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Original Article

Tumour deposits in colon cancer predict recurrence and reduced survival in a nationwide population-based study

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Abstract

Background: Tumour deposits are suggested to impact prognosis in colon cancer negatively. This study assessed the impact of tumour deposits on oncological outcomes.

Methods: Data from the Swedish Colorectal Cancer Registry for patients who underwent R0 abdominal surgery for TNM stage I–III colon cancer between 2011 and 2014 with 5-year follow-up were analysed with multivariable analysis. Patients were categorized for their tumour deposit status and compared for the local recurrence and distant metastasis rates and 5-year survivals (overall and relative). Subgroup analyses were performed according to the nodal disease status.

Results: Of 8146 stage I–III colon cancer patients who underwent R0 resection, 8014 patients were analysed (808 tumour deposits positive, 7206 tumour deposits negative). Patients with tumour deposits positive tumours had increased local recurrence and distant metastasis rates (7.2 *versus* 3.0 per cent; $P < 0.001$ and 33.9 *versus* 12.0 per cent; $P < 0.001$ respectively) and reduced 5-year overall and relative survival (56.8 per cent *versus* 74.9 per cent; $P < 0.001$ and 68.5 *versus* 92.6 per cent; $P < 0.001$ respectively). In multivariable analysis, tumour deposits moderately increased the risks of local recurrence and distant metastasis (hazard ratio 1.50, 95 per cent c.i. 1.09 to 2.07; $P = 0.013$ and HR 1.91, 95 per cent c.i. 1.64 to 2.23; $P < 0.001$ respectively) and worse 5-year overall and relative survival (hazard ratio 1.60, 95 per cent c.i. 1.40 to 1.82; $P < 0.001$ and excess hazard ratio 2.24, 95 per cent c.i. 1.81 to 2.78; $P < 0.001$ respectively). Subgroup analysis of N stages found that N1c patients had worse outcomes than N0 for distant metastasis and relative survival. For patients with lymph node metastases tumour deposits increased the risks of distant metastasis and worse overall and relative survival, except for N2b patients.

Conclusion: Tumour deposits negatively impact the prognosis in colon cancer and must be considered when discussing adjuvant chemotherapy.

Introduction

Colon cancer is the fifth most commonly diagnosed cancer and the fifth leading cause of cancer deaths worldwide[1]. The TNM stage, based on pathologic findings in surgical resection specimens and radiology, remains the key determinant of prognosis. However, there is stage-independent variability in oncological outcomes, underscored by the TNM staging system[2,3]. The TNM staging system considers three categories and does not account for other histopathological prognostic factors, such as tumour grading, lymphovascular and perineural invasion or tumour budding. Furthermore, neither molecular nor genetic prognostic factors, such as KRAS, BRAF or MSI mutations, are integrated.

Surgery is the primary treatment for most colon cancer patients. Guidelines recommend adjuvant chemotherapy for high-risk stage II and III patients[4–6]. However, recent studies suggest that subgroups of patients with locally advanced tumours may benefit from neoadjuvant chemotherapy[7–9]. Debatably, the presence of pericolic tumour deposits (TDs) in the absence of lymph node metastases (LNMs) was designated stage III (N1c) in the seventh edition of the TNM staging system[2,10–12].

TDs are associated with poor prognosis in colon cancer[10,12–18]. The reported prevalence of TDs is approximately 20 per cent, but is highly dependent on the studied population[10,12]. Despite some recent population-based publications, earlier studies on TDs in colon cancer are relatively few and limited by retrospective single-centre design and uncertainty regarding pathology quality[10,12]. In many publications, colon and rectal cancer patients, subsequently impacted by neoadjuvant treatment, are merged, further complicating interpretation of the results[13,14,16,17]. Additionally, most studies report survival as the only outcome and recurrence data are not provided[12].

This population-based study aimed to assess the impact of TDs on rates of local recurrence (LR) and distant metastasis (DM), as well as overall and relative survival in colon cancer. The secondary aims were to perform subgroup analyses of the

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prognostic value of TDs in different N stages and in patients with LNMs.

Methods

This study was approved by the Ethical Review Board of Lund University, Sweden (2020/01769), and followed the Declaration of Helsinki guidelines. The study was not preregistered.

Swedish colorectal cancer registry

Since 2007, all patients in Sweden with adenocarcinoma of the colon have been registered in the Swedish Colorectal Cancer Registry (SCRCR) nationwide quality registry. The SCRCR contains data on patients, tumours, diagnostic work-up, treatment characteristics, histopathological examinations and short-term outcomes registered 30 days after surgery[19–21]. Long-term outcomes, including late complications, recurrences and deaths, are reported 3 and 5 years after primary surgery[19–21]. In 2008, national treatment guidelines established follow-up routines for patients treated with surgery including computed tomography (CT) of the thorax and abdomen in conjunction with serum levels of carcinoembryonic antigen 12 and 36 months after surgery, as well as colonoscopy every 5 years until the age of 75[4]. The date of death was obtained from the Cause of Death Registry. The SCRCR is a robust registry with a low proportion of missing data and high internal and external validity for key variables useful for quality assurance and research[21]. To date, 70 499 patients with colon cancer have been registered in the SCRCR[19]. In 2011, TDs were included in the SCRCR data set[19].

