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Risk of metachronous peritoneal metastases in patients with pT4a versus pT4b colon cancer: An international multicentre cohort study

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ABSTRACT

Introduction: With evolving treatment strategies aiming at prevention or early detection of metachronous peritoneal metastases (PM), identification of high-risk colon cancer patients becomes increasingly important. This study aimed to evaluate differences between pT4a (peritoneal penetration) and pT4b (invasion of other organs/structures) subcategories regarding risk of PM and other oncological outcomes.
Materials and methods: From eight databases deriving from four countries, patients who underwent curative intent treatment for pT4N0-2M0 primary colon cancer were included. Primary outcome was the 5-year metachronous PM rate assessed by Kaplan-Meier analysis. Independent predictors for metachronous PM were identified by Cox regression analysis. Secondary endpoints included 5-year local and distant recurrence rates, and 5-year disease free and overall survival (DFS, OS).
Results: In total, 665 patients with pT4a and 187 patients with pT4b colon cancer were included. Median follow-up was 38 months (IQR 23–60). Five-year PM rate was 24.7% and 12.2% for pT4a and pT4b categories, respectively ($p = 0.005$). Independent predictors for metachronous PM were female sex, right-sided colon cancer, peritumoral abscess, pT4a, pN2, R1 resection, signet ring cell histology and post-operative surgical site infections. Five-year local recurrence rate was 14% in both pT4a and pT4b cancer ($p = 0.138$). Corresponding five-year distant metastases rates were 35% and 28% ($p = 0.138$). Five-year DFS and OS were 54% vs. 62% ($p = 0.095$) and 63% vs. 68% ($p = 0.148$) for pT4a vs. pT4b categories, respectively.
Conclusion: Patients with pT4a colon cancer have a higher risk of metachronous PM than pT4b patients. This observation has important implications for early detection and future adjuvant treatment strategies.

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Introduction

Approximately 10–15% of patients with colon cancer present with locally advanced (T4) disease [1–3]. The 8th edition of the TNM classification subdivides the T4 category into T4a and T4b: T4a referring to tumours penetrating the visceral peritoneum, and T4b defined as tumours directly invading other organs or structures [4]. The T4 category is an important risk factor for developing metachronous peritoneal metastases (PM). It is hypothesised that full-thickness invasion of the bowel wall with peritoneal penetration enables tumour cells to enter the peritoneal cavity, disseminate and form metastatic implants [5]. The incidence of metachronous PM in patients with histopathologically proven T4 colon cancer is reported to be up to 30% [6,7]. Clinical trials focusing on prevention of outgrowth or early detection of PM therefore often include patients with clinical and/or pathological T4 (pT4) colon cancer [8–10].

To develop tailored intensified follow-up and treatment strategies, identification of risk factors within the high-risk subset of T4 colon cancer patients is increasingly relevant. It might be hypothesised that metachronous PM are less often found after resection of pT4b, as compared to pT4a tumours, because direct invasion into other organs/structures is often accompanied with an inflammatory response around the tumour that precedes subsequent tumour infiltration [11,12]. This might prevent intraperitoneal seeding of exfoliated cancer cells at the time the tumour penetrates the peritoneum. Moreover, pT4b tumours originating from the ascending or descending colon that grow into retroperitoneal organs might not involve the peritoneum at all. Previous studies investigating differences in peritoneal recurrence in pT4 colon cancer patients are limited by small number of patients with a low absolute number of events. The purpose of this international, multicentre cohort study was to determine the incidence of metachronous PM in patients who underwent curative intent resection of pT4a and pT4b colon cancer separately. Secondary aims were to determine the local and distant recurrence rates, disease free survival (DFS) and overall survival (OS) for these two groups.

Material and methods

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [13].

Patients and databases

In this international, multicentre cohort study, individual patient data from different databases derived from Belgian, Dutch, Italian and Spanish hospitals were pooled: four prospectively maintained databases [14–16], three retrospectively maintained databases, and one multicentre randomised controlled trial [8]. Details of these databases are displayed in Table A.1. Patients who underwent curative intent treatment (R0/R1 resection) for pT4N0-2M0 primary colon cancer were included. Patients with any recurrence detected within 30 days after surgery were excluded, as these were considered to have M1 disease. For the purpose of this study, patients who died or were lost to follow-up within 30 days after surgery were also excluded, based on a minimal required follow-up to determine the risk of PM. Furthermore, patients were excluded if the pathology report of the primary resection specimen was missing or if the histology of the primary tumour was other than adenocarcinoma, mucinous carcinoma, signet ring cell carcinoma, or medullary carcinoma.

