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Metachronous peritoneal metastases in patients with pT4b colon cancer: An international multicenter analysis of intraperitoneal versus retroperitoneal tumor invasion

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ABSTRACT

Background: It was hypothesized that colon cancer with only retroperitoneal invasion is associated with a low risk of peritoneal dissemination. This study aimed to compare the risk of metachronous peritoneal metastases (mPM) between intraperitoneal and retroperitoneal invasion.

Methods: In this international, multicenter cohort study, patients with pT4bN0-2M0 colon cancer who underwent curative surgery were categorized as having intraperitoneal invasion (e.g. bladder, small bowel, stomach, omentum, liver, abdominal wall) or retroperitoneal invasion only (e.g. ureter, pancreas, psoas muscle, Gerota's fascia). Primary outcome was 5-year mPM cumulative rate, assessed by Kaplan-Meier analysis.

Results: Out of 907 patients with pT4N0-2M0 colon cancer, 198 had a documented pT4b category, comprising 170 patients with intraperitoneal invasion only, 12 with combined intra- and retroperitoneal invasion, and 16 patients with retroperitoneal invasion only. At baseline, only R1 resection rate significantly differed: 4/16 for retroperitoneal invasion only versus 8/172 for intra- +/− retroperitoneal invasion ($p = 0.010$). Overall, 22 patients developed mPM during a median follow-up of 45 months. Two patients with only retroperitoneal invasion developed mPM, both following R1 resection. The overall 5-year mPM cumulative rate was 13% for any intraperitoneal invasion and 14% for retroperitoneal invasion only (Log Rank, $p = 0.878$), which was 13% and 0%, respectively, in patients who had an R0 resection (Log Rank, $p = 0.235$).

Conclusion: This study suggests that pT4b colon cancer patients with only retroperitoneal invasion who undergo an R0 resection have a negligible risk of mPM, but this is difficult to prove because of its rarity. This observation might have implications regarding individualized follow-up.

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1. Introduction

Among patients that undergo curative surgery for colon cancer, approximately 10% develop metachronous peritoneal metastases (mPM). [1] These metastases carry a poor prognosis due to a different type of dissemination and more aggressive biology as compared to for example liver metastases. Delayed diagnosis related to difficult detection on imaging limits the possibilities for intentional curative treatment using cytoreductive surgery. [2–4]

In particular the pathological (p)T4 category, according to the American Joint Committee on Cancer (AJCC) Tumor Node and Metastases (TNM) classification, has been demonstrated to be an important risk factor for mPM. [5,6] The pT4 category represents the most advanced types of local growth of colon cancer, either penetration of tumor cells through the free peritoneal surface (pT4a) or when there is direct tumor invasion into adjacent organs or structures (pT4b). The concurrent combination of both types may also occur. The hypothesis is when tumor cells have breached the peritoneal membrane they are able to spread into the peritoneal cavity before or during resection of the tumor, and can subsequently develop into mPM. Considering this hypothesis, pT4b tumors may have a reduced risk compared to pT4a tumors, as these tumors might not have been in contact with the free peritoneal cavity. In particular, pT4b tumors that have grown into structures or organs in the retroperitoneal space have not been in contact with the peritoneum at all. Multiple cohort studies indeed found a decreased risk of pT4b tumors, compared to pT4a tumors, [7-9] but separate pT4b subgroups have not been investigated yet. Our hypothesis is that patients with pT4b colon cancer are heterogeneous regarding type of involved organ(s) and/or structure(s) and with a low or absent risk of mPM in patients with exclusive retroperitoneal invasion. Therefore, intensive follow-up with for example second look laparoscopy might not be needed in specific subgroups of patients with pT4 colon cancer.

This international multicenter cohort study aimed to compare the risk of mPM between any intraperitoneal invasion versus exclusive retroperitoneal invasion. Secondary aims were to determine the influence of the number and type of involved organ(s) and/or structures on the risk of mPM.