Study population

The study was a retrospective analysis of prospectively registered data of patients with colon cancer registered in the SCRCR between 1 January 2011 and 31 December 2014. Included in the final analysis were patients with TNM stage I–III disease who underwent R0 abdominal resection surgery (hemicolectomies/colectomies) and were alive 90 days after surgery with a registered 5-year follow-up.

Definitions

During the studied interval, staging was reported according to the seventh edition of the TNM classification of malignant tumours[2]. In the absence of LNMs, TDs were placed in the nodal category designated N1c.

Colon cancer was defined by the SCRCR as an adenocarcinoma with the ICD-O-3 site codes C18.0–C18.9. Tumour location was dichotomized to right-sided if situated proximal to the splenic flexure and left-sided if situated in or distal to the splenic flexure.

R0 resection was defined as negative macroscopic margins after surgery, according to the surgeon, and negative microscopic margins in the surgical resection specimen, according to the pathologist.

A colorectal surgeon was defined as an accredited colorectal surgeon or a surgeon with a clinical subspecialization in colorectal surgery.

Emergency surgery was defined as a medically indicated procedure performed during an unplanned admission.

TDs were defined as macroscopic or microscopic nests or nodules, in the pericolic adipose tissue's lymph drainage area of a primary carcinoma without histological evidence of residual lymph node in the nodule that may represent discontinuous spread, venous invasion with extravascular spread or a totally replaced lymph node[2].

Histopathological tumour grading was dichotomized to low grade (well and moderately differentiated) and high grade (poorly differentiated and undifferentiated).

Lymphovascular invasion was defined as tumour infiltration of lymphatic or venous vessels, irrespective of size and intra- or extramural location.

Perineural invasion was defined as tumour infiltration of nerves in the tumour or tumour spread along the nerve pathway.

A mucinous tumour was defined as a tumour composed of more than 50 per cent extracellular mucin. This entity includes signet-ring cell carcinoma.

LR was defined as tumour recurrence at the anastomosis/resection line or in the peritoneum, mesenteric lymph nodes adjacent to the original primary tumour as well as abdominal incisions/port sites, as documented by clinical, radiological or pathological examination, or examination at surgery or autopsy more than 90 days after primary surgery.

DM was defined as tumour recurrence in the peritoneum or mesenteric lymph nodes remote from the original primary tumour as well as in any other organ (the liver, lung, ovary, bone, brain or any other parenchymatous organ) as documented by clinical, radiological or pathological examination, or examination at surgery or autopsy more than 90 days after primary surgery.

Overall survival was defined as the proportion of observed survivors in the studied cohort of colon cancer patients with a registered 5-year follow-up from the date of surgery.

Relative survival was defined as the ratio of the proportion of observed survivors in the studied cohort of colon cancer patients with a registered 5-year follow-up from the date of surgery to the proportion of expected survivors in a comparable cancer-free population.

Statistical analysis

The categorical data are presented as absolute numbers with percentages. For intergroup comparisons of categorical data, an χ^2 test was used. Continuous data are presented as median (range) and Student's *t* test was used for intergroup comparison. Cumulative LR, DM and overall survival rates were calculated from the time of surgery to the end of follow-up. The Kaplan–Meier method was used to analyse overall survival and the log rank test to examine differences between groups. To assess the impact of TDs on the rates of LR, DM and 5-year overall survival, univariable and multivariable Cox regression analyses were performed using the following covariates: age, sex, adjuvant chemotherapy, tumour location, T stage, lymphovascular invasion, perineural invasion and tumour grading. Only cases with complete data were analysed in multivariable analyses. Hazard ratios (HRs) were calculated with 95 per cent confidence intervals. HRs larger than 1.00 indicated worse outcome for the test category *versus* the reference category. Relative survival was calculated using the Ederer II method to estimate expected survival differences between groups; subsequently, Poisson regression was employed in univariable and multivariable analyses[22,23]. Excess hazard ratio (EHR) was calculated with 95 per cent c.i. EHR larger than 1.00 indicated worse outcome for the test category *versus* the reference category.

For all tests, $P < 0.050$ was considered statistically significant. Data analyses were undertaken using SPSS® version 28.0 for

