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RESEARCH

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A high number of tumor deposits (≥ 4) is an isolated predictor of local recurrence and distant metastasis in non-metastatic colorectal cancer: a single center study

Ahmed Bendari[1*], Ebubekir Ucar[2], Alaa Bendari[3], Hamed Hammoud[4], FNU Kiran[5], Reham Al-Refai[1], Sunder Sham[1], Sanjay Kirshan Kumar[6], Ryan Des Jean[1] and Manju Harshan[1]

Abstract

Introduction Local recurrence and distant metastasis after curative surgery and chemotherapy for colorectal cancer (CRC) is a serious complication and is considered a failure of the therapeutic strategy. The aim of this study is to identify the different prognostic factors associated with tumor recurrence and distant metastasis in CRC.

Design An analytical cross-sectional design was employed, and our hospital clinical and pathology databases were queried for non-metastatic CRC (stage I-III). Patients were included if they underwent surgery and chemotherapy between 01/2016 to 12/2018 and demographic information, tumor characteristics and postoperative outcomes were extracted from each case. The data were entered into a database using SPSS version 21. Univariate analysis was initially performed, followed by a multivariate analysis to develop a prognostic model for tumor recurrence and distant metastasis in CRC.

Result A total of 138 non-metastatic CRC patients were enrolled in this study. The demographic characteristics of all patients are summarized in Table 1. Our study included 65 male and 73 female patients with a Median (IQR) age of 69 (17.7) years. Among the cases, 91 (65.9%) patients had no recurrence, and 47 (34.1%) patients developed a recurrence during follow-up. Univariate analysis revealed that positive lymph nodes ($p = 0.03$) and tumor deposits ≥ 4 ($p = 0.04$) were significantly associated with colorectal tumor recurrence and/or metastasis. However, variables such as age, sex, smoking, alcohol consumption, family history of CRC, PNI, LVI, tumor size, and histological features like mucinous or signet ring cell morphology did not show any statistical significance ($p > 0.05$). Multivariate analysis adjusted for age, lymph node status, and tumor deposits, identified that tumor deposits ≥ 4 was the only predictor of tumor recurrence following colorectal surgery and chemotherapy. Conversely, positive lymph node status did not show statistical significance ($p = 0.3$). Further analysis revealed that patients who had tumor deposit number ≥ 4 tend to experience local recurrence/distant metastasis more than patients with tumor deposit number < 4.

Conclusion In non-metastatic CRC patients, TD ≥ 4 is a strong predictor of local tumor recurrence and distant metastasis. Based on these findings, patients who have TDs in primary CRC resection should be subjected to enhanced surveillance.

*Correspondence:
Ahmed Bendari
abendari@northwell.edu
Full list of author information is available at the end of the article

Introduction

Colorectal cancer (CRC) is the second most common cause of cancer death in the United States (Siegel et al. 2021; Chen et al. 2016).TNM classification is essential to the staging of colon cancer, it is used in treatment decisions as well as to predict disease prognosis (Siegel et al. 2021; National Comprehensive Cancer Network 2023; Nagtegaal et al. 2007; Nagtegaal et al. 2011).

Tumor deposits (TDs) are defined in AJCC 8th edition as discrete tumor nodules within the lymph drainage area of the primary carcinoma without identifiable lymph node tissue or identifiable vascular or neural structure (Amin 2017). TDs are found in approximately 17–22% of patients with CRC and correlate with poor prognosis, which includes shorter disease-free and overall survival (Tateishi et al. 2005; Nagtegaal et al. 2017).

This impact is apparent in the latest TNM system, where the presence of TDs is classified as pN1c in the absence of lymph node involvement (Delattre et al. 2020). Furthermore, current NCCN guidelines state that the number of tumor deposits should be recorded in the pathology report due to their significant impact on survival rates (National Comprehensive Cancer Network 2023).