2. Methods

2.1. Study design & patient cohort

This study comprises a retrospective, multicenter, cohort study. Nine centers from four different countries (the Netherlands, Italy, Belgium, Spain) provided individual patient data for one collaborative dataset on pT4 colon cancer patients who underwent intentional curative surgery (R0/R1) between 2000 and 2019. Finally, this dataset consisted of four prospectively maintained databases, four retrospectively maintained databases, [10-12] and one multicenter randomized trial. [13] Detailed information of these databases is presented in Supplementary Table 1. Patients were only included if they did not have any recurrence or death within 30 days after the primary resection, and only if follow-up was beyond 30 days. In addition, the pathology report of the primary resection had to be available. For the present study, patients with a documented pT4b category according to the 8th edition of the TNM classification [14] were selected from the international, multicenter dataset. Patients with rectal cancer, or goblet cell carcinoma or metastatic disease at time of diagnosis were excluded from the present analysis. This study was approved by the Institutional Review Board of the Amsterdam UMC and is compliant with the STROBE recommendations for reporting observational studies. [15]

2.2. Definitions of subgroups & variables

To investigate the difference in risk of developing mPM between any intraperitoneal invasion and only retroperitoneal invasion of the primary tumor, the following pT4b subgroups were defined, based on the involved organ(s)/structure(s) in relation to the peritoneal cavity. *Intraperitoneal invasion* was defined as pT4b tumors that had invaded through peritoneal adhesion into at least one of the following organs or structures: urinary bladder, uterus, ovaries, small bowel, colon, appendix, stomach, omentum, liver, spleen, or abdominal wall. *Retroperitoneal invasion* was defined as pT4b tumors invading into the ureter, kidney, pancreas, duodenum, psoas muscle, Gerota's fascia, cervix, vagina, prostate, seminal vesicle, spermatic cord, or pelvic side wall. These tumors were considered not to have traversed a peritoneal adhesion in order to enter the other organ or structure.

For the main aim of the present study, patients were categorized as either intraperitoneal invasion, also including those with invasion in both intraperitoneal and retroperitoneal organs, or retroperitoneal invasion only. Other subgroups for further explorative analyses were: invasion into one versus more than one organ, and invasion into either the abdominal wall, gastrointestinal organs (i.e. small bowel, pancreas, spleen, liver, colon, appendix, or stomach), or urogenital organs (i.e. uterus, bladder, kidney, ureter, vagina, cervix, ovary, tube, or spermatic cord).

Variables concerning patient characteristics, surgical procedure and histopathology details were extracted from individual patient files, procedure reports, and pathology reports. Emergency setting was defined as resection within 72 h after first acute presentation. Right-sided tumors were defined as tumors in the caecum, appendix, ascending colon, hepatic flexure and transverse colon. Left-sided tumors were defined as tumors in the splenic flexure, descending colon and sigmoid colon. Tumor-related infectious complications comprised a peritumoral abscess, a fistula originating from the tumor or purulent peritonitis due to tumor perforation or proximal blow-out due to obstruction. Multivisceral resection (MVR) was defined as either limited (abdominal wall, omentum, Gerota's fascia, ovaries) or extended (any other structure/organ). Resection margin was classified as a microscopically radical resection with >1 mm tumor-free margin (R0), or a microscopically non-radical resection with tumor-free margin $\leq$1 mm (R1). Postoperative surgical site infections (SSI) contained incisional and organ/space SSIs, and were only reported when the Clavien-Dindo score was $\geq$2. [16]

2.3. Endpoints

The primary outcome parameter was the 5-year cumulative risk of mPM. mPM included all metastases on the parietal or visceral peritoneum, or in the abdominal wall, omentum or ovaries that were detected beyond the 30th day postoperative period. Secondary outcome parameter was 5-year overall survival (OS). Follow-up was performed according to the concerned national guidelines.

2.4. Statistical methods

Baseline characteristics were obtained using descriptive statistics. Categorical variables were presented as numbers and percentages. Continuous data were presented as means with standard deviations (SD) or median values with interquartile range (IQR), when appropriate. Categorical variables were tested for statistical significance using a Chi-square test for categorical variables or Fisher's exact test, where appropriate. Primary and secondary outcome were determined with Kaplan-Meier analysis, with the corresponding Log-Rank test. A p-value of <0.05 was considered

statistically significant. Analyses were performed using IBM SPSS statistics, version 26.0 (IBM Corp Armonk, NY, USA).