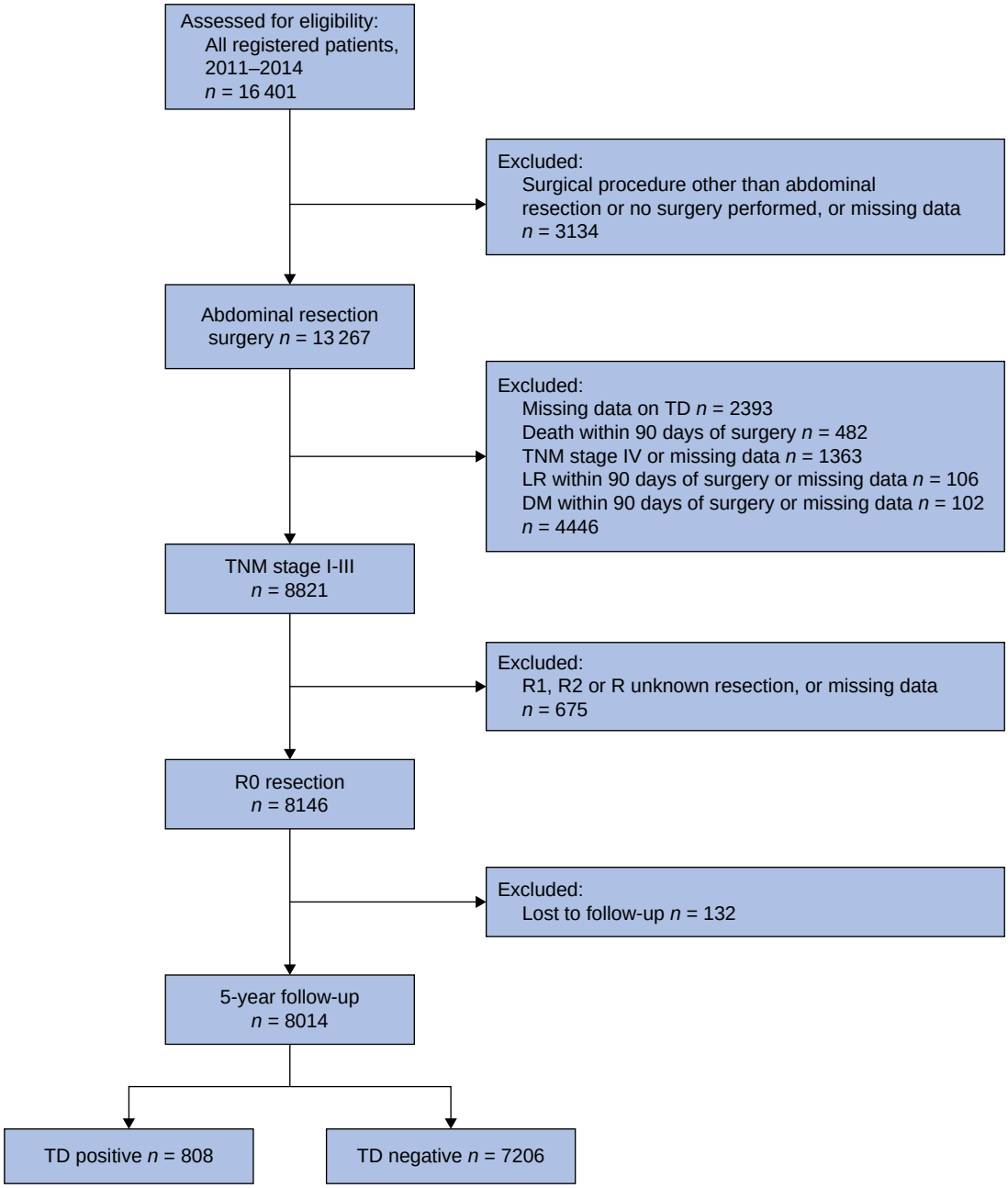

Fig. 1 Study flow chart

TD, tumour deposits; LR, local recurrence; DM, distant metastasis.

Windows® (IBM, Armonk, NY, USA) and Stata®/MP version 16.1 (Stata Corp, College Station, TX, USA).

Results

During the studied interval, 16 401 patients were registered in the SCRCR and 13 267 (80.9 per cent) had abdominal resection surgery. After exclusion, 8014 patients remained (808 TD positive and 7206 TD negative) for analysis (*Fig. 1*). Thus, TDs were present among 10.1 per cent of the patients in the study cohort. The median TD count was 2 (range 1–40) in TD positive patients. Among stage III patients, 189 of 3033 (6.2 per cent) were staged as N1c (*Table 1*).

As shown in *Table 1*, patients with TD positive tumours had a higher T and N stage, tumour grading and incidence of lymphovascular and perineural invasion. The patients with TD positive tumours were younger, more frequently underwent elective surgery and were more likely to have left-sided tumours. No difference in the frequency of postoperative or surgical complications was detected between the two groups (*Supplementary materials, Table S1*). Patients with TD positive tumours were more extensively treated with adjuvant chemotherapy. Among N1c patients, 41.8 per cent had adjuvant chemotherapy, whereas the corresponding figures were 53.8 per cent for N1a, 60.8 for N1b, 65.5 for N2a and 67.4 for N2b patients ($P < 0.001$).

