Tumor Deposits in Stage III Colon Cancer

Correlation With Other Histopathologic Variables, Prognostic Value, and Risk Stratification—Time to Consider "N2c"

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Objectives: National Comprehensive Cancer Network (NCCN) guidelines for stage III colon cancer define low-risk versus high-risk patients based on T (1 to 3 vs. 4) and N (1 vs. 2) status, with some variations in treatment. This study analyzes the impact of tumor deposits (TDs), T and N status, poor differentiation (PD), perineural invasion (PNI), and lymphovascular invasion (LVI) on survival.

Materials and Methods: A retrospective analysis (2010-2015) of the National Cancer Database of stage III colon cancer patients treated with both surgery and chemotherapy was conducted. Data was extracted on sex, race, age at diagnosis, Charlson-Deyo Score, histopathologic variables, and survival rates. Statistical analysis used the test of proportions, log-rank test for Kaplan-Meier curves, and Cox proportional hazard models.

Results: For the 42,901 patients analyzed, 5-year survival rates were similar for LN^+TD^- (59.8%) and LN^-TD^+ (58.2%), but significantly worse for LN^+TD^+ (41.5%) ($P < 0.001$). The presence of LN^+TD^+ was more often associated with T4 (36.9%), N2 (55.1%), PD^+ (37.4%), PNI^+ (34.5%), and LVI^+ (69.1%), than LN^+TD^- or LN^-TD^+ ($P < 0.001$). The hazard ratios for each variable were: TD: 1.34; T4: 1.71; N2: 1.44; PD^+: 1.37; PNI: 1.11; LVI^+: 1.18. LN^- patients with ≥ 3 TD^+ (N1c) had worse overall survival than those with 1 to 2 TD^+ ($P < 0.01$), but similar to ≥ 4 LN^+TD^- (N2) and 1 to 3 LN^+TD^+ (N1a-b). In our model, 5-year survival ranged from 23.4% for high-risk to 78.1% for low-risk patients ($P < 0.001$).

Conclusion: This National Cancer Database (NCDB) analysis offers greater risk stratification and may prompt consideration of changes in American Joint Committee on Cancer (AJCC) classification (N2c, in addition to N1c) to reflect the different prognosis and guide management, as well as survivorship strategies, for TD^+ stage III colon cancer patients.

Key Words: national cancer database, colon cancer, tumor deposits

Colorectal cancer remains the third most common cancer and the third leading cause of cancer-related deaths in the United States for both men and women. For colon cancer alone,

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101,220 new cases were projected to occur in 2019, causing 51,020 deaths.[1] Despite significant improvements in both prevention and screening over the last twenty years, about 36,500 (36%) of such cases are still being diagnosed in stage III, with regional lymph node involvement (LN^+, N1a-b, N2a-b) or tumor deposits (TD^+, N1c).

Adjuvant chemotherapy is generally advised after adequate surgical resection, with only slight variations in the choice of agents and duration of therapy. In its October 2018 edition, the National Comprehensive Cancer Network (NCCN) Guidelines recommend 3 months of capecitabine plus oxaliplatin (CAPEOX) or 3 to 6 months of 5-fluorouracil, leucovorin plus oxaliplatin (FOLFOX) for low-risk patients (T1-T3, N1); and 3 to 6 months of CAPEOX or 6 months of FOLFOX for high-risk patients (T4, N2). Single-agent capecitabine or 5-fluorouracil//leucovorin maybe used in patients in both risk groups when oxaliplatin therapy is contraindicated.[2]

TDs, also called extranodal TDs, peritumoral deposits, or satellite nodules, are defined as discrete tumor foci in the mesocolic (or perirectal) fat, within the lymphatic drainage space of the primary tumor, but without identifiable residual LN tissue or vascular structures.[3] They were first listed in the seventh edition of the American Joint Committee on Cancer (AJCC) Staging Manual, effective January 1, 2010, under "Regional Lymph Nodes" as N1c, in the absence of LN involvement, indicative of stage III disease.[4] This listing was maintained without changes in the eighth edition in 2018.[5] A few retrospective, mostly single-institution, studies with a limited number of patients had associated the presence of TDs in colorectal cancer with an adverse prognosis, even before such AJCC staging modifications were implemented, and likely prompted such changes.[6–9] Although it is recommended that the number of TD be recorded in the pathology report, AJCC has not correlated a higher number of TD with staging, unlike LNs (ie, N1 = metastasis in 1 to 3 regional LNs, N2 = metastasis in ≥ 4 regional LNs). In addition, in cases with positive LN, AJCC does not offer a staging option different than number of positive LN alone, regardless of the presence or absence and number of positive TD found in the mesocolon.