3. Results

3.1. Patient enrolment

Patient enrolment is schematically presented in Fig. 1. In total, the pT4 colon cancer cohort derived from all participating centers consisted of 907 patients. After exclusion of patients that underwent an abdominoperineal resection indicating rectal cancer (n = 3), M1 disease at time of diagnosis (n = 2), and patients with a goblet cell carcinoma of the appendix (n = 1), 901 patients with pT4N0-2M0 colon cancer remained. Of those patients, 198 with a documented pT4b colon cancer were included for final analysis.

3.2. Patient, tumor and procedure characteristics

Characteristics of the included patients, and tumor and procedural characteristics are shown in Table 1. Of the 198 patients with pT4bN0-2M0 colon cancer, 170 had exclusive intraperitoneal invasion, 12 had combined intraperitoneal and retroperitoneal invasion, and 16 patients had retroperitoneal invasion only. If comparing patients with any intraperitoneal invasion with those with exclusive retroperitoneal invasion, there were no differences in patient demographics, tumor characteristics or type of treatment. Patients with intraperitoneal invasion received more often a radical resection (95.6%) than patients with retroperitoneal invasion (75.0%, p = 0.010).

In Table 2, details about invasion regarding number and type of involved structures and organs are displayed. All patients with exclusive retroperitoneal invasion had only one organ involved instead of multiple organs. Of all 198 patients, 32 (16.2%) had tumor invasion into the abdominal wall, 94 (47.5%) invasion into gastrointestinal organs, and 73 (36.9%) had invasion into urogenital organs.

3.3. Metachronous peritoneal metastases

In total, 24 (12.1%) of the 198 pT4bN0-2M0 colon cancer patients developed mPM during a median follow-up of 45 (IQR 25–83) months, of whom 22 patients had any intraperitoneal invasion and two retroperitoneal invasion only. The 5-year mPM rate was 13% in patients with any intraperitoneal invasion and 14% in patients with only retroperitoneal invasion, as shown in Fig. 2A (Log Rank, p = 0.878). In subgroup analysis, only including patients with a R0 resection (n = 184), 20 patients with any intraperitoneal invasion versus zero patients with retroperitoneal invasion only developed mPM, with 5-year mPM rate of 13% and 0%, respectively (Log Rank, p = 0.235, Fig. 2B).

When comparing the number of involved organs, the 5-year mPM rate was 14% for one involved organ and 7% for two or more involved organs (Log Rank, p = 0.261, Fig. 3). Regarding the different structures and organs that were involved, invasion into the abdominal wall was associated with the highest 5-year risk of mPM (29% versus 10% for other involved structures or organs; Log Rank, p = 0.003, Fig. 4). There was no difference in the amount of R1 resections between patients with or without invasion into the abdominal wall (6.3% versus 6.1%, p = 0.614).

3.4. Survival analysis

Five-year overall survival rates did not significantly differ between patients with any intraperitoneal invasion versus patients with retroperitoneal invasion only (65% versus 68%, Log Rank, p = 0.589, Fig. 5A), neither did the five-year disease-free survival rate (Log Rank p = 0.644, Fig. 5B).

4. Discussion

In this international, multicenter cohort study, we have shown that exclusive retroperitoneal invasion is a rare entity within the group of patients with pT4b colon cancer, and that the R1 resection rate was significantly higher within this group as compared to the group with any intraperitoneal invasion. None of the patients who underwent an R0 resection of a pT4b colon cancer with

