusion of node-negative patients in our analysis provides a unique perspective, highlighting the need to reevaluate the clinical implications of TD in this subgroup [2, 15–17].

A recent study by Wang et al. (2021) observed that TD-positive early-stage CRC patients had survival outcomes comparable to stage III patients, suggesting that TD may represent a more aggressive tumor phenotype independent of nodal involvement [18].

Recent advancements in CRC staging have highlighted the limitations of traditional nodal classification, prompting a shift toward incorporating additional prognostic factors. Arrichiello et al. (2022) underscored the significance of TD beyond conventional N staging, suggesting that TD may not merely represent an extension of nodal or vascular invasion but rather an indicator of tumor aggressiveness and disease dissemination. Our findings reinforce this perspective by demonstrating a strong correlation between TD positivity, elevated CEA levels, and poorly differentiated tumors, further supporting the hypothesis that TD may signify a biologically distinct, more aggressive CRC subset. Notably, TD-positive early-stage CRC patients in our cohort exhibited survival outcomes that were more aligned with node-positive cases, raising critical questions regarding the adequacy of current staging systems. Given these findings, a reevaluation of risk stratification models is warranted, integrating TD as a key prognostic parameter to refine patient management strategies and optimize therapeutic decision-making [19].

Recent studies, including those by Wang et al. and Arrichiello et al., suggest that TD represents a biologically aggressive tumor phenotype rather than a mere extension of nodal involvement. Our findings align with this perspective, reinforcing the need for integrating TD into future staging models [18, 19].

A key strength of this study lies in the use of advanced statistical methodologies, including PSM and multivariate Cox regression analysis. These approaches significantly reduce the risk of selection bias and provide a robust framework for evaluating the independent impact of TD on survival outcomes. Unlike traditional retrospective analyses, PSM ensures a well-balanced comparison by matching TD-positive and TD-negative patients based on key demographic and clinical characteristics. This allowed us to isolate the prognostic effect of TD more reliably and reduce potential confounding factors.

Our subgroup analyses further highlight the consistency of TD's impact across different patient categories. Notably, TD positivity remained a significant predictor of poor survival in all age groups and across tumor grades. This consistency reinforces the robustness of our findings and suggests that TD is a reliable marker of poor prognosis, regardless of other clinical variables.

Kaplan–Meier survival curves clearly illustrate the survival disadvantage associated with TD, with a marked separation between TD-positive and TD-negative groups in both

OS and DSS analyses. The hazard ratios derived from Cox regression analysis provide additional quantitative confirmation of this survival disparity, with TD-positive patients demonstrating a significantly higher risk of mortality.

The clinical significance of these findings is considerable. Traditionally, early-stage CRC has been regarded as having a favorable prognosis, with surgical resection often deemed curative. However, our results challenge this assumption by demonstrating that the presence of TD significantly reduces survival even in early-stage disease. This suggests that TD-positive patients represent a distinct high-risk subgroup that warrants closer follow-up and potentially more aggressive adjuvant treatment strategies.

Incorporating TD status into clinical practice could enhance patient management in several ways. First, TD-positive patients should be considered for more intensive postoperative monitoring to detect early signs of recurrence. Surveillance protocols for these patients may need to be adjusted, including more frequent cross-sectional imaging (e.g., CT or MRI) and serum biomarker assessments (e.g., CEA monitoring). Given that TD-positive patients exhibit survival patterns more similar to node-positive disease, existing follow-up guidelines for stage III CRC may be more appropriate for this subgroup.

Our findings support the need for reconsidering adjuvant therapy in TD-positive early-stage CRC patients. Current treatment guidelines, including those from the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO), often do not recommend adjuvant chemotherapy for node-negative early-stage disease. However, TD positivity may be a sufficient indicator of high-risk disease to justify its use. Prospective clinical trials evaluating the benefit of adjuvant chemotherapy in TD-positive early-stage patients are crucial to establish evidence-based recommendations.

Additionally, integrating TD status into existing prognostic models alongside TNM staging, vascular invasion, perineural invasion, and CEA levels could refine risk stratification and personalized treatment decisions. Such an approach may reduce overtreatment in genuinely low-risk patients while ensuring that high-risk individuals receive appropriate interventions.

The strong association between TD and adverse histopathological features (e.g., high-grade tumors, lymphovascular invasion) suggests a potential underlying molecular basis that merits further investigation. Future research should focus on the genomic and transcriptomic profiles of TD-positive tumors to identify novel therapeutic targets and refine treatment approaches. In addition, studies integrating liquid biopsy techniques (e.g., circulating tumor DNA, exosomal RNA profiling) may provide non-invasive methods for detecting minimal residual disease in TD-positive patients.