Even though the presence of TD in the pathology report for colorectal cancer specimens, even in the absence of positive regional LN, should be classified and treated as stage III,[10] 2 recent larger retrospective studies have shown that TD^+LN^- patients are less likely to receive adjuvant chemotherapy than LN^+ patients.[11,12] Such findings appear indicative of an opportunity to improve awareness and understanding of the clinical significance of TDs in colorectal cancer, especially with respect to appropriate risk stratification, choices for adjuvant treatment and more diversified survivorship strategies.

The objectives of this study were multiple:
- Assess the incidence of TD^+ in stage III colon cancer, alone (TD^+LN^-) and in combination with positive LNs (TD^+LN^+).

- Analyze the association of TD with T and N status, as well as other known adverse histopathologic features, ie, poor differentiation (PD+), perineural invasion (PNI+), and lymphovascular invasion (LVI+).
- Assess 5-year survival probability for LN+TD−, LN−TD+, and LN+TD+ patients.
- Determine the hazard ratio of TD+ and other adverse histopathologic variables.
- Determine if a higher number of TD+ correlates with a worse prognosis, as is the case for a higher number of LN+.
- Stratify survival probability for stage III colon cancer patients into low-risk, intermediate-risk, and high-risk categories, on the basis of presence or absence of adverse histopathologic features.

MATERIALS AND METHODS

Data Source

The National Cancer Database (NCDB) is a joint project of the American Cancer Society and the Commission on Cancer (CoC) of the American College of Surgeons (ACS), dedicated to the evaluation, management, and surveillance of cancer patients in the United States. The ACS has executed a Business Associate Agreement that includes a data use agreement with each of its CoC-accredited hospitals. The NCDB was established in 1989 as a nationwide, facility-based, comprehensive clinical surveillance resource oncology dataset that currently captures information on ~70% of all newly diagnosed malignancies annually in the United States. The database is populated by information entered by certified tumor registrars from CoC-accredited cancer programs.

For this study, we obtained a participant user file to query datasets limited to stage III adenocarcinoma of the colon. We elected to exclude cases of rectal or "rectosigmoid" cancer, which are often managed with neoadjuvant chemotherapy and radiation in stage III disease, with the added variable of the tumor and nodal regression affecting the review of histopathologic features in the resected specimen. Also, we limited our investigation to patients treated with both surgical resection and chemotherapy, to compare more homogeneous groups.

The time frame for data collection ranged from January 1, 2010 (the year in which the N1c designation was implemented) through December 31, 2015, to ensure adequate long-term survival in a sizable number of patients available for statistical analysis. Patient characteristics included sex, age at diagnosis, race/ethnicity, health insurance status, and comorbidities (Charlson-Deyo Score).[13] Charlson-Deyo Score is based on comorbid conditions from listed ICD-9 codes, with a score of 0 indicating no comorbidities, and point values of 1 or 2 being assigned on the basis of number and severity of comorbid conditions.

Hospital characteristics included cancer facility type providing care, according to the CoC accreditation criteria, based on the total number of yearly new cancer diagnoses, diagnostic and treatment services, research participation, and residency educational programs (Academic/Research, Community, Comprehensive Community, and Integrated Network Cancer Centers).

Tumor variables included T and N status, histologic grade, LVI, PNI, presence or absence of TD, alone or in combination with LN+ status.

Vital status at last contact provided survival information.

Statistical Analysis

The primary outcome of the study was overall survival. Patients were divided into 3 groups according to TD and LN status. Demographic data was stratified into 3 groups: LN+TD−, LN−TD+, and LN+TD+. A χ^2 test was used to compare whether the distribution of the demographic factors was different between the 3 groups. For the distribution of tumor-related characteristics grouped by LN+TD− or LN−TD+ versus LN+TD+, the *P*-values were calculated using a test of proportions. All plots of survival curves were created using group-specific Kaplan-Meier estimators, and all tests of equality of survival curves between groups were performed using a log-rank test.

Five-year survival estimators and associated confidence intervals were calculated using the Kaplan-Meier curves. Hazard ratios were estimated using a main effect multivariable Cox proportional hazards model.

RESULTS

A total of 42,901 patients, who had all the required information in the database, were found eligible and were analyzed in the study.

The mean follow-up time was 40.7 months. Patient demographic factors are listed in Table 1. There was a difference in the age distribution and insurance status categories among the 3 groups.