Variables and outcomes

The 8th edition of the TNM classification was used for pathological staging, subdividing T4 tumours into pT4a and pT4b: pT4a referring to tumours penetrating the visceral peritoneum, and pT4b tumours defined as tumours directly invading other organs or structures [4]. Tumour related infectious complications were defined as an abscess at the level of the tumour diagnosed pre- or intraoperatively, fistulae originating from the primary tumour, and faecal or purulent peritonitis due to perforation at the level of the tumour or proximal due to obstruction (i.e. cecal blow-out). Multivisceral resections (MVRs) for local ingrowth were categorised as either limited or extended. Limited MVRs encompassed resections of the abdominal wall, the omentum, or ovaries. Extensive MVRs were defined as resections including the stomach, small bowel, colon, pancreas, spleen, liver, kidney, adrenal glands, Gerota's fascia, ureters, bladder, uterus, vagina, prostate, psoas muscle or bony structures. Completeness of resection was classified as R0 (radical resection, >1 mm tumour-free margin) and R1 (microscopically irradical resection, ≤1 mm tumour-free margin) resection. Postoperative surgical site infections (SSIs) included incisional (both superficial and deep) and organ/space SSIs (i.e. anastomotic leakage and abdominal abscess) that occurred within 30 days after primary surgery or during the index admission. All SSIs were retrospectively extracted from patient files and categorised according to the Clavien-Dindo (CD) score [17]. Only SSIs with a CD score of ≥2 were used for analysis, as retrospective data collection was considered not accurate enough to identify SSIs graded as CD 1.

The primary outcome was 5-year metachronous PM rate. Secondary outcomes were the proportion of patients with isolated PM, 5-year local recurrence rate, 5-year distant metastases rate, 5-year DFS and 5-year OS. Metachronous PM included all peritoneal, abdominal wall, omental and ovarian metastases diagnosed beyond 30 days after primary resection. Isolated PM were defined as PM without preceding or concomitant distant metastases. Local recurrence was defined as recurrent disease located in the direct vicinity of the initial tumour location (local, anastomotic recurrence), located in the adjacent mesentery (mesenteric), or located in regional lymph nodes (nodal) [18]. Distant metastases covered all recurrences that did not meet the conditions of PM or local recurrence (e.g. lung metastases, liver metastases, retroperitoneal nodal metastases). DFS was defined as the interval between the primary resection and the date of first recurrence or death from any cause, with censoring of patients who were lost to follow-up. OS was defined as the time between date of primary resection and date of death from any cause or last follow-up. Follow-up was performed according to the national guidelines. Data was collected until 5 years after primary resection.

Statistical analysis

Baseline characteristics were assessed using descriptive statistics. Continuous variables were reported as median values with interquartile range (IQR). Categorical variables were presented as numbers and percentages. Differences in baseline characteristics between patients with pT4a and pT4b colon cancer were assessed using the Chi square test, or the Fisher's exact test in case of low counts (<5). The primary outcome as well as secondary outcomes were determined with Kaplan-Meier analysis with the log-rank test. Independent predictors for metachronous PM, DFS and OS were identified by Cox regression analyses. Variables were included in the univariable Cox regression analysis based on initial analyses of baseline characteristics and previous literature. Variables with $p < 0.10$ in univariable analysis were subsequently selected for