Despite previous studies establishing the link between TDs, advanced tumor growth, and poor prognosis, a consensus on the quantity of TDs is lacking. To address this gap, we conducted a retrospective study at our institution, investigating the impact of TDs on the prognostic factors of colorectal carcinoma.

Design

Data collection and tumor deposit definition

An analytical cross-sectional design was employed, and our hospital clinical and pathology databases were queried for non-metastatic CRC (stage I-III) patients who underwent surgery and chemotherapy between 01/2016 and 12/2018. The definition of TDs was determined according to the AJCC 8th TNM as a tumor focus in the pericolic/perirectal fat or in the adjacent mesentery (mesocolic or rectal fat) within the lymph drainage area of the primary tumor, but without identifiable lymph node tissue or vascular structure. If the vessel wall or its remnant is identified by H&E staining, we classified it as vascular (venous) invasion and not as a tumor deposit. Similarly, if a tumor focus is present in or around a large nerve, we classified it as perineural invasion and not as a tumor deposit (Fig. 1 shows H&E images of 5 included cases diagnosed with tumor deposits).

To establish a prognostic model for predicting out comes (local recurrence /distant metastasis), we reviewed the clinicopathological features of all patients, including age, sex, tumor location, tumor grade, perineural invasion, presence of TDs, etc. Exclusion criteria included (1) neoadjuvant therapy; (2) no information available on TDs; (3) colorectal cancer is not the only primary cancer; (4) patients with incomplete information about follow-up; (5) presence of distant metastasis at the first-time CRC diagnosis.

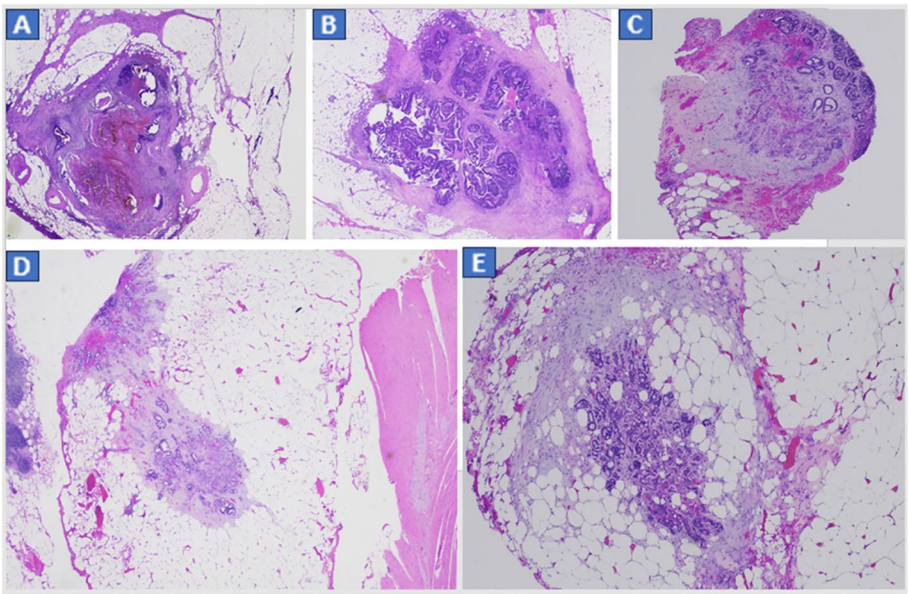

Fig. 1 H&E images of 5 included cases diagnosed with tumor deposits

Study outcomes

The end point of the study was estimating the outcome in the form of (local recurrence and or distant metastasis) over 5 years follow up. Local recurrence was defined as tumor recurrence in the bowel close to the original site. Distant metastasis was defined as the presence of liver, lung, bone, or brain metastases during or after CRC diagnosis.