A comparison of histopathologic variables is presented in Table 2, showing that LN+TD+ tumors were associated with other adverse features such as T4 status, PD, PNI, LVI, significantly more often than either LN+TD− or LN−TD+ tumors.

TABLE 1. Patient Demographics and Facility Types

Groups	n (%)			
	LN+TD−	LN−TD+	LN+TD+	P
Incidence	33,073 (76.2)	1683 (3.92)	8145 (18.8)	
Sex				
Female	17,327 (52.4)	864 (51.3)	4162 (51.1)	0.092
Age (y)				
Mean	67.5	68.8	67.1	
18-50	4242 (12.7)	160 (9.5)	1104 (13.6)	<0.001
51-65	9759 (29.6)	488 (29.0)	2468 (30.3)	
66-99	19,072 (57.7)	1035 (61.5)	4573 (56.1)	
Race				
White	27,277 (83.1)	1382 (82.7)	6747 (83.5)	0.63
Black	4144 (12.6)	206 (12.3)	993 (12.3)	
Other	1414 (4.3)	83 (5.0)	343 (4.2)	
C-D score				
0	22,804 (69.0)	1139 (67.7)	5707 (70.1)	0.10
1	7479 (22.6)	401 (23.8)	1817 (22.3)	
2	2778 (8.4)	143 (8.5)	621 (7.6)	
Health insurance				
Medicare	18,243 (55.9)	997 (59.7)	4480 (55.7)	<0.001
Private	11,240 (34.4)	486 (29.1)	2707 (33.7)	
Medicaid	1641 (5.0)	88 (5.3)	466 (5.8)	
Uninsured	1252 (3.9)	76 (4.6)	335 (4.2)	
Other government	282 (0.8)	22 (1.3)	48 (0.6)	
Facility				
Academic Research	8438 (26.4)	503 (30.5)	2066 (26.3)	0.008
Community	4270 (13.3)	192 (11.6)	1098 (13.8)	
Comprehensive Community	15,691 (48.9)	775 (47.0)	3819 (48.5)	
Integrated Network	3665 (11.4)	179 (10.9)	896 (11.4)	

P-values based on χ^2 test.
LN indicates lymph node; TD, tumor deposit.

TABLE 2. Histopathologic Variables Comparing LN⁺TD⁻ With LN⁻TD⁺ and LN⁺TD⁺

Groups	n (%)			P
	LN⁺TD⁻	LN⁻TD⁺	LN⁺TD⁺	
T1	1468 (4.5)	42 (2.5)	78 (1.0)	
T2	3400 (10.3)	114 (6.8)	255 (3.1)	
T3	21,721 (66.0)	1127 (67.2)	4787 (59.0)	
T4	6332 (19.2)	395 (23.5)	3000 (36.9)	<0.001
N1a-b	22,791 (68.9)	0	3660 (44.9)	
N1c	0	1683 (100)	0	
N2a-b	10,282 (31.1)	0	4485 (55.1)	<0.001
PD				
Absent	23,416 (72.8)	1284 (78.7)	4975 (62.7)	
Present	8770 (27.2)	348 (21.3)	2963 (37.3)	<0.001
PNI				
Absent	25,827 (85.8)	1253 (80.6)	4825 (65.5)	
Present	4278 (14.2)	302 (19.4)	2557 (34.5)	<0.001
LVI				
Absent	15,949 (53.1)	1002 (66.1)	2352 (30.9)	
Present	14,110 (46.9)	513 (33.9)	5253 (69.1)	<0.001

T4 is compared with T1, T2, or T3.
P-values based on the test of proportions.
LN indicates lymph node; LVI, lymphovascular invasion; PD, poor differentiation; PNI, perineural invasion; TD, tumor deposit.

LN⁺TD⁺ tumors were also associated with N2 status more often than LN⁺TD⁻ tumors.

Estimated hazard ratios, calculated to quantify the contribution to the prognosis of each adverse histopathologic factors, are presented in Table 3.

Survival probability graphs according to LN and TD status combinations in the 3 groups are shown in Figure 1. Five-year survivals are shown in parentheses. Overall and 5-year survival was significantly worse for LN⁺TD⁺ patients (41.5%), than either LN⁺TD⁻ (59.8%) or LN⁻TD⁺ patients (58.2%) (*P* < 0.001).

A subset analysis to address the question of a higher number of TD⁺ possibly having a worse prognosis, as it is the case for a higher number of LNs, is shown in Figure 2. In fact, LN⁻ patients with ≥ 3 TD⁺ (currently staged as N1c), had an overall survival of 51.4%, worse than those with 1 to 2 TD⁺ (60.6%), but similar to ≥ 4 LN⁺TD⁻ (currently staged as N2) (48.9%) and 1 to 3 LN⁺TD⁺ (currently staged as N1a-b) (50.7%) (*P* < 0.01).