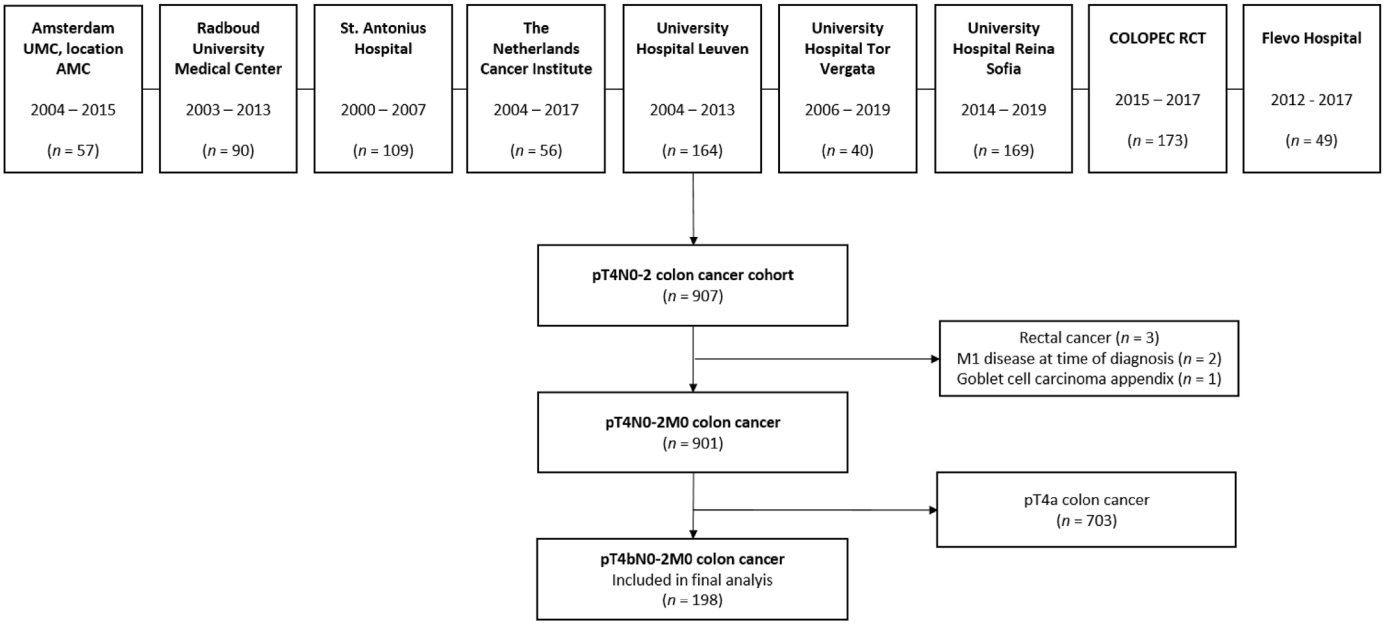


Fig. 1. Flowchart of patient inclusion.

Table 1
Patient, surgical and tumour characteristics of pT4b patients stratified for any intraperitoneal invasion and retroperitoneal invasion only.

		Total (N = 198) No. (%)	Intra±Retro (N = 182) No. (%)	Retro (N = 16) No. (%)	p-value
Gender	Male	102 (51.5)	95 (52.2)	7 (43.8)	0.517
	Female	96 (48.5)	87 (47.8)	9 (56.3)	
Age	≤70 years old	122 (61.6)	114 (62.6)	8 (50.0)	0.319
	>70 years old	76 (38.4)	68 (37.4)	8 (50.0)	
Centre	Amsterdam UMC, location AMC	16 (8.1)	15 (8.2)	1 (6.3)	0.072
	Radboud University Medical Centre	24 (12.1)	23 (12.6)	1 (6.3)	
	St. Antonius Hospital	33 (16.7)	29 (15.9)	4 (12.1)	
	University Hospital Leuven	26 (13.1)	23 (12.6)	3 (18.9)	
	The Netherlands Cancer Institute	34 (17.2)	34 (18.7)	0 (0.0)	
	University Hospital Tor Vergata	9 (4.5)	6 (3.3)	3 (33.3)	
	University Hospital Reina Sofia	15 (7.6)	13 (7.1)	2 (12.5)	
	COLOPEC trial	30 (15.2)	28 (15.4)	2 (6.7)	
	Flevo Hospital	11 (5.6)	11 (6.0)	0 (0.0)	
Surgical setting	Elective	175 (88.4)	161 (88.5)	14 (87.5)	0.579
	Emergency	23 (11.6)	21 (11.5)	2 (12.5)	
Primary tumor location	Left (including splenic flexure)	115 (58.1)	105 (57.7)	10 (62.5)	0.709
	Right/Transverse	83 (41.9)	77 (42.3)	6 (37.5)	
Tumor related infectious complications	None	170 (85.9)	156 (86.7)	14 (87.5)	0.383
	Yes, abscess at the level of the tumour	13 (6.6)	13 (7.2)	0 (0.0)	
	Yes, fistula originating from the tumour	10 (5.1)	8 (4.4)	2 (12.5)	
	Yes, faecal or purulent peritonitis	3 (1.5)	3 (1.7)	0 (0.0)	
Surgical procedure	Ileocecal resection	4 (2.0)	3 (1.6)	1 (6.3)	0.660
	(Extended) right hemicolectomy	65 (32.8)	60 (33.0)	5 (31.3)	
	Transverse resection	7 (3.5)	7 (3.8)	0 (0.0)	
	(Extended) left hemicolectomy	29 (14.6)	27 (14.8)	2 (12.5)	
	Sigmoid resection/(Low) anterior resection	82 (41.4)	74 (40.7)	8 (50.0)	
	Subtotal colectomy/proctocolectomy	11 (5.6)	11 (6.0)	0 (0.0)	
Surgical approach	Laparoscopic	22 (11.1)	22 (12.1)	0 (0.0)	0.423
	Laparoscopic, converted	22 (11.1)	20 (11.0)	2 (12.5)	
	Open	154 (77.8)	140 (76.9)	14 (87.5)	
MVR	Yes, limited	37 (18.7)	37 (20.3)	0 (0.0)	0.091
	Yes, extended	159 (80.3)	143 (78.6)	16 (100)	
pN category	N0	110 (55.6)	103 (56.6)	7 (43.8)	0.557
	N1	53 (26.8)	48 (26.4)	5 (31.3)	
	N2	35 (17.7)	31 (17.0)	4 (25.0)	
Radicality	R0	184 (92.9)	172 (95.6)	12 (75.0)	0.010
	R1	12 (6.1)	8 (4.4)	4 (25.0)	
Histology	Adenocarcinoma, well/moderately differentiated	125 (63.1)	114 (62.6)	11 (68.8)	0.708
	Adenocarcinoma, poorly differentiated	38 (19.2)	35 (19.2)	3 (18.8)	
	Mucinous carcinoma	26 (13.1)	25 (13.7)	1 (6.3)	
	Signet ring cell carcinoma	6 (3.0)	5 (2.7)	1 (6.3)	
	Medullary carcinoma	3 (1.5)	3 (1.6)	0 (0.0)	
Neoadjuvant therapy	No	177 (89.4)	164 (90.6)	13 (81.3)	0.140
	Yes, chemotherapy	18 (9.1)	16 (8.8)	2 (12.5)	
	Yes, (chemo)radiotherapy	2 (1.0)	1 (0.6)	1 (6.3)	
Adjuvant chemotherapy	No	96 (48.5)	90 (49.5)	6 (37.5)	0.359
	Yes	102 (51.5)	92 (50.5)	10 (62.5)	
Adjuvant HIPEC within the COLOPEC trial	No	183 (92.4)	168 (92.3)	15 (93.8)	0.645
	Yes	15 (7.6)	14 (7.7)	1 (6.2)	
Postoperative SSI	No	155 (78.3)	142 (78.9)	13 (81.3)	1.000
	Yes	41 (20.7)	38 (21.1)	3 (18.8)	

Intra±retro: patients with exclusively intraperitoneal invasion or with intraperitoneal and retroperitoneal invasion. Retro: patients with retroperitoneal invasion only. AMC, Academic Medical Centre; MVR, multivisceral resection; pN, pathological nodal (N); pT, pathological tumour (T); SSI, surgical site infection; UMC, University Medical Centers. *Emergency: within 72 h after acute presentation.

retroperitoneal invasion only developed mPM within 5 years, while a 13% 5-year mPM rate was found in patients with any intraperitoneal invasion. Although not statistically significant because of small patient numbers, this finding supports our hypothesis that there is a low risk of developing peritoneal metastases in pT4b tumors without peritoneal involvement (i.e. not growing across peritoneal adhesion) if an R0 resection was performed. Furthermore, this study demonstrated that pT4b tumors with invasion into the abdominal wall had a significantly higher risk (29% versus 10%, Log Rank, $p = 0.003$) of developing mPM than pT4b tumors with invasion into gastrointestinal or urogenital organs.