Table 1 Patient characteristics, treatment details and tumour data for patients who had elective R0 abdominal resection surgery for TNM stage I–III colon cancer in Sweden, 2011–2014

Variables	All patients (*n* = 8014)	TD positive (*n* = 808)	TD negative (*n* = 7206)	P*
Age, years†	74 (19–98)	72 (19–98)	74 (29–97)	0.017‡
Sex				0.371
Male	3927 (49.0)	408 (50.5)	3519 (48.8)	
Female	4087 (51.0)	400 (49.5)	3687 (51.2)	
ASA score				0.828
I	1042 (13.0)	102 (12.6)	940 (13.0)	
II	4314 (53.8)	439 (54.3)	3875 (53.8)	
III	2396 (29.9)	234 (29.0)	2162 (30.0)	
IV	180 (2.2)	21 (2.6)	159 (2.2)	
Missing	82 (1.0)	12 (1.5)	70 (1.0)	
BMI, kg/m^2†	25.4 (12.8–49.4)	25.5 (14.7–46.5)	25.3 (12.8–49.4)	0.033‡
Missing	443 (5.5)	50 (6.2)	393 (5.5)	
Emergency surgery				<0.001
No	6989 (87.2)	648 (80.2)	6341 (88.0)	
Yes	1025 (12.8)	160 (19.8)	865 (12.0)	
Surgical approach				
Open	6561 (81.9)	677 (83.8)	5884 (81.7)	0.087
Laparoscopic	1408 (17.6)	124 (15.3)	1284 (17.8)	
Missing	45 (0.6)	7 (0.9)	38 (0.5)	
Surgical competence				0.038
Colorectal surgeon	7457 (93.0)	736 (91.1)	6721 (93.3)	
General surgeon	502 (6.3)	64 (7.9)	438 (6.1)	
Missing	55 (0.7)	8 (1.0)	47 (0.7)	
Intraoperative perforation				0.022
No	7831 (97.7)	782 (96.8)	7049 (97.8)	
Yes	123 (1.5)	20 (2.5)	103 (1.4)	
Missing	60 (0.7)	6 (0.7)	54 (0.7)	
Intraoperative bleeding, ml†	100 (0–9500)	150 (0–6000)	100 (0–9500)	0.020‡
Missing	270 (3.4)	15 (1.9)	255 (3.5)	
Adjuvant chemotherapy				<0.001
No	5723 (71.4)	311 (38.5)	5412 (75.1)	
Yes	2240 (28.0)	486 (60.1)	1754 (24.3)	
Missing	51 (0.6)	11 (1.4)	40 (0.6)	
Tumour location				<0.001
Right-sided	4650 (58.0)	403 (49.9)	4247 (58.9)	
Left-sided	3358 (41.9)	405 (50.1)	2953 (41.0)	
Missing	6 (0.1)	0 (0.0)	6 (0.1)	
TNM stage				<0.001
I	1504 (18.8)	0 (0.0)	1504 (20.9)	
II	3477 (43.4)	0 (0.0)	3477 (48.3)	
III	3033 (37.8)	808 (100)	2225 (30.9)	
T stage				<0.001
1	585 (7.3)	11 (1.4)	574 (8.0)	
2	1194 (14.9)	32 (4.0)	1162 (16.1)	
3	4857 (60.6)	467 (57.8)	4390 (60.9)	
4	1372 (17.1)	297 (36.8)	1075 (14.9)	
Missing	6 (0.1)	1 (0.0)	5 (0.1)	
No. of lymph nodes examined†	20 (0–99)	21 (4–99)	20 (0–99)	<0.001‡
Missing	58 (0.7)	3 (0.4)	55 (0.8)	
N stage				<0.001
0	4959 (61.9)	0 (0.0)	4959 (68.8)	
1	1989 (24.8)	489 (60.5)	1500 (20.8)	
2	1042 (13.0)	319 (39.5)	723 (10.0)	
Missing	24 (0.3)	0 (0.0)	24 (0.3)	
N1 stage subgroups				<0.001
1a	863 (43.4)	105 (21.5)	758 (50.5)	
1b	880 (44.2)	185 (37.8)	695 (46.3)	
1c	189 (9.5)	189 (38.7)	0 (0.0)	
Missing	57 (2.9)	10 (2.0)	47 (3.1)	
N2 stage subgroups				<0.001
N2a	554 (53.2)	147 (46.1)	407 (56.3)	
N2b	454 (43.6)	165 (51.7)	289 (40.0)	
Missing	34 (3.3)	7 (2.2)	27 (3.7)	
Tumour grading				<0.001
Low grade	6031 (75.3)	547 (67.7)	5484 (76.1)	
High grade	1586 (19.8)	217 (26.9)	1369 (19.0)	
Missing	397 (5.0)	44 (5.4)	353 (4.9)	

(continued)

Table 1 (continued)

Variables	All patients (*n* = 8014)	TD positive (*n* = 808)	TD negative (*n* = 7206)	P*
Lymphovascular invasion				<0.001
No	6033 (75.3)	378 (46.8)	5655 (78.5)	
Yes	1901 (23.7)	425 (52.6)	1476 (20.5)	
Missing	80 (1.0)	5 (0.6)	75 (1.0)	
Perineural invasion				<0.001
No	6719 (83.8)	516 (63.9)	6203 (86.1)	
Yes	955 (11.9)	273 (33.8)	682 (9.5)	
Missing	340 (4.2)	19 (2.4)	321 (4.4)	
Mucinous tumour				0.878
No	6498 (81.1)	649 (80.3)	5849 (81.2)	
Yes	1353 (16.9)	137 (17.0)	1216 (16.9)	
Missing	163 (2.0)	22 (2.7)	141 (1.9)	

Values in parentheses are percentages unless indicated otherwise; *χ^2 test, except ‡Student's *t* test. †values are median (range). TD, tumour deposit.