Finally, a prognostic stratification into low, intermediate, and high-risk groups was done to assess the cumulative impact of adverse histopathologic variables on survival. Patients with T1-T2 tumors; N1a-b with TD⁻, or LN⁻ with 1 to 2 TD⁺; and negative PD, PNI, and LVI, were assigned to the low-risk

TABLE 3. HRs of Different Adverse Histopathologic Variables

| Variables	HRs	CI	P
TD⁺	1.34	1.29-1.39	<0.001
T4	1.71	1.65-1.77	<0.001
N2	1.44	1.39-1.49	<0.001
PD⁺	1.37	1.32-1.42	<0.001
PNI⁺	1.11	1.06-1.15	<0.001
LVI⁺	1.18	1.14-1.23	<0.001

P-values based on multivariate Cox proportional hazard models.
CI indicates confidence interval; HR, hazard ratio; LVI, lymphovascular invasion; PD, poor differentiation; PNI, perineural invasion; TD, tumor deposit.
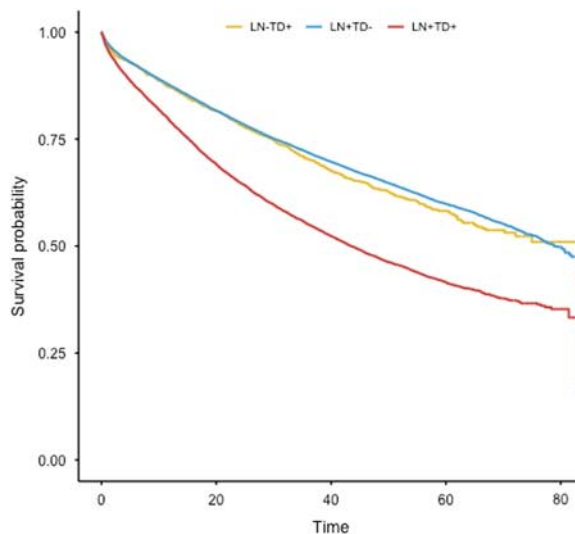

FIGURE 1. Kaplan-Meier curves comparing survival for LN⁺TD⁻, LN⁻TD⁺, and TD⁺LN⁺. Overall and 5-year survival was similar for LN⁺TD⁻ (0.598; 95% CI: 0.593-0.604) and LN⁻TD⁺ (0.582; 95% CI: 0.556-0.609), but significantly worse for LN⁺TD⁺ (0.415; 95% CI: 0.403-0427) compared with each of the other 2 groups (*P* < 0.001). CI indicates confidence interval; LN, lymph node; TD, tumor deposit.