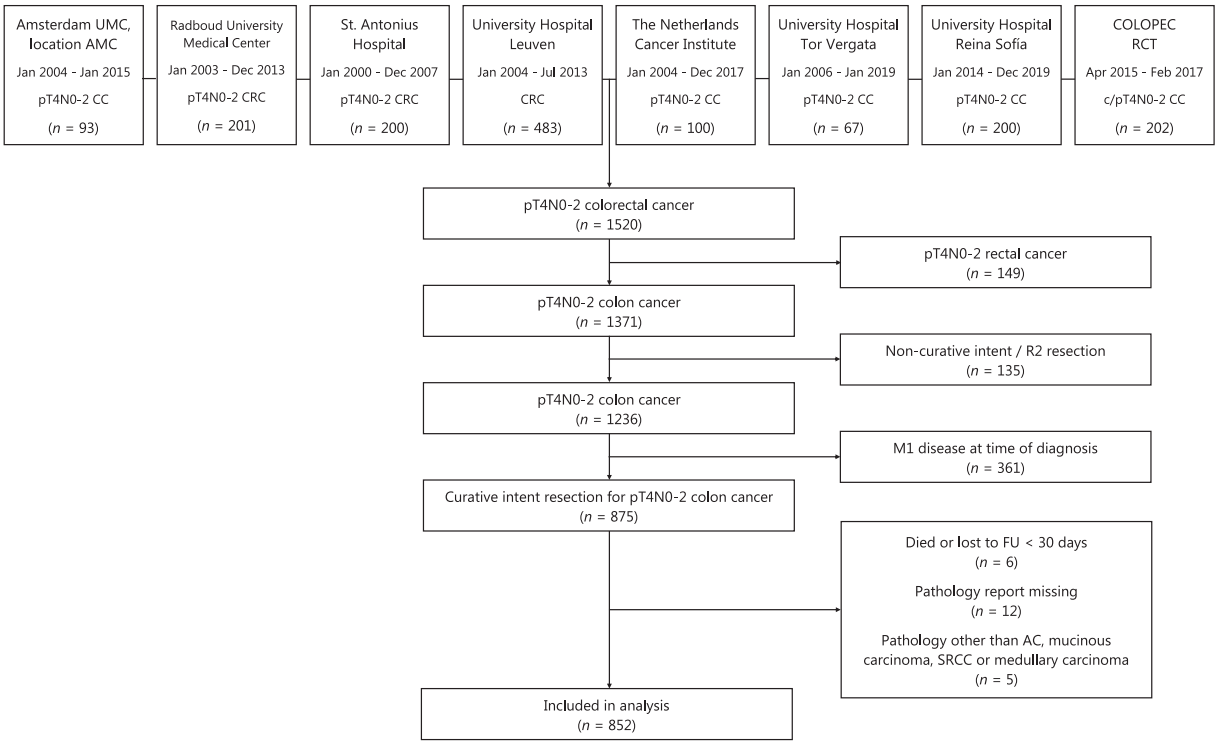

Fig. 1. Flowchart of patient inclusion.
AC, adenocarcinoma; Apr, April; AMC, Academic Medical Centre; c/pT, clinical or pathological tumour (T) category; CC, colon cancer; CRC, colorectal cancer; Dec, December; Feb, February; Jan, January; pT/N, pathological T/N category; RCT, randomised controlled trial; SRCC, signet-ring cell carcinoma; UMC, University Medical Centres.

multivariable logistic regression analysis with backward stepwise selection. Multicollinearity was assessed for all multivariable analyses and appeared not to be present. Results were reported as hazard ratio (HR) with corresponding 95% confidence interval (CI). Statistical significance was defined as a two-sided p-value of <0.05. Analyses were performed with IBM SPSS statistics, version 26.0 (IBM Corp Armonk, NY, USA).

Results

Patients

A total of 1236 patients who underwent a curative intent resection of pT4N0-2 colon cancer were eligible for inclusion. Of these, 361 were excluded because of metastatic disease at the time of diagnosis. Another 23 patients were excluded based on missing pathology reports (n = 12), death or loss to follow-up within 30 days after primary resection (n = 6), and based on the histology of the primary tumour (n = 5). As a result, 852 patients were included in the present study (Fig. 1).

Median age was 69 years (IQR 61–76) and 52.8% of patients was male. The primary tumour was most frequently located in the sigmoid colon (n = 300, 35.2%), coecum (n = 191, 22.4%) or ascending colon (n = 121, 14.2%). Laparoscopic surgery was performed in 321 patients (37.7%), with conversion to open surgery in 59 (18.4%) patients. Resection took place in an emergency setting in 157 patients (18.4%). MVRs were performed in 274 (32.2%) patients.

The pathology report revealed adenocarcinoma in the majority of patients (n = 715, 83.9%). Pathological T category was pT4a in 665 (78.1%) and pT4b in 187 (21.9%) patients. Lymph node positivity was found in 494 patients (58.0%). Resection was classified as an R0 resection in 821 patients (96.4%). Postoperative SSIs (CD 2 or higher) were observed in 119 patients (14.0). Neoadjuvant therapy and adjuvant chemotherapy was administered in 43 (5.0%) and 507 patients (59.5%), respectively. Median follow-up was 38 months (IQR 23–60).

Clinical, pathological and treatment differences between pT4a and pT4b colon cancer

Baseline characteristics of patients with pT4a and pT4b colon cancer are displayed in Table 1. Patients with pT4a colon cancer less frequently presented with tumour related infectious complications (8.8% vs. 13.0%, p = 0.007). Patients with pT4a colon cancer more often underwent emergency procedures (20.2% vs. 12.3%, p = 0.014), whereas open surgery (81.3% vs. 57.0, p < 0.001) and MVRs (100% vs. 13.1%, p < 0.001) were more frequently performed in pT4b colon cancer patients. The tumour more often originated from the right or transverse colon in pT4a colon cancer patients (50.1% vs. 38.5%, p = 0.005). Lymph node positivity (61.8% vs. 44.4%, p < 0.001) was more frequently present in patients with pT4a colon cancer, whereas an R1 resection was more often seen in patients with pT4b colon cancer (6.5% vs. 2.1%, p = 0.002). Neoadjuvant therapy was more frequently administered in pT4b colon cancer patients (10.8% vs. 3.5%, p < 0.001), while patients with pT4a colon cancer were more often treated with adjuvant chemotherapy (62.1% vs. 52.9%, p = 0.024). pT4b was associated with a higher frequency of postoperative SSIs (21.4% vs. 11.9%, p = 0.001) than pT4a.

Peritoneal metastases

Metachronous PM developed in 156 (18.3%) out of 852 patients. Median time to diagnosis of PM was 14 months (IQR 7–21) and 94.2% was detected within 3 years following primary surgery. The 5-year metachronous PM rates were 24.7% and 12.2% for patients

Table 1
Patient, tumour and surgical characteristics.