Table 2 Recurrence data for patients who had elective R0 abdominal resection surgery for TNM stage I–III colon cancer in Sweden, 2011–2014

	All patients (*n* = 8014)	TD positive (*n* = 808)	TD negative (*n* = 7206)	P*
Local recurrence				<0.001
No	7741 (96.6)	750 (92.8)	6991 (97.0)	
Yes	273 (3.4)	58 (7.2)	215 (3.0)	
Distant metastasis				<0.001
No	6876 (85.8)	534 (66.1)	6342 (88.0)	
Yes	1138 (14.2)	274 (33.9)	864 (12.0)	

Values in parentheses are percentages. *χ^2 test. TD, tumour deposit.

Recurrence

In the overall study population, LR was registered in 273 patients (3.4 per cent) within 5 years of primary surgery (*Table 2*). The LR rate was higher in TD positive patients (7.2 *versus* 3.0 per cent; $P < 0.001$). Metachronous DM was recorded in 1138 patients (14.2 per cent), with a higher frequency among TD positive patients (33.9 *versus* 12.0 per cent; $P < 0.001$).

In multivariable Cox regression analysis, adjusted for the covariables: age, sex, adjuvant chemotherapy, tumour location, T stage, lymphovascular invasion, perineural invasion and tumour grading, a TD positive tumour was an independent risk factor for LR (HR 1.50, 95 per cent c.i. 1.09 to 2.07; $P = 0.013$) and DM (HR 1.91, 95 per cent c.i. 1.64 to 2.23; $P < 0.001$) (*Table 3*).

The HR for DM was higher for patients with N1c stage than N0 (HR 1.71, 95 per cent c.i. 1.14 to 2.56; $P = 0.010$), but not for LR (*Table 3*).

In a subgroup analysis of patients with LNMs, the HR for DM was higher in N1a, N1b and N2a patients with TD positive tumours than with TD negative tumours, but not for LR (*Table 3*). In the N2b stage, no difference was found in HR between TD positive and TD negative tumours for LR or DM.

Survival

The 5-year overall survival rate for patients with TD positive tumours was 56.8 per cent, compared with 74.9 per cent among TD negative tumours ($P < 0.001$) (*Fig. 2a*). Five-year relative survival rates were 68.5 and 92.6 per cent respectively ($P < 0.001$) (*Fig. 2b*).

In multivariable Cox regression analysis, adjusted for the covariables: age, sex, adjuvant chemotherapy, tumour location, T stage, lymphovascular invasion, perineural invasion and tumour grading, a TD positive tumour was an independent risk factor for decreased overall (HR 1.60, 95 per cent c.i. 1.40 to 1.82; $P < 0.001$) and relative survival (EHR 2.24, 95 per cent c.i. 1.81 to 2.78; $P < 0.001$) respectively (*Table 4*).

The relative survival was decreased in patients with N1c stage compared with N0 patients (EHR 2.11, 95 per cent c.i. 1.08 to 4.14; $P = 0.014$) (*Table 4*); however, overall survival did not differ between the two groups.

Overall, HR was reduced in a subgroup analysis of patients with LNMs. EHR for decreased relative survival was higher in N1a, N1b and N2a patients with TD positive tumours compared with TD negative (*Table 4*). In the N2b stage, no difference in HR or EHR was found between patients with TD positive *versus* negative tumours for decreased overall and relative survival.

Discussion

In this study, TDs were an independent prognostic risk factor for LR and DM, reducing overall and relative survival rates in colon cancer. The negative prognostic impact remained in a subgroup analysis of N stages and patients with LNMs.

Data on the impact of TDs on recurrence in colon cancer are limited[12]. In a meta-analysis of colorectal cancer patients and two studies of stage III colon cancer patients, reduced disease-free survival (DFS) among patients with TD positive tumours was reported[10,15,18]. In the actual N stage subset analysis, N1c stage had worse prognosis regarding DM and relative survival than N0. In subgroup analysis of the patients with LNMs, the negative impact of TDs on prognosis remained for DM in N1a-b and N2a, but not in N2b patients. In prior studies, reduced DFS has been reported across all N stages for TD positive tumours without subdivision of N stages 1 and 2 into a and b[15,18]. The lack of impact of TDs on relative survival among N2b patients in the present analysis might be due to a type II error, as the number of patients in this group of tumours with advanced N stage was small. Alternatively, the prognostic impact of TDs might be overridden with more advanced N stage. In rectal cancer, TDs are proposed to relate to venous tumour spread as part of the vascular highway to DM, in contrast to local spread by LNMs, perineural and lymphatic invasion[10,15,24]. If this suggested pathway is true for colon cancer, this might