group. Patients with T3 tumors; N2 TD⁻, or LN⁻ with ≥ 3 TD⁺; and only 1 positive either PD, PNI, or LVI, were assigned to the intermediate-risk group. Patients with T4 tumors; N2 TD⁺; and 2 to 3 positive PD, PNI, and LVI, were assigned to the high-risk group. Five-year survival was 78.1% for the low-risk group, 57.2% for the intermediate-risk group, and 23.4% for the high-risk group (*P*-values comparing overall and 5-year survival for all 3 groups <0.001) (Fig. 3).
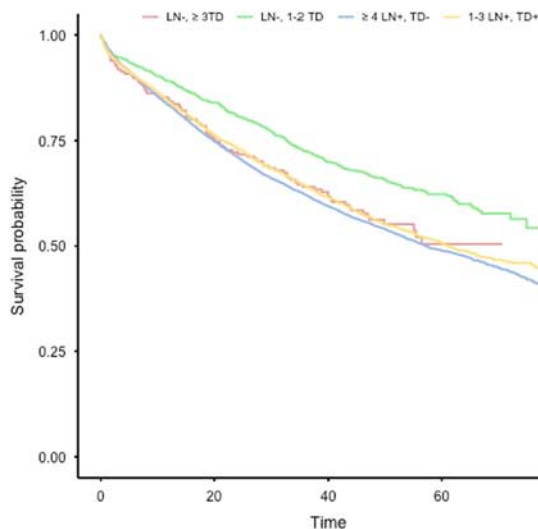
FIGURE 2. Kaplan-Meier survival curves for subgroups of patients. LN⁻, ≥ 3 TD⁺ (N1c) had worse overall survival (0.504; 95% CI: 0.426-0.597) than LN⁻, 1 to 2 TD⁺ (N1c) (0.623; 95% CI: 0.591-0.657), similar to ≥ 4 LN⁺, TD⁻ (N2) (0.489; 95% CI: 0.478-0.500) and 1 to 3 LN⁺, TD⁺ (N1a-b) (0.507; 95% CI: 0.489-0.526) (*P* < 0.01). CI indicates confidence interval; LN, lymph node; TD, tumor deposit.
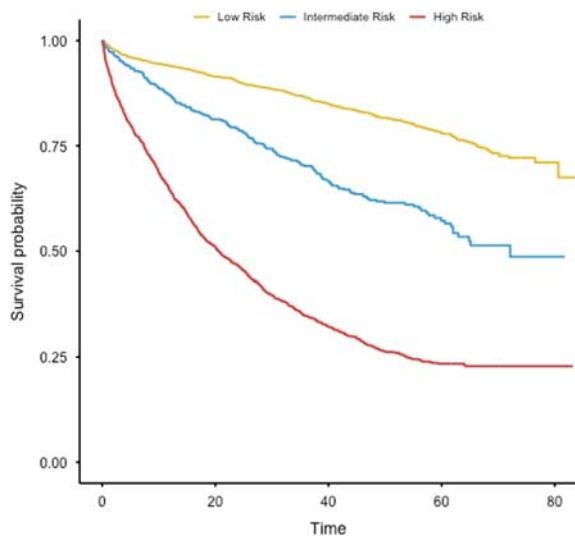
FIGURE 3. Kaplan-Meier survival curves for low-risk, intermediate-risk, and high-risk groups, on the basis of histopathologic variables T, N, TD, PD, PNI, and LVI. Overall and 5-year survival was significantly higher (0.781; 95% CI: 0.762-0.801) for low-risk patients; average (0.572; 95% CI: 0.524-0.625) for intermediate-risk patients; and significantly lower (0.234; 95% CI: 0.211-0.259) for high-risk patients ($P < 0.001$ for all 3 groups). CI indicates confidence interval; LVI, lymphovascular invasion; PD, poor differentiation; PNI, perineural invasion; TD, tumor deposit.

CONCLUSIONS

The addition of N1c in the AJCC classification of colon cancer staging was prompted by several publications, before 2010. Some investigators focused on appropriate histologic differentiation of TD from LN metastases at the time of histologic evaluation,[8,12,14] while noting that interobserver variability among pathologists may at times affect consistent interpretation and reporting.[15] Other authors reported on mostly single-institution data on the adverse prognosis of TD in colorectal cancer,[16,17] contributing to the AJCC Staging Manual classification changes implemented in its seventh edition.

In a pathology study, the authors opined that "despite the apparent adverse prognosis of TDs, it should be noted that the N1c category does not necessarily imply a worse prognosis than N1a or N1b."[15] However, additional publications in pathology, oncology and surgery journals from larger databases (eg, Surveillance, Epidemiology, and End Results [SEER] and NCDB), provided evidence that the presence of TD in colorectal cancer should be considered a significant adverse prognostic factor for overall survival.[18–24] A recent study has shown the presence of TD in patients with stage III colon cancer to be associated with a 2.2-fold increased risk of developing disease recurrence.[25]

After the eighth edition of the AJCC Staging Manual for colorectal cancer in 2018, which left the N1c classification unchanged, the issue of appropriately assessing the increased risks posed by TD$^+$ remains incompletely addressed. The current classification includes only LN$^-$TD$^+$ as "low-risk" stage III as N1c, comparable to N1a (1LN$^+$), and N1b (2 to 3 LN$^+$). "High-risk" is limited to N2a (4 to 6 LN$^+$) and N2b (> 6 LN$^+$). Over one fourth of stage III colon cancers are TD$^+$. About 20% of stage III colon cancer patients are LN$^+$TD$^+$; yet only the number of LN$^+$ is used for staging purposes, completely disregarding the additional presence of TDs and their "additional" adverse prognostic value. For example, had the TD$^+$ lesions been read as LN$^+$, their combined total number may well have

made the difference between N1a-b and N2a-b. Finally, in the roughly 7% of stage III colon cancer cases that are LN$^-$TD$^+$, the possible increased risk posed by a higher number of TD$^+$, as it is the case for a higher number of LN$^+$, is currently not addressed by AJCC staging.