		pT4a (n = 665) No. (%)	pT4b (n = 187) No. (%)	p-value
Sex	Male	354 (53.2)	96 (51.3)	0.646
	Female	311 (46.8)	91 (48.7)	
Age	≤70 years old	372 (55.9)	118 (63.1)	0.080
	>70 years old	293 (44.1)	69 (36.9)	
Database	Amsterdam UMC, location AMC	41 (6.2)	16 (8.6)	<0.001
	Radboud University Medical Centre	66 (9.9)	24 (12.8)	
	St. Antonius Hospital	76 (11.4)	33 (17.6)	
	University Hospital Leuven	138 (20.8)	26 (13.9)	
	The Netherlands Cancer Institute	20 (3.0)	34 (18.2)	
	University Hospital Tor Vergata	29 (4.4)	9 (4.8)	
	University Hospital Reina Sofía	154 (23.2)	15 (8.0)	
	COLOPEC RCT	141 (21.2)	30 (16.0)	
Surgical setting	Elective	531 (79.8)	164 (87.7)	0.014
	Emergency[a]	134 (20.2)	23 (12.3)	
Primary tumour location	Left (including splenic flexure)	332 (49.9)	115 (61.5)	0.005
	Right/Transverse	333 (50.1)	72 (38.5)	
Tumour related infectious complications	None	602 (91.2)	161 (87.0)	0.007
	Yes, abscess at the level of the tumour	37 (5.6)	11 (5.9)	
	Yes, fistula originating from the tumour	7 (1.1)	10 (5.4)	
	Yes, faecal or purulent peritonitis	14 (2.1)	3 (1.6)	
Surgical procedure	Ileocecal resection	23 (3.5)	4 (2.1)	0.001
	(Extended) right hemicolectomy	281 (42.3)	55 (29.4)	
	Transverse resection	4 (0.6)	7 (3.7)	
	(Extended) left hemicolectomy	87 (13.1)	29 (15.5)	
	Sigmoid resection/(Low) anterior resection	238 (35.8)	82 (43.9)	
	Subtotal colectomy/proctocolectomy	32 (4.8)	10 (5.3)	
Surgical approach	Laparoscopic	247 (37.1)	15 (8.0)	<0.001
	Laparoscopic, converted	39 (5.9)	20 (10.7)	
	Open	379 (57.0)	152 (81.3)	
MVR	No	578 (86.9)	0 (0.0)	<0.001
	Yes, limited	24 (3.6)	28 (15.0)	
	Yes, extended	63 (9.5)	159 (85.0)	
pN category	N0	254 (38.2)	104 (55.6)	<0.001
	N1	228 (34.3)	50 (26.7)	
	N2	183 (27.5)	33 (17.6)	
Radicality	R0	648 (97.9)	173 (93.5)	0.002
	R1	14 (2.1)	12 (6.5)	
Histology	Adenocarcinoma, well/moderately differentiated	470 (70.7)	123 (65.8)	0.314
	Adenocarcinoma, poorly differentiated	88 (13.2)	34 (18.2)	
	Mucinous carcinoma	89 (13.4)	23 (12.3)	
	Signet ring cell carcinoma	15 (2.3)	5 (2.7)	
	Medullary carcinoma	3 (0.5)	2 (1.1)	
Neoadjuvant therapy	No	641 (96.5)	166 (89.2)	<0.001
	Yes, chemotherapy	10 (1.5)	18 (9.7)	
	Yes, (chemo)radiotherapy	13 (2.0)	2 (1.1)	
Adjuvant chemotherapy	No	249 (37.9)	88 (47.1)	0.024
	Yes	408 (62.1)	99 (52.9)	
Postoperative SSI	No	586 (88.1)	147 (78.6)	0.001
	Yes	79 (11.9)	40 (21.4)	

Percentages are presented as percentages of the whole group not including missing values.
AMC, Academic Medical Centre; MVR, multivisceral resection; pN, pathological nodal (N); pT, pathological tumour (T); RCT, randomised controlled trial; SSI, surgical site infection; UMC, University Medical Centres.
[a] Emergency: within 72 h after acute presentation.

with pT4a and pT4b colon cancer, respectively (Fig. 2, p = 0.005). In patients with peritoneal recurrence, PM were present without preceding or concomitant distant metastases (i.e. isolated PM) in 77 of 135 patients (57.0%) with pT4a colon cancer and 14 of 21 patients (66.7%) with pT4b colon cancer (p = 0.405). The univariable and multivariable analyses of factors associated with the risk of developing PM within this pT4 colon cancer population are presented in Table 2. In multivariable analysis, female sex (HR 1.399, 95% CI 1.014–1.929), right or transverse colon cancer (HR 1.602, 95% CI 1.154–2.223), the presence of a peritumoural abscess (HR 1.973, 95% CI 1.097–3.548), pN2 category (HR 2.488, 95% CI 1.668–3.712), R1 resection (HR 2.784, 95% CI 1.322–5.861), signet ring cell histology (HR 2.599, 95% CI 1.335–5.058), and postoperative SSIs (HR 1.837, 95% CI 1.186–2.846) were identified as independent risk factors of metachronous PM. pT4b, as compared with pT4a, was associated with a lower risk of developing metachronous PM (HR 0.544, 95% CI 0.338–0.875).

Local and distant recurrences

A total of 93 of 852 patients (10.9%) developed local recurrence with a median time to diagnosis of 16 months (IQR 8–27). Using Kaplan-Meier analysis, 5-year local recurrence rate was 14.0% and 14.1% for patients with pT4a and pT4b colon cancer, respectively (p = 0.949, Fig. A.1). During follow-up, 237 of 852 patients (27.8%) were diagnosed with distant metastases. Median time to diagnosis was 13 months (IQR 7–23). Kaplan-Meier analysis revealed 5-year distant metastases rates of 35.0% and 28.2% for patients with pT4a and pT4b colon cancer, respectively (p = 0.138, Fig. A.2).

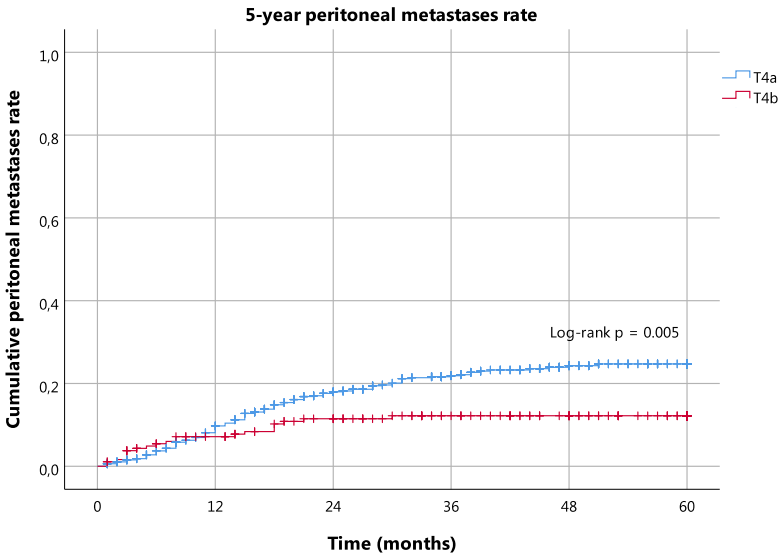

Fig. 2. Peritoneal metastases in patients with pT4a and pT4b colon cancer.

Survival

Five-year DFS and OS for all patients included in the analysis were 55.9% and 64.2%, respectively. For patients with pT4a colon cancer, 5-year DFS was 54.1%, as opposed to 62.2% for those with pT4b colon cancer (p = 0.095, Fig. 3). Corresponding 5-year OS was 63.1% and 68.1%, respectively (p = 0.148, Fig. 4).

Results of the cox-regression analysis for DFS are presented in Table A.2. In multivariable analysis, an abscess at the level of the tumour (HR 1.765, 95% CI 1.144–2.724), pN2 category (HR 2.800, 95% CI 2.102–3.729), R1 resection (HR 2.015, 95% CI 1.165–3.488), signet ring cell histology (HR 1.768, 95% CI 1.038–3.012) and postoperative SSIs (HR 1.843, 95% CI 1.359–2.498) were independently associated with worse DFS. Adjuvant chemotherapy treatment was an independent favourable prognostic factor (HR 0.648, 95% CI 0.512–0.820). T4 subcategory was not associated with DFS.

Table A.3 summarises the results of the cox regression analysis for OS. Independent risk factors were age over 70 years (HR 1.859, 95% CI 1.409–2.451), emergency surgery (HR 1.681, 95% CI 1.253–2.256), pN2 category (HR 2.850, 95% CI 2.072–3.919), R1 resection (HR 2.308, 95% CI 1.403–3.799), and postoperative SSIs (HR 1.696, 95% CI 1.205–2.387), while adjuvant chemotherapy treatment was associated with better OS (HR 0.528, 95% CI 0.399–0.698). No association between T4 subcategory and OS was found.

Discussion

In this international, multicentre cohort study including 852 patients who underwent macroscopic complete resection of pT4N0-2M0 colon cancer, the risk of developing metachronous PM was significantly higher in patients with pT4a colon cancer as compared to patients with pT4b colon cancer, also after correction for confounders. Within this subset of high-risk patients, other independent risk factors for metachronous PM were pN2 category, R1 resection, female sex, right or transverse colon cancer, the presence of a peritumoural abscess, signet ring cell histology and postoperative SSIs. In contrast, metachronous PM was not associated with perforation, pN1 category, mucinous histology, or adjuvant chemotherapy. The distant metastases, DFS and OS rates were not significantly different between the pT4a and pT4b groups, but larger datasets are required to exclude a type II statistical error.

Previously published studies investigating risk factors for PM also found peritoneal recurrence to be more common in patients with pT4a colon cancer, although relatively small number of patients impeded statistical significance. Hompes et al. (2012) reported metachronous PM in 7 of 14 patients with pT4a (50%) and 1 of 5 patients (20%) with pT4b colon cancer [19]. Van Santvoort et al. (2014) analyzed 200 patients who underwent curative resection of pT4 colon cancer, and these patients are also included in the present cohort. Similarly, pT4a had a higher incidence of metachronous PM, but the study was underpowered with an apparent type II statistical error (24% vs. 17%, p = 0.330) [20]. A Swedish population-based cohort study showed that PM (both synchronous and metachronous) were more frequently diagnosed in patients with pT4a colon cancer than in patients with pT4b colon cancer, but neither reaching statistical significance (28.2% vs. 11.1%, p = 0.075) [6]. In another study published by the same authors, pT4a category was identified as the strongest risk factor for metachronous PM, whereas an association between pT4b category and peritoneal recurrence could not be demonstrated [21].

In the current study, a statistically significant difference in risk of developing metachronous PM was found between pT4a and pT4b colon cancer patients (24.7% vs. 12.2%, p = 0.005). A possible explanation for this difference is the inflammatory response around the tumour preceding subsequent tumour infiltration into adjacent structures or organs [11,12]. This inflammatory response might induce the development of fibrous adhesions, which might prevent intra-abdominal seeding of exfoliated cancer cells. However, the presence of a peritumoural abscess appeared to be an independent predictor of metachronous PM in our cohort, contradicting this hypothesis. Another hypothesis for the lower risk of metachronous PM in the pT4b subcategory may be the absence of peritoneal penetration, if colon cancer is only growing into retroperitoneal structures such as Gerota's fascia or the ureter.

The observed difference in peritoneal recurrence rate between pT4a and pT4b tumours might be even larger. A former study showed that 29% of pT4bN0-2M0-1 colon cancers also contain separate areas showing penetration of tumour cells to the free peritoneal surface (i.e. simultaneous pT4a) [22]. In the same study,

Table 2
Uni- and multivariable logistic regression for the risk of peritoneal metastases in patients who underwent curative intent treatment for pT4N0-2M0 colon cancer.

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Sex				
Male	Reference		Reference	
Female	1.356 (0.989–1.857)	**0.058**	1.399 (1.014–1.929)	**0.041**
Age				
≤70 years old	Reference			
>70 years old	0.890 (0.643–1.232)	0.483		
Surgical setting				
Elective	Reference			
Emergency[a]	1.225 (0.823–1.825)	0.317		
Primary tumour location				
Left (including splenic flexure)	Reference		Reference	
Right/Transverse	1.589 (1.156–2.183)	**0.004**	1.602 (1.154–2.223)	**0.005**
Tumour related infectious complications				
None	Reference		Reference	
Yes, abscess at the level of the tumour	1.698 (0.961–3.001)	**0.068**	1.973 (1.097–3.548)	**0.023**
Yes, fistula originating from the tumour	0.374 (0.052–2.677)	0.328	0.528 (0.072–3.866)	0.530
Yes, faecal or purulent peritonitis	1.312 (0.418–4.121)	0.641	1.231 (0.388–3.905)	0.724
Surgical approach				
Laparoscopic	Reference			
Laparoscopic, converted	1.159 (0.630–2.131)	0.635		
Open	0.906 (0.643–1.276)	0.572		
pT category				
T4a	Reference		Reference	
T4b	0.522 (0.329–0.826)	**0.006**	0.544 (0.338–0.875)	**0.012**
pN category				
N0	Reference		Reference	
N1	1.266 (0.845–1.897)	0.254	1.263 (0.832–1.917)	0.274
N2	2.513 (1.723–3.665)	**<0.001**	2.488 (1.668–3.712)	**<0.001**
Radicality				
R0	Reference		Reference	
R1	2.469 (1.211–5.033)	**0.013**	2.784 (1.322–5.861)	**0.007**
Histology				
Adenocarcinoma, well/moderately differentiated	Reference		Reference	
Adenocarcinoma, poorly differentiated	1.232 (0.790–1.924)	0.358	0.940 (0.588–1.503)	0.797
Mucinous carcinoma	1.099 (0.687–1.758)	0.694	0.975 (0.604–1.574)	0.919
Signet ring cell carcinoma	3.404 (1.777–6.521)	**<0.001**	2.599 (1.335–5.058)	**0.005**
Medullary carcinoma[b]	–	–	–	–
Neoadjuvant therapy				
No	Reference			
Yes	1.468 (0.795–2.710)	0.220		
Adjuvant chemotherapy				
No	Reference			
Yes	1.120 (0.805–1.558)	0.501		
Postoperative SSI				
No	Reference		Reference	
Yes	1.459 (0.958–2.224)	**0.079**	1.837 (1.186–2.846)	**0.006**

Bold in univariable analysis indicates variables ($p < 0.10$) that were entered in multivariable analysis. Bold in multivariable analysis indicates statistical significance ($p < 0.05$).
CI, confidence interval; HR, hazard ratio; pN, pathological nodal (N); pT, pathological tumour (T); SSI, surgical site infection.
[a] Emergency: within 72 h after acute presentation.
[b] Not enough events for statistical analysis.

the subgroup of pT4a + b colon cancers carried the worst cancer-specific survival compared to "pure" pT4a or pT4b colon cancers. Currently, pT4a + b is not considered a formal pT4 subgroup and by convention pathologists will categorise cases showing both pT4a and pT4b to the higher pT4b category. However, cases registered as pT4b, but simultaneously showing pT4a, should probably be classified as pT4a as this appears to be associated with the worst outcome based on the present data.

To our knowledge, this is the first multicentre study providing separate analyses for PM and other oncological outcomes within a clearly defined large cohort of pT4 colon cancer patients. Even within this subpopulation, risk factors for metachronous PM as reported in unselected colon cancer populations were found: right-sided colon cancer, pN2 category, R1 resection and signet ring cell histology [6,23–26]. Female gender also appeared to be an independent predictor for metachronous PM, possibly explained by ovarian metastases being considered as PM. This study also illuminates for the first time the clinically relevant differences between pT4a and pT4b tumours, as illustrated by the baseline characteristics of these two patient groups. pT4a and pT4b colon cancer might be considered as two distinct clinical entities with differences in clinical presentation, surgical approach, (neo)adjuvant therapies, histopathological results and postoperative course.

A potential implication of our observations could be a more intensive follow-up regimen for colon cancer patients who are diagnosed with pT4a colon cancer. Patients with limited PM are potential candidates for curative intent treatment, consisting of cytoreductive surgery (CRS) in combination with hyperthermic intraperitoneal chemotherapy (HIPEC), underlining the importance of early detection. The frequent combination with hematogenous spread has raised questions regarding the potential role of early detection and curative intent treatment of peritoneal spread. However, the present study showed that the peritoneum was the sole site of recurrence in nearly 60% of pT4a patients with

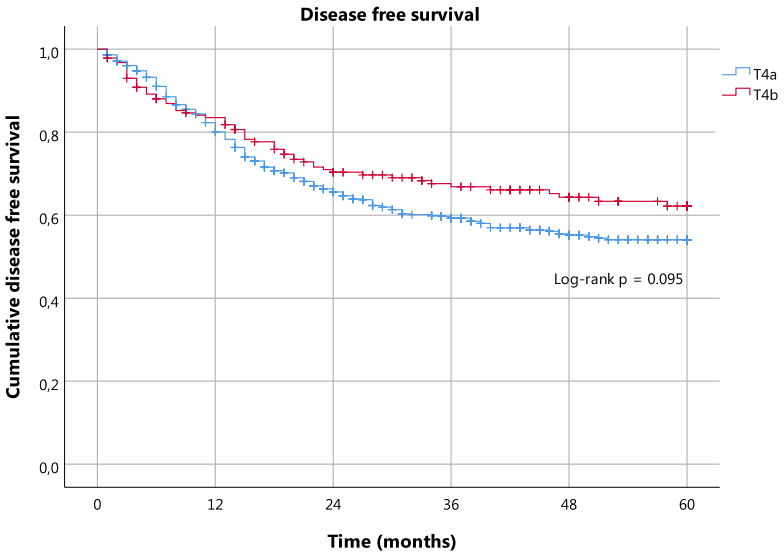

Fig. 3. Disease-free survival in patients with pT4a and pT4b colon cancer.

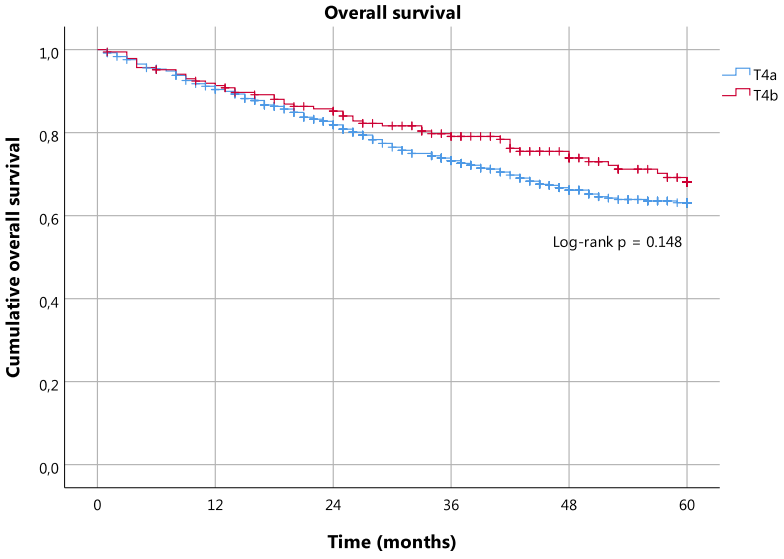

Fig. 4. Overall survival in patients with pT4a and pT4b colon cancer.

metachronous PM. Moreover, different dissemination patterns might be sequential and might even allow combined or repeat local treatment, especially in patients responding to induction systemic therapy [27]. Therefore, preceding or concurrent distant metastases are less often considered a contraindication for CRS/HIPEC than historically. The COLOPEC 2 trial (NCT03413254) prospectively determines the value of CT and diagnostic laparoscopy at 6 months, and subsequently randomises patients without evidence of disease after these examinations to regular follow-up with 18 month CT with or without a third look diagnostic laparoscopy [28]. Such trials should shed more light on the impact of intensified surveillance protocols on survival in high risk groups.

Other trials are focusing on adjuvant treatment strategies. To prevent overtreatment with unfavourable harm/benefit ratio, it is of utmost importance to include the patients at highest risk in such trials. Unfortunately, preoperative diagnosis of T4 category by imaging is complicated by restricted sensitivity to detect areas of peritoneal penetration or limited ingrowth into other organs. In the earlier mentioned study by van Santvoort et al., T4 category was recognised on abdominal CT and during surgery in only 38 (19%) and 107 of 200 patients (54%). Radiological and intraoperative findings combined, T4 category was diagnosed preoperatively in 108 of 200 patients (54%) with pT4 colon cancer. Similarly, in a population-based study by Klaver et al. (2017), 61% of pT4 tumours were preoperatively classified as cT1-3 [2]. These data indicate that T4a should mainly be regarded as a microscopic diagnosis, often presenting as an unexpected postoperative finding. Trials including patients with clinical T4 colon cancer for prophylactic peritoneal treatment will mainly select T4b colon cancer and will miss the patients at highest risk for developing metachronous PM. Adjuvant intraperitoneal chemotherapy is ideally given at the time of primary tumour resection to prevent entrapment of tumour cells in adhesions. This is not possible in patients with unexpected pT4a colon cancer, and other diagnostic and therapeutic strategies

should be developed for those patients.

Although a significantly lower risk of developing metachronous PM was found for pT4b colon cancer patients, as compared to pT4a colon cancer patients, their 5-year cumulative rate was still considerably higher than reported incidences for lower staged colon cancer patients (pT1-3) [6,7,25,26,29]. Moreover, two-thirds of pT4b colon cancer patients with metachronous PM did not have concurrent distant metastases, making them potential candidates for curative intent treatment with CRS/HIPEC. It might be hypothesised that the risk of PM and local and distant metastases in pT4b category colon cancer is influenced by the location, number and type of organ(s)/structures involved (e.g. intraabdominal vs. retroperitoneal ingrowth). Therefore, future research should be devoted to potential differences in oncological outcomes within the heterogeneous subgroup of pT4b colon cancer patients.

Strengths of this study include the multicentre design and completeness of data (98.1%), both increasing external validity. Limitations of the current analysis are inherent to the retrospective nature of this study, such as a potential underestimation of tumour related infectious complications and SSIs, and missing data regarding microsatellite stability, mutation status, and type, number of course and interval between surgery and start of adjuvant chemotherapy. Furthermore, the lack of a gold standard to assess our primary outcome might have led to an underestimation of the PM rate, due to the restricted sensitivity of current imaging modalities. Finally, this cohort encompasses different time periods with different diagnostic and treatment guidelines and institutional practices. Combined with missing data regarding initiated treatment for metachronous recurrence, the dataset does not enable analysis on the impact of different detection and/or treatment strategies of PM on survival.

In conclusion, this large multicentre cohort of 852 patients who underwent curative intent treatment for pT4N0-2M0 colon cancer showed that patients with pT4a colon cancer have a significantly higher risk of developing metachronous PM than pT4b patients, even after correction for confounders. Besides a difference in metachronous PM rate, important differences in clinical, pathological and treatment characteristics were found between pT4a and pT4b colon cancer, implying that these subgroups should be approached as two different entities. As long as the preoperative diagnosis of pT4 tumours is hampered by the low sensitivity of imaging modalities, especially regarding T4a colon cancer, future trials focusing on early detection and adjuvant treatment of metachronous PM should have a design that enables inclusion of high-risk patients with a postoperative diagnosis of pT4a. In addition, further insight in potential risk factors within the heterogeneous subgroup of pT4b colon cancer patients is required.

CRediT authorship contribution statement

Vivian P. Bastiaenen: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization, Project administration. **Arend G.J. Aalbers:** Investigation, Writing – review & editing. **Alvaro Arjona-Sánchez:** Investigation, Writing – review & editing. **Vittoria Bellato:** Investigation, Writing – review & editing. **Jarmila D.W. van der Bilt:** Conceptualization, Methodology, Investigation, Writing – review & editing. **André D. D'Hoore:** Investigation, Writing – review & editing. **Esther Espinosa-Redondo:** Investigation, Writing – review & editing. **Charlotte E.L. Klaver:** Investigation, Writing – review & editing. **Iris D. Nagtegaal:** Investigation, Writing – review & editing. **Bert van Ramshorst:** Investigation, Writing – review & editing. **Hjalmar C. van Santvoort:** Investigation, Writing – review & editing. **Giuseppe S. Sica:** Investigation, Writing – review & editing. **Petur Snaebjornsson:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Karin A.T.G.M. Wasmann:** Investigation, Writing – review & editing. **Johannes H.W. de Wilt:** Investigation, Writing – review & editing. **Albert M. Wolthuis:** Investigation, Writing – review & editing. **Pieter J. Tanis:** Conceptualization, Methodology, Investigation, Writing – review & editing, Supervision.

Declaration of competing interest

None.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2021.05.009.

Ethics approval and consent to participate

The study protocol was reviewed by the Institutional Review Board of the Amsterdam UMC, which decided that the Dutch Medical Research Involving Human Subjects Act did not apply to this study. Local approval for the execution of this study and sharing of non-identifiable data was obtained in the three centres that provided the retrospective databases. Informed consent was not obtained due to the retrospective character and the expected large proportion of deceased patients. The study was performed in accordance with the Declaration of Helsinki.

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