Statistical analysis

All statistical analyses were performed using SPSS version 21. The chi-square test was used to analyze categorical variables' demographic and clinical characteristics. The logistic regression coefficients were used to estimate the odds ratios (OR) for the relationship between TDs and distant metastasis patterns. Calculated hazard ratio (HR), 95.0% confidence interval (CI), and Cox proportional hazards model were used for univariate and multivariate analysis. In multivariate analyses, the clinicopathological characteristics with $p < 0.05$ in univariate analysis were included to determine independent prognostic factors. Significance was set at $p < 0.05$.

Result

Baseline characteristics of the study population

A total of 138 non-metastatic CRC patients were enrolled in this study. The demographic characteristics of all patients are summarized in Table 1. Our study included 65 male and 73 female patients with a *Median (IQR)* age of 69 (17.75) years. Among the cases, 91(65.9%) patients had no recurrence, and 47 (34.1%) patients developed a recurrence for 5 years follow-up. The *Median (IQR)* BMI of the included patients was calculated as 27 (8) (Table 1).

Histopathologic findings

With regard to tumor size, the median (IQR) size of the tumor was found to be 5.40 cm (3.30). Mucinous features were identified in 24(17.4%) cases, medullary features were identified in 6(4.3%) cases, and Signet ring histology were identified in 3(2.2%) cases. Most of the cases were moderately differentiated 68(49.3%). The median (IQR) number of extracted lymph node was 19(10), the number of cases that had positive lymph node were 85(61.6%) with *Median (IQR) number of positive lymph node was* 1(4). Lymphvascular invasion was identified in 98(71%) cases and perineural invasion was identified 52(37.7%) (Table 2).

Predictors of tumor recurrence and/ or distant metastasis

Table 3 expresses the adjusted and unadjusted analysis between the tumor recurrence/ distant metastasis and the main independent variables. Among the patients who developed local recurrence or distant metastasis, 31 have a number of tumor deposit < 4 and 16 patients have ≥ 4. Univariate analysis revealed that positive lymph nodes ($p = 0.03$) and tumor deposits ≥ 4 ($p = 0.004$) were significantly associated with colorectal tumor recurrence and/or metastasis. However, variables such as age, sex, smoking, alcohol consumption, family history of CRC, PNI, LVI, tumor size, and histological features like mucinous or signet ring cell morphology did not show any statistical significance ($p > 0.05$). Multivariate analysis, adjusted for age, lymph node status, and tumor deposits, identified that tumor deposits ≥ 4 were the only predictor of tumor recurrence following colorectal surgery and chemotherapy. Conversely, positive lymph node status did not show statistical significance ($p = 0.3$) (Tables 3 and 4).

Table 1 Demographic characteristics of the studied participants

	Total ($n = 138$)
Age (years)	
Median (IQR)	69 (17.75)
Range	(28 – 103)
Sex *(N. %)*	
Male	65 (47.1%)
Female	73 (52.9%)
BMI	
Median (IQR)	27 (8)
Race *(N. %)*	
White	76 (55.1%)
Asian	22 (15.9%)
African American	22 (15.9%)
Latino	3 (2.2%)
Other/Not specified	15 (10.9%)
Smokers *(N. %)*	60 (43.5%)
Alcohol use *(N. %)*	65 (47.1%)
Family history *(N. %)*	43 (31.2%)

Discussion

The results of this study indicate that four or more tumor deposits (TDs) are a robust predictor for local tumor recurrence and distant metastasis in patients with non-metastatic colorectal cancer (CRC). Considering these observations, it is advisable to implement enhanced surveillance for patients undergoing primary CRC resection who exhibit TDs. We didn't find any significant association between local recurrence/distant metastasis and age, sex, smoking, alcohol consumption, family history of CRC, LVI, PNI, tumor size, MSI status, mucinous histology, signet ring morphology, positive lymph nodes and use of adjuvant chemotherapy.

Table 2 Clinical and Histopathological tumor characteristics

	Total (*n* = 138)
MSI *(N. %)*	
Intact	106 (76.8%)
Loss	23 (16.7%)
Not available	9 (6.5%)
Tumor size (cm)	
Median (IQR)	5.40 (3.30)
No. of tumor deposits	
Median (IQR)	1 (3)
Mucinous histology *(N. %)*	24 (17.4%)
Medullary histology *(N. %)*	6 (4.3%)
Signet ring *(N. %)*	3 (2.2%)
Tumor grade *(N. %)*	
Well	6 (4.3%)
Well to moderate	0 (0%)
Moderate	68 (49.3%)
Moderate to poorly	43 (31.2%)
Poorly differentiated	21 (15.2%)
L.N status *(N. %)*	
Positive	85(61.6%)
Negative	53 (38.4%)
No. of positive L.N	
Median (IQR)	1 (4)
No. of extracted L.N	
Median (IQR)	19 (10)
T stage *(N. %)*	
T1	0 (0%)
T2	7 (5.1%)
T3	48 (34.8%)
T4	83 (60.1%)
N stage *(N. %)*	
N0	32 (23.2%)
N1a	16 (11.6%)
N1b	25 (18.1%)
N1c	22 (15.9%)
N2a	24 (17.4%)
N2b	19 (13.8%)
AJCC-8th edition stage *(N. %)*	
II B	8 (5.8%)
III A	88 (63.8%)
III B	42 (30.4%)
LVI *(yes) (N. %)*	98 (71%)
PNI *(yes) (N. %)*	52 (37.7%)
Resection margin *(N. %)*	
Negative	132 (95.7%)
Positive	5 (3.6)
Not mentioned	1 (0.7%)
Closet resection margin *(N. %)*	
Radial	99 (71.7%)
Distal	20 (14.5%)
Proximal	14 (10.1%)
Not mentioned	5 (3.6%)
Distance (cm)	
Median (IQR)	2 (3.70)

Since its inclusion in the AJCC TNM staging system, numerous studies on tumor deposits in colorectal carcinoma consistently indicate their significance as an important prognostic factor (Ueno et al. 2014). However, only a limited number of studies have successfully elucidated the influence of TDs on both local recurrence and distant metastasis.

Delattre et al. showed that the presence of TDs is a major prognostic factor related to a higher risk of recurrence or death in patients with TDs, both qualitatively and quantitatively in a large prospective phase III trial first time (IDEA France). (Delattre et al. 2020) Wu et al. retrospectively analyzed CRC patients from two large independent cohorts, the Surveillance Epidemiology and End Results (SEER) database (n=58,775) and colon cancer center in China (=742). He reported that CRC cancer patients without TDs have better survival benefits than patients with TDs (Wu et al. 2022). Nagayoshi et al. also investigated TDs in patients with CRC (n=171) and revealed that patients with TD-positive CRC had significantly lower recurrence-free rates compared to TD-negative CRC. Their follow-up showed that patients with TD-positive CRC developed more frequent local and/or distant tumor recurrence (Nagayoshi et al. 2014).

Association of other variables with local recurrence/distant metastasis such as age, sex, smoking, alcohol, family history, MSI status, mucinous histology, signet ring histology, tumor size, lymph node status, number of total and extracted lymph nodes, lymphovascular invasion, perineural invasion, adjuvant therapy has been widely studied. Xu et al. published an umbrella review of all systematic reviews of observational studies (with/without meta-analysis) and investigated risk factors of CRC recurrence and metastasis (Xu et al. 2020). Based on their evaluation, extranodal extension, perineural invasion, MRI-detected extramural vascular invasion and intramural vascular invasion are highly suggestive risk factors for the recurrence of the CRC. They also reviewed prognostic models developed for prediction of local recurrence and identified following predictors: distance from the anal verge, TNM stage, surgery type, residual tumor status, radiotherapy, age, concomitant chemotherapy and adjuvant chemotherapy. They also reviewed prognostic models

Table 3 Logistic regression analysis for predictors of recurrence / distant metastasis

Variable	Recurrence/distant metastasis			
	Univariate		Multivariate	
	p-value	Crude OR(95% CI)	*p*-value	AOR[a] (95% CI)
Age	0.2	0.98 (0.96–1.01)	0.4	0.99 (0.06–6.97)
Sex	0.7	1.2 (0.6–2.4)	-	-
Smoking	0.4	1.4 (0.69–2.84)	-	-
Alcohol	0.8	1.2 (0.55–2.26)	-	-
Family history	0.2	1.63 (0.78–3.46)	-	-
MSI: Loss-Intact	0.5	1.56 (0.39–6.15)	-	-
Mucinous histology	0.6	0.76 (0.39–1.99)	-	-
Signet ring	0.9	0.96 (0.08–10.95)	-	-
Tumor size	0.1	1.1 (0.98–1.26)	-	-
Lymph node status	0.03*	0.42 (0.19–0.91)	0.3	0.59 (0.24–1.49)
No. of lymph nodes	0.5	1.03 (0.94–1.14)	-	-
No. of LN extracted	0.4	0.95 (0.94–1.02)	-	-
No. of tumor deposits	0.04*	1.17 (1.007–1.37)	0.04*	1.17 (1.001–1.37)
LVI	0.07	2.18 (0.94–5.08)	-	-
PNI	0.9	1.04 (0.5–2.15)	-	-
Adjuvant therapy	0.02*	2.68 (1.22–5.92)	0.1	2.01 (0.79–5.12)

AOR Adjusted Odds Ratio, *BMI* Body Mass Index, *CI* confidence interval, *MSI* Microsatellite instability, *OR* Odds Ratio, *LVI* lymphovascular invasion, *PNI* perineural invasion, *AJCC* American Joint Committee on cancer

* $p \leq 0.05$

[a] AOR: Adjusted for (Age, lymph node status and adjuvant therapy) factors

Table 4 Logistic regression analysis for predictors of recurrence/distant metastasis based on number of tumor deposits

	Recurrence/distant metastasis		*P*-value
	No ($n=91$)	Yes ($n=47$)	
No. of tumor deposits < 4 ($n=119$)	81 (72.3%)	31 (27.7%)	0.001
No. of tumor deposits ≥ 4 ($n=19$)	10 (38.5%)	16 (61.5%)	

developed for prediction of distant metastasis of CRC and described following common predictors: positive lymph nodes, tumor grade or differentiation, tumor histological type, biomarker-carcinoembryonic antigen, age, gender and clinical treatment (such as surgery, chemotherapy and radiotherapy) (Xu et al. 2020). Dumont et al. showed that local recurrence was associated with a higher incidence of lymph node involvement (Dumont et al. 2020). Wiesmueller et al. revealed that positive lymph node status and/or advanced pT category were independent risk factors for recurrence within 16 months on multivariate analysis (Wiesmueller et al. 2021). Stipa et al. showed that local recurrence risk for patients with colon cancer was determined by histological tumor grade (Stipa et al. 1991). Schellenberg et al. described predictive risk factors of the colorectal cancer as T stage, N stage, vascular invasion and positive margins in univariable analysis, however they didn't find any significant effect of age, type or histological grade of the tumor (Schellenberg et al. 2022). Holt et al. showed that higher recurrence was associated with tumors with a mucinous and/or signet component, patients with positive nodes and patients who had less than 12 lymph nodes examined in multivariate analysis (Holt et al. 2021). van der Linden et al. stated that poorly differentiated histology and MSI status were significant relevant risk factors for local recurrence or distant metastasis with patients diagnosed with Stage I and II CRC. They didn't find any difference on recurrence for the angioinvasion, lymph invasion or amount of lymph nodes (van der Linden et al. 2020). Michelassi et al. showed that lymphatic or capillary microinvasion is related with local recurrence (Michelassi et al. 1990). Tokodai et al. revealed that lymphatic invasion in stage II patients is independent predictor of local or distant recurrence (Tokodai et al. 2016). Shanmugam et al. showed that increased number of resected lymph nodes is associated with reduced risk of recurrence for Stage II and III CRC (Shanmugam et al. 2011). Tsai et al. showed that presence of vascular invasion and number

of examined lymph node were significantly prognostic factors of the postoperative relapse after resection of Stage II CRC, however, they didn't find any significant differences regarding the gender, age, tumor size, tumor grade and tumor type (Tsai et al. 2008). Guo et al. constructed nomograms to determine prognostic role of different variables including distant metastasis (Guo et al. 2020). Based on their nomogram, different independent factors have their own score and effect on distant metastasis including age, tumor size, N stage, tumor grade and CEA.

Our data showed an association between tumor deposits and heightened occurrences of both local and distant recurrence. This finding is substantiated by prior studies. However, our study showed that the number of tumor deposit has a significant effect. Patients who have ≥ 4 tumor deposit tend to experience local recurrence/distant metastasis more than patients with < 4 tumor deposit.

Given that our study is a retrospective analysis conducted at a single institution, it is important to exercise caution when generalizing our results to the broader population. Additionally, the characteristics of TDs, such as size and histological origins (perivascular, perineural etc.) were not considered. Additionally, this study does not specify distant metastasis types such as liver, lung etc.

Conclusions

In summary, individuals with colorectal cancer and ≥ 4 TDs demonstrate a higher propensity for both local and distant recurrence compared to those with < 4TDs. Therefore, we propose an amendment to the AJCC classification of colon cancer, upgrading LN − ≥ 4 TD + into a new subset category which could be named"N2c". And patients with LN −, 1 to 3 TD + would remain staged as N1c. Also, it is required to conduct extensive, multicenter clinical investigations to identify the correlation between TDs and locally advanced colorectal cancer.

Institutional review board statement

I confirm that all relevant ethical guidelines have been followed, and any necessary IRB (Institutional Review Board) and/or ethics committee approvals have been obtained (the Feinstein Institutes for Medical Research/Northwell Health system located in New York City, USA). Ethical approval was waived; IRB approval number: 24–0186.

Informed consent statement

Not applicable.

Author contributions

Conceptualization, A.B. (Ahmed Bendari), E.U., H.H., A.B. (Alaa Bendari), and M.H.; methodology, A.B. (Ahmed Bendari) and H.H.; software, A.B. (Ahmed Bendari), and H.H.; validation, A.B. (Ahmed Bendari), H.H., and S.K.K.; formal analysis, A.B. (Ahmed Bendari), E.U., H.H., A.B. (Alaa Bendari); investigation, A.B. (Ahmed Bendari), E.U. H.H., R.A., A.B. (Alaa Bendari), and R.D.J. ; resources, R.A., F.K., E.U.; data curation, A.B.(Ahmed Bendari), R.A., E.U., and F.K.; writing—original draft preparation, A.B. (Ahmed Bendari), E.U.; writing—review and editing, A.B. (Ahmed Bendari), E.U., A.B. (Alaa Bendari), R.D.J., and M.H.; visualization, A.B. (Ahmed Bendari); supervision, A.B. (Ahmed Bendari) and M.H.; project administration, A.B. (Ahmed Bendari); funding acquisition, N/A. All authors have read and agreed to the published version of the manuscript.

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Data availability

All data and materials are available upon request from the corresponding author.

Declarations

Competing interests

The authors declare no conflict of interest.

Author details

[1]Department of Pathology and Laboratory Medicine, Lenox Hill Hospital, 100 E 77th Street, New York, USA. [2]Department of Pathology and Laboratory Medicine, Long Island Jewish Hospital, New York, USA. [3]Department of Medical Biochemistry, Faculty of Medicine, Zagazig University, Zagazig, Egypt. [4]Qatar Metabolic Institute, Hamad Medical Corporation, Doha, Qatar. [5]Department of Pathology and Laboratory Medicine, Staten Island Hospital, New York, USA. [6]Department of Medicine and Allied, Bahria University Health Sciences, Karachi, Pakistan.

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