Our study's purpose was to conduct a deeper and more focused analysis of the available NCDB data to assess the relevance of those 2 outstanding issues. This study represents the largest NCDB analysis of the impact of TD in the prognosis of stage III colon cancer patients treated with both surgery and chemotherapy, with the longest accrual time (6 years) and longest follow-up for survival figures (up to over 80 mo). A previously published 2010-2014 NCDB review study had evidenced the high incidence of TDs, in ~25% of all stage III colon cancers, of which 6.8% were LN$^-$TD$^+$, with only 52% of LN$^-$TD$^+$ receiving adjuvant chemotherapy.[12] Our patient cohort has a lower incidence of TD$^+$LN$^-$ (3.9%), because we limited our analysis to patients who received both surgery and chemotherapy, to have more homogeneous comparison groups, as there is no question about the survival improvement provided by the addition of chemotherapy for all stage III colon cancer patients.

In our data, there was no difference in demographics between the 3 comparison groups (LN$^+$TD$^-$, LN$^-$TD$^+$, and LN$^+$TD$^+$), with only variations in age at diagnosis and insurance status showing changes in various groups, not clinically relevant to our study purpose (Table 1).

Other variables, such as T4 and N2, which have been definitively associated with worse survival expectations, have been found to occur more frequently in LN$^+$TD$^+$ patients in previous publications.[11,12,26] Our data confirmed such association as well: 55.1% for N2 in LN$^+$TD$^+$ patients, versus 31.1% in LN$^+$TD$^-$ patients; and 36.9% for T4 in LN$^+$TD$^+$ patients, versus 19.2% in LN$^+$TD$^-$ and 23.5% in LN$^-$TD$^+$ patients ($P < 0.001$). In addition, we found a significant association between LN$^+$TD$^+$ patients and other adverse histopathologic features, especially LVI (69.1%), but also PD (37.4%), and PNI (34.5%), prognostic factors known to contribute to poorer long-term survival figures (Table 2). The frequent association between TD$^+$ and LVI$^+$ may provide additional insight as to the nature and origin of TDs.

We found that each adverse variable carried a significant hazard ratio, which we quantified individually as well as in combination, for a cumulative effect on the mortality probability (Table 3).

When analyzing our survival graphs (Figs. 1–3), it is also apparent that, in poorer risk patients, a rapid decline occurs within 2 years of diagnosis, emphasizing the need for timely systemic treatment of adequate duration.[27] In subsets of TD$^+$ patients, survival figures may actually be so poor they resemble stage IV colon cancer, as noted recently by other authors, advocating staging classification changes.[28]

In recent years "survival calculators" and "prognostic calculators" have been developed for different cancer sites at some cancer centers in the United States, based on regional as well as NCDB data.[29] The availability of prognostic indicators and risk calculators is becoming part of the assessment and decision-making progress for physicians and patients as well, who increasingly seek more information and involvement in a personalized approach to their care for a variety of medical conditions.[30,31] Interestingly, the variables utilized differed widely among 3 programs evaluated in 1 study. Age, sex, grade, and a number of total positive/examined nodes were common to all 3 programs, but the total number of items analyzed varied from as few as 5 to as many as 15 out of a possible

total of 18. The predicted survival was different among programs, with 1 program being defined as clearly more "optimistic," while the more comprehensive program was more "realistic." The authors concluded that a more comprehensive list of variables would provide a more accurate tool.[32] Of note, to date no survival calculator for colon cancer has included TD status. Data from our study and from other publications addressing the role of TD+ in colon cancer would add valuable information for practitioners and patients and maybe considered for inclusion in such "risk calculators."

Some authors had hypothesized that a prognostic relationship existed between the number of positive LNs and TD positivity,[33] whereas others proposed that TD+ be counted as LN+, to obtain a larger total number.[34] A higher number of TD+ maybe associated with a worse prognosis, as it is the case for a higher number of LN+. Therefore, we compared survival probability in certain subsets of patients currently staged as N1 (a, b, or c) and found that to be similar to patients currently staged as N2, depending on TD status. In fact, LN− patients with ≥3 TD+ (currently staged as N1c) had worse overall survival than those with only 1or 2 TD+ (also currently staged as N1c), but similar survival to ≥4 LN+TD− (currently staged as N2) and 1 to 3 LN+TD+ (currently staged as N1a-b) (Fig. 2). These observations may prompt consideration of AJCC classification changes, to accurately reflect the additional risk of a higher number of TD+, alone and in combination with number of LN+.