Ultimately, our findings advocate for a paradigm shift in how early-stage CRC is managed. Recognizing TD as a clinically relevant high-risk feature could facilitate more precise oncological decision-making and ultimately improve patient outcomes.

The strengths of our study include the large, population-based cohort derived from the SEER database and the use of propensity score matching to reduce bias and ensure balanced comparison between TD-positive and TD-negative groups. Furthermore, our focus on early-stage disease provides novel insights into a previously underexplored area of CRC research. Multivariate Cox regression analysis allowed for precise quantification of the independent effect of TD on survival outcomes, further reinforcing the robustness of our findings.

However, several limitations should be acknowledged. First, the retrospective nature of the study may introduce inherent biases despite the use of PSM. Second, the SEER database lacks detailed information on the location and morphology of TD, which may influence their prognostic impact. Additionally, treatment-related data, such as the specifics of adjuvant therapy, are not comprehensively recorded in SEER, limiting our ability to assess the impact of different treatment modalities on outcomes.

Despite its methodological strengths, our study has certain limitations. First, as a retrospective analysis, inherent selection biases and missing data cannot be entirely excluded, even with the use of PSM. The reliance on the SEER database, while providing a large and diverse patient cohort, limits access to granular pathological details such as tumor budding, perineural invasion subtypes, and molecular alterations (e.g., KRAS, BRAF, and MSI status). Future studies incorporating molecular profiling could provide deeper insights into the biological mechanisms underlying TD-related tumor aggressiveness.

Another key limitation is the lack of standardized histopathological criteria for TD assessment, which remains a subject of debate. Interobserver variability in TD identification could impact the reproducibility of findings across different institutions. Establishing a consensus-driven, standardized classification system for TD is essential for ensuring consistency in future studies.

In addition, the SEER database occasionally contains inconsistencies between TD status and nodal staging. To resolve this, we applied a rule-based reclassification in accordance with AJCC TNM definitions—reassigning N0 patients with TD to N1c and treating N1c cases as TD-positive regardless of explicit TD coding. While this approach aimed to ensure internal consistency and mitigate potential misclassification, it introduces a layer of assumption that may affect the accuracy of group definitions. Therefore, results should be interpreted with caution, and future validation using datasets with more reliable TD and nodal annotations is warranted.

Furthermore, our study does not directly evaluate the impact of TD on treatment response, particularly in the context of adjuvant chemotherapy. Although our findings suggest that TD-positive early-stage CRC patients may benefit from more intensive systemic treatment, prospective clinical trials are needed to validate this hypothesis. Additionally, long-term follow-up studies assessing recurrence patterns and disease progression in TD-positive patients would further clarify their clinical relevance.

Despite these limitations, our study provides strong evidence supporting the prognostic significance of TD in early-stage CRC and highlights the need for revising current staging and treatment paradigms. Future multicenter, prospective trials will be crucial to fully elucidate the role of TD in CRC prognosis and therapeutic decision-making.

## Conclusion

Our study highlights the independent prognostic value of TD in early-stage CRC. These findings challenge the traditional perception that early-stage CRC is universally favorable and emphasize the need for closer surveillance and potentially tailored therapeutic strategies for TD-positive patients. Recognizing TD as a critical prognostic factor may not only enhance current staging systems but also drive more precise risk stratification, ultimately improving clinical outcomes in this patient population.

This study serves as a wake-up call to the clinical community: even in early-stage CRC, tumor deposits are far from incidental findings—they are harbingers of poor prognosis and demand our full attention. Integrating TD into clinical decision-making could reshape how we manage early-stage CRC, ensuring that patients at higher risk receive appropriate monitoring and, when necessary, intensified treatment.

Recognizing TD as an independent prognostic factor in early-stage CRC is not merely an academic observation—it is a clinical imperative. By acknowledging and addressing this hidden risk, we can pave the way for more personalized, evidence-based management strategies, ultimately transforming survival outcomes for patients worldwide.

These findings challenge the conventional understanding of early-stage colon cancer and emphasize that tumor deposits are far from incidental findings—they are critical prognostic indicators that demand urgent clinical attention.

**Author contributions** All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Bilal Turan and all authors. The first draft of the manuscript was written by all author and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

**Data availability** No datasets were generated or analysed during the current study.

## Declarations

**Ethical approval** 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). As this study utilized de-identified data from the SEER database, which is publicly available and maintains patient anonymity, ethical approval and informed consent were not required.

**Competing interests** The authors declare no competing interests.



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