Table 3 Univariable and multivariable analysis relating the impact of tumour deposits, N stages and lymph node metastases on recurrence after elective R0 abdominal resection surgery for TNM stage I–III colon cancer in Sweden, 2011–2014

			Local recurrence		Distant metastasis	
		n	Hazard ratio	*P*	Hazard ratio	*P*
TD status				**Univariable**		
Negative		7206	1.00		1.00	
Positive		808	2.69 (2.01–3.60)	<0.001	3.38 (2.95–3.88)	<0.001
				Multivariable*		
Negative		6508	1.00		1.00	
Positive		732	1.50 (1.09–2.07)	0.013	1.91 (1.64–2.23)	<0.001
N stage				**Univariable**		
N0		4959	1.00		1.00	
N1a		863	2.05 (1.37–3.07)	<0.001	2.81 (2.32–3.40)	<0.001
N1b		880	3.14 (2.21–4.44)	<0.001	3.63 (3.04–4.32)	<0.001
N1c		189	2.35 (1.14–4.83)	0.021	2.27 (1.54–3.34)	<0.001
N2a		554	3.82 (2.59–5.63)	<0.001	5.97 (4.99–7.15)	<0.001
N2b		454	7.25 (5.11–10.27)	<0.001	9.02 (7.57–10.75)	<0.001
				Multivariable*		
N0		4488	1.00		1.00	
N1a		791	1.46 (0.94–2.28)	0.091	2.27 (1.83–2.81)	<0.001
N1b		803	2.08 (1.39–3.12)	<0.001	2.66 (2.16–3.28)	<0.001
N1c		172	1.64 (0.78–3.43)	0.189	1.71 (1.14–2.56)	0.010
N2a		494	2.47 (1.57–3.88)	<0.001	4.13 (3.32–5.14)	<0.001
N2b		397	3.88 (2.51–6.00)	<0.001	6.11 (4.90–7.63)	<0.001
LN status	**TD status**			**Univariable**		
N1a	Negative	758	1.00		1.00	
	Positive	105	1.36 (0.52–3.54)	0.526	1.96 (1.32–2.90)	0.001
N1b	Negative	695	1.00		1.00	
	Positive	185	1.17 (0.60–2.30)	0.641	2.14 (1.59–2.88)	<0.001
N2a	Negative	407	1.00		1.00	
	Positive	147	1.56 (0.78–3.14)	0.211	1.47 (1.08–2.00)	0.015
N2b	Negative	289	1.00		1.00	
	Positive	165	1.39 (0.78–2.46)	0.265	1.43 (1.08–1.90)	0.012
				Multivariable*		
N1a	Negative	692	1.00		1.00	
	Positive	99	1.46 (0.54–3.99)	0.455	1.74 (1.13–2.66)	0.011
N1b	Negative	631	1.00		1.00	
	Positive	172	1.03 (0.50–2.15)	0.932	1.95 (1.40–2.71)	<0.001
N2a	Negative	360	1.00		1.00	
	Positive	134	1.14 (0.55–2.39)	0.724	1.40 (1.00–1.96)	0.053
N2b	Negative	254	1.00		1.00	
	Positive	143	1.23 (0.66–2.29)	0.520	1.21 (0.89–1.64)	0.222

Values in parentheses are 95 per cent c.i. *Adjusted for age, sex, adjuvant chemotherapy, tumour location, T stage, lymphovascular invasion, perineural invasion and tumour grading. LN, lymph node; TD, tumour deposit.

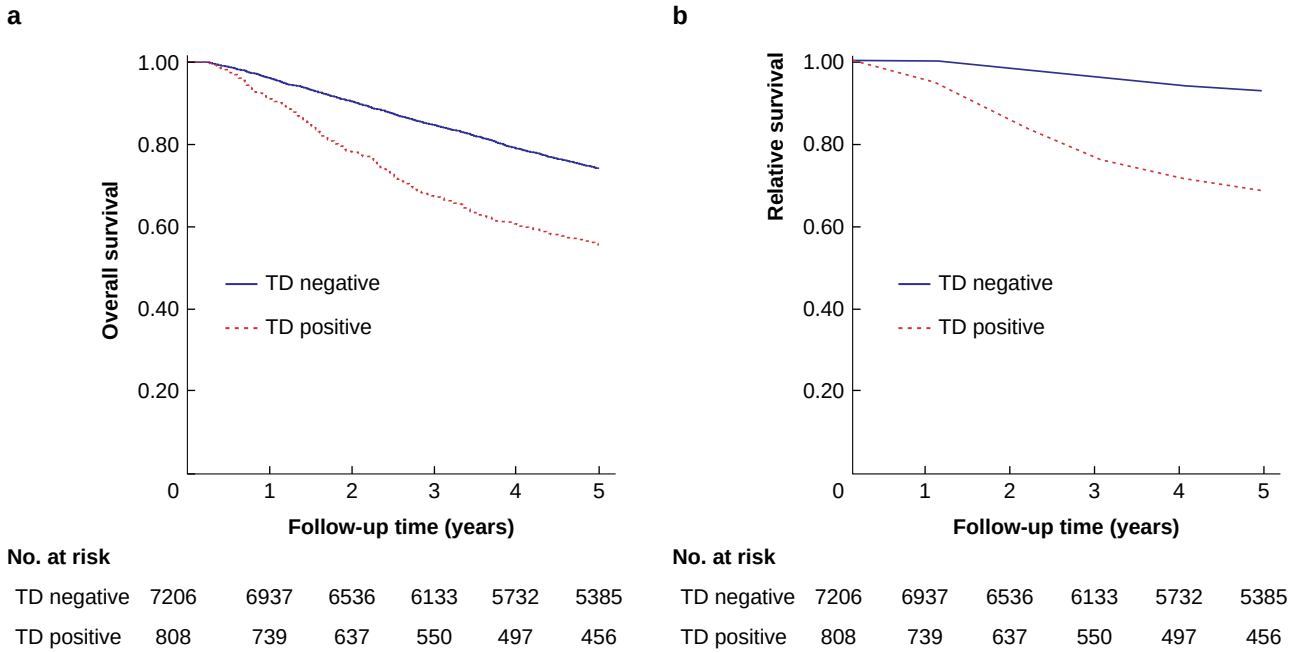

Fig. 2 Five-year survival of patients who had elective R0 abdominal resection surgery for TNM stage I–III colon cancer in Sweden, 2011–2014
a Overall and **b** relative survival. **a** $P < 0.001$ (log rank test), **b** $P < 0.001$ (the Ederer II method). TD, tumour deposit.

Table 4 Univariable and multivariable analysis relating the impact of tumour deposits, N stages and lymph node metastases on survival after elective R0 abdominal resection surgery for TNM stage I–III colon cancer in Sweden, 2011–2014

			Overall survival		Relative survival	
		n	Hazard ratio	*P*	Excess hazard ratio	*P*
TD status					**Univariable**	
Negative		7206	1.00		1.00	
Positive		808	2.02 (1.80–2.27)	<0.001	4.61 (3.74–5.69)	<0.001
					Multivariable*	
Negative		6508	1.00		1.00	
Positive		732	1.60 (1.40–1.82)	<0.001	2.24 (1.81–2.78)	<0.001
N stage					**Univariable**	
N0		4959	1.00		1.00	
N1a		863	1.43 (1.25–1.64)	<0.001	3.16 (2.09–4.76)	<0.001
N1b		880	1.65 (1.45–1.88)	<0.001	4.12 (2.83–6.01)	<0.001
N1c		189	1.31 (0.99–1.74)	0.058	2.68 (1.23–5.85)	0.014
N2a		554	2.08 (1.80–2.41)	<0.001	7.36 (5.13–10.55)	<0.001
N2b		454	3.67 (3.20–4.21)	<0.001	17.41 (12.61–24.02)	<0.001
					Multivariable*	
N0		4488	1.00		1.00	
N1a		791	1.45 (1.25–1.68)	<0.001	2.80 (1.92–4.10)	<0.001
N1b		803	1.66 (1.43–1.93)	<0.001	3.58 (2.50–5.13)	<0.001
N1c		172	1.20 (0.89–1.61)	0.223	2.11 (1.08–4.14)	0.030
N2a		494	2.19 (1.85–2.61)	<0.001	5.13 (3.57–7.37)	<0.001
N2b		397	3.67 (3.10–4.34)	<0.001	9.55 (6.76–13.48)	<0.001
LN status	**TD status**				**Univariable**	
N1a	Negative	758	1.00		1.00	
	Positive	105	1.39 (0.99–1.95)	0.061	3.11 (1.67–5.77)	<0.001
N1b	Negative	695	1.00		1.00	
	Positive	185	1.58 (1.22–2.05)	0.001	2.59 (1.58–4.27)	<0.001
N2a	Negative	407	1.00		1.00	
	Positive	147	1.45 (1.08–1.93)	0.012	2.10 (1.34–3.31)	0.001
N2b	Negative	289	1.00		1.00	
	Positive	165	1.43 (1.11–1.83)	0.005	1.49 (1.08–2.06)	0.016
					Multivariable*	
N1a	Negative	692	1.00		1.00	
	Positive	99	1.50 (1.04–2.15)	0.029	2.08 (1.09–3.96)	0.026
N1b	Negative	631	1.00		1.00	
	Positive	172	1.62 (1.22–2.16)	0.001	1.98 (1.22–3.20)	0.005
N2a	Negative	360	1.00		1.00	
	Positive	134	1.37 (0.99–1.88)	0.055	1.70 (1.08–2.69)	0.023
N2b	Negative	254	1.00		1.00	
	Positive	143	1.20 (0.91–1.57)	0.191	1.21 (0.87–1.68)	0.252

Values in parentheses are 95 per cent c.i. *Adjusted for age, sex, adjuvant chemotherapy, tumour location, T stage, lymphovascular invasion, perineural invasion and tumour grading. TD, tumour deposit; LN, lymph node.

explain the observed lack of impact on LR in patients with LNMs in the present analysis.

In the current cohort, patients with TD positive tumours had worse overall and relative survival rates. In the N stage subset analysis, relative survival, but not overall survival, was reduced in the N1c stage. Among the patients with LNMs, the impact of TDs on overall survival was not detected among N2a and b patients, nor on relative survival in N2b patients, possibly because of the low number of patients or more advanced N stage. In all other N stages, TDs reduced overall and relative survival. These findings are consistent with previous studies[10,12–18]. In American database studies, the combination of TDs and LNMs has the worst prognosis concerning overall survival[13,14,16,17]; however, detailed N stage subset data are not presented. In a small study, TDs negatively impacted overall survival in N1 and N2 stage patients, but the stages were not further subdivided[18]. Others demonstrated reduced disease-specific survival (DSS) in the presence of TDs in colorectal cancer[10]. Otherwise, data on the impact of TDs in colon cancer on DSS, cancer-specific survival and relative survival are seldom provided.

The prevalence of TDs in the studied cohort, including stage I–III patients, was as expected, lower than in other studies selectively including stage III patients, as TDs are associated with more advanced tumours[10,12–18]. Furthermore, the study strictly excluded non-radically operated patients, stage IV, recurrences, and deaths within 90 days of surgery to ensure that the analysed recurrences were true recurrences and not tumour progression.

In the study, TDs were more common among younger patients and left-sided tumours. Another author reported the same concerning tumour location[15], but the higher prevalence among young patients was a novel finding[15,17,18].

In agreement with earlier reports, TDs in the present study were related to other histopathologic risk factors for poor prognosis such as higher T and N stage, high tumour grading, lymphovascular, as well as perineural invasion[10,12–18]. An association with extramural venous invasion has also been demonstrated[10,12,24], but unfortunately, this variable was not included in the SCRCR until 2017.

Although guidelines[4–6] recommend adjuvant chemotherapy for stage III colon cancer patients, N1c stage patients receive less chemotherapy than others within stage III[13,14]. A recent audit of N1c stage patients in the National Cancer Database proved the underutilization of adjuvant chemotherapy and

improved overall survival among treated patients in the N1c group[25]. The duration and regimen of adjuvant chemotherapy in N1c patients need further exploration[13,14,25]. The underuse of adjuvant chemotherapy in the current study might be explained by the close introduction of the seventh edition of the TNM staging system and the fact that its application in local MDTs was not yet established. However, in an American study[14], including patients resected between 2010 and 2014, the difference within the stage III group remained after stratification by year, a disadvantage for N1c stage patients.

The independent prognostic impact of TDs has not been addressed in studies on neoadjuvant chemotherapy in colon cancer[7–9]. However, preoperative TNM staging of colon cancer is based on multidetector CT, which has limited accuracy for the T and N stages[26,27].

The present data are prospectively collected and from a robust, national, population-based registry[19–21] reflecting routine clinical care. The risk of selection bias is eliminated, and the number of events makes multivariable analysis with adjustment for an acceptable, although limited, number of confounders possible. Limitations include possible quality variations in pathology assessment and a relatively high frequency of missing data since the study interval started immediately after the inclusion of TDs in the SCRCR data set. Moreover, staging in the SCRCR today is according to the eighth edition of the TNM staging system[3]. In contrast, during the study interval, the staging was according to the seventh[2]. Some patients with N1c tumours in the actual study might today be downstaged to stage II N0, since the definition of TDs in the eighth edition has been changed from 'no evidence of residual lymph node in the nodule' to also include 'or identifiable vascular or neural structures'[2,3,11,12].

Because the prognostic information of TDs is lost in the current TNM staging system, modifications are suggested[10–18,24]. Various scenarios with different benefits and limitations are debated. However, most suggested modifications recommend that existing TDs should not be ignored in the presence of LNMs, and the number of TDs should be considered.

The present study proves an independent prognostic value of TDs across N stages and irrespective of the presence of LNMs partially ignored by the current TNM staging system[3]. The findings might support modifications of the TNM staging system to prevent the loss of prognostic information. Recognition of the negative prognostic impact of TDs in colon cancer when discussing adjuvant chemotherapy at postoperative MDTs is stressed. Future topics of relevance concerning TDs in colon cancer include associations to other patient- and tumour-related negative prognostic factors, preoperative radiologic staging, standardization of pathology assessment in routine clinical care, awareness of the negative prognostic impact, and the role of neoadjuvant and adjuvant chemotherapy.

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Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS Open* online.

Data availability

Data can be provided upon reasonable request.

Author contributions

Fredrik Jörgren (Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Supervision, Writing—review & editing), Erik Agger (Conceptualization, Investigation, Methodology, Supervision, Writing—review & editing), Marie-Louise Lydrup (Conceptualization, Investigation, Methodology, Supervision, Writing—review & editing) and Pamela Buchwald (Conceptualization, Investigation, Methodology, Supervision, Writing—review & editing).

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