Finally, the survival probability curves that the study generated, on the basis of the type and number of adverse variables, demonstrate the wide range of survival in stage III colon cancer. In patients with the worst possible T, N, TD, PD, PNI, and LVI status (high risk), according to our model, the estimated 5-year survival is only 23.4%, even after receiving chemotherapy at CoC-accredited cancer programs. In the "best-case scenario" stage III, with T1-T2, favorable LN and TD combinations, and no PD, PNI, or LVI (low risk), the survival estimate is as high as 78.1%. The intermediate-risk group was found to have an estimated 5-year survival of 57.2% (Fig. 3). Such data provide validation of the accuracy of our tumor-related prognostic assessment, which could be combined with clinical individual patient data (eg, age and Charlson-Deyo Score) to better tailor therapeutic strategies in patients with different risk profiles. It appears obvious that such a wide difference in prognosis would warrant a more diversified approach. Particularly for the high-risk patients, with such low survival expectations, a much more vigorous systemic therapy regimens may need to be considered, even in an adjuvant setting. Such a wide prognostic variability should prompt a reconsideration of not only adjuvant therapy regimens but also more diversified survivorship plans, tailored to each subset of patients.

Limitations of this study include its retrospective design, necessary to access such a large multi-institutional database. Also, survival data do not account for disease-free or disease-specific survival figures, nor do they include disease recurrence or progression. However, a large number of patients evaluated should minimize variation from other causes of death. In addition, no information was available with respect to TD incidence in patients with hereditary or genetic colorectal cancer syndromes. Finally, no detailed information was available about specific chemotherapeutic medications used, other than single or multiple agents.

In conclusion, the incidence of TD+ in stage III colon cancer, about 1 in 4 cases, makes it a relevant cancer variable. TD+ tumors, when LN+, are frequently associated with other adverse histopathologic features (T4, N2, PD, PNI, LVI). The variability in prognosis for stage III colon cancer is wide enough to merit a more diversified approach in management.

The association of TD+ and LN+ is indicative of poor prognosis, currently not addressed by AJCC staging, A high number of TDs (≥3), even in the LN− patients, is indicative of poor prognosis, currently not addressed by AJCC staging.

Therefore, we propose an amendment to the AJCC classification of stage III colon cancer, which would appropriately reflect LN+TD+ or LN− ≥3 TD+ into a new subset category which could be named "N2c." Only patients with LN−, 1 to 2 TD+ would remain staged as N1c.

Such modifications should draw greater attention to the issue of TD positivity and prompt appropriate risk stratification, consideration of a more vigorous therapeutic approach and closer survivorship planning for this subset of high-risk stage III colon cancer patients.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019;69:7–34.
2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Colon Cancer, version 4.2018.
3. Kakar S, Shi C, Berho ME, et al. Protocol for the examination of specimens from patients with primary carcinoma of the colon and rectum. Copyright College of American Pathologists; 2017. Available at: https://documents.cap.org/protocols/cp-gilower-colonrectum-17protocol-4010.pdf. Accessed June 30, 2019.
4. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC staging manual and the future of TNM. *Ann Surg Oncol*. 2010;17:1471–1474.
5. Amin MB, Greene F, Edge S, et al. The Eight Edition AJCC Cancer Staging Manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J Clin*. 2017;67:93–99.
6. Ueno H, Mochizuki H. Clinical significance of extrabowel skipped cancer infiltration in rectal cancer. *Surg Today*. 1997;27:617–622.
7. Goldstein NS, Turner JR. Pericolonic tumor deposits in patients with T3NMO colon adenocarcinomas: markers of reduced disease free survival and intraabdominal metastases and their implications for TNM Classification. *Cancer*. 2000;88:2228–2238.
8. Nagtegaal I, Quirke P. Colorectal tumour deposits in the meso-rectum and pericolon; a critical review. *Histopathology*. 2007;51: 141–149.
9. Ueno H, Mochizuki H, Hashiguchi Y, et al. Extramural cancer deposits without nodal structure in colorectal cancer: optimal categorization for prognostic staging. *Am J Clin Pathol*. 2007;127: 287–294.
10. Belt EJ, van Stijn MF, Bril H, et al. Lymph node negative colorectal cancers with isolated tumor deposits should be classified and treated as stage III. *Ann Surg Oncol*. 2010;17:3203–3211.
11. Mirkin KA, Kulaylat AS, Hollenbeak CS, et al. Prognostic significance of tumor deposits in stage III colon cancer. *Ann Surg Oncol*. 2018;25:3179–3184.
12. Wong-Chong N, Motl J, Hwang G, et al. Impact of tumor deposits on oncologic outcomes in stage III colon cancer. *Dis Colon Rectum*. 2018;61:1043–1052.
13. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45:613–619.
14. Puppa G, Maisonneuve P, Sonzogni A, et al. Pathological assessment of pericolonic tumor deposits in advanced colonic carcinoma: relevance to prognosis and tumor staging. *Mod Pathol*. 2007;20:843–855.
15. Rock JB, Washington MK, Montgomery EA, et al. Debating deposits: an interobserver variability study of lymph nodes and pericolonic tumor deposits in colonic adenocarcinoma. *Arch Pathol Lab Med*. 2014;138:636–642.
16. Prabhudesai A, Arif S, Finlayson CJ, et al. Impact of extranodal tumor deposits on the outcome of patients with rectal cancer. *Dis Colon Rectum*. 2003;46:1531–1537.

17. Lo DS, Pollett A, Siu LL, et al. Prognostic significance of mesenteric tumor nodules in patients with stage III colorectal cancer. *Cancer*. 2008;112:50–54.

18. Al Sahaf O, Myers E, Jawad M, et al. The prognostic significance of extramural deposits and extracapsular lymph node invasion in colon cancer. *Dis Colon Rectum*. 2011;54:982–988.

19. Ueno H, Mochizuki H, Shirouzu K, et al. Multicenter study for optimal categorization of extramural tumor deposits for colorectal cancer staging. *Ann Surg*. 2012;255:739–746.

20. Chen VW, Hsieh MC, Charlton ME, et al. Analysis of stage and clinical/prognostic factors for colon and rectal cancer from SEER registries: AJCC and collaborative stage data collection system. *Cancer*. 2014;120:3793–3806.

21. Ueno H, Hashiguchi Y, Shimazaki H, et al. Peritumoral deposits as an adverse prognostic indicator of colorectal cancer. *Am J Surg*. 2014;207:70–77.

22. Jin M, Roth R, Rock JB, et al. The impact of tumor deposits on colonic adenocarcinoma AJCC TNM staging and outcome. *Am J Surg Pathol*. 2015;39:109–115.

23. Mayo E, Llanos AA, Yi X, et al. Prognostic value of tumour deposit and perineural invasion status in colorectal cancer patients: a SEER-based population study. *Histopathology*. 2016;69:230–238.

24. Bouquot M, Creavin B, Goasquen N, et al. Prognostic value and characteristics of N1c colorectal cancer. *Colorectal Dis*. 2018;20:248–255.

25. Landau MA, Zhu B, Akwuoe FN, et al. Histopathological predictors of recurrence in stage III colon cancer: reappraisal of tumor deposits and tumor budding using AJCC8 criteria. *Int J Surg Pathol*. 2019;27:147–158.

26. Yamano T, Semba S, Noda M, et al. Prognostic significance of classified extramural tumor deposits and extracapsular lymph node invasion in T3-4 colorectal cancer: a retrospective single center study. *BMC Cancer*. 2015;15:1885–1886.

27. Grothey A, Sobrero AF, Shields AF, et al. Duration of adjuvant chemotherapy for stage III colon cancer. *N Engl J Med*. 2018;378:1177–1188.

28. Lino-Silva LS, Anchondo-Nunez P, Chit-Huerta A, et al. Stage I-III colon cancer patients with tumor deposits behave similarly to stage IV patients. Cross section analysis of 392 patients. *J Surg Oncol*. 2019;120:300–307.

29. Bardia A, Loprinzi C, Grothey A, et al. Adjuvant chemotherapy for resected stage II and III colon cancer: comparison of two widely used prognostic calculators. *Semin Oncol*. 2010;37:39–46.

30. Renfro LA, Grothey A, Xue Y, et al. ACCENT-based web calculators to predict recurrence and overall survival in stage III colon cancer. *J Natl Cancer Inst*. 2014;106:1–9.

31. Sjoquist KM, Renfro LA, Simes RJ, et al. Personalizing survival predictions in advanced colorectal cancer: the ARCAD nomogram project. *J Natl Cancer Inst*. 2018;110:638–648.

32. Lemini R, Attwood K, Pecenka S, et al. Stage II-III colon cancer: a comparison of survival calculators. *J Gastrointest Oncol*. 2018;9:1091–1098.

33. Nagayoshi K, Ueki T, Nishioka Y, et al. Tumor deposit is a poor prognostic indicator for patients who have stage II and III colorectal cancer with fewer than 4 lymph node metastases but not for those with 4 or more. *Dis Colon Rectum*. 2014;57:467–474.

34. Li J, Yang S, Hu J, et al. Tumor deposits counted as positive lymph nodes in TNM staging for advanced colorectal cancer: a retrospective multicenter study. *Oncotarget*. 2016;7:18269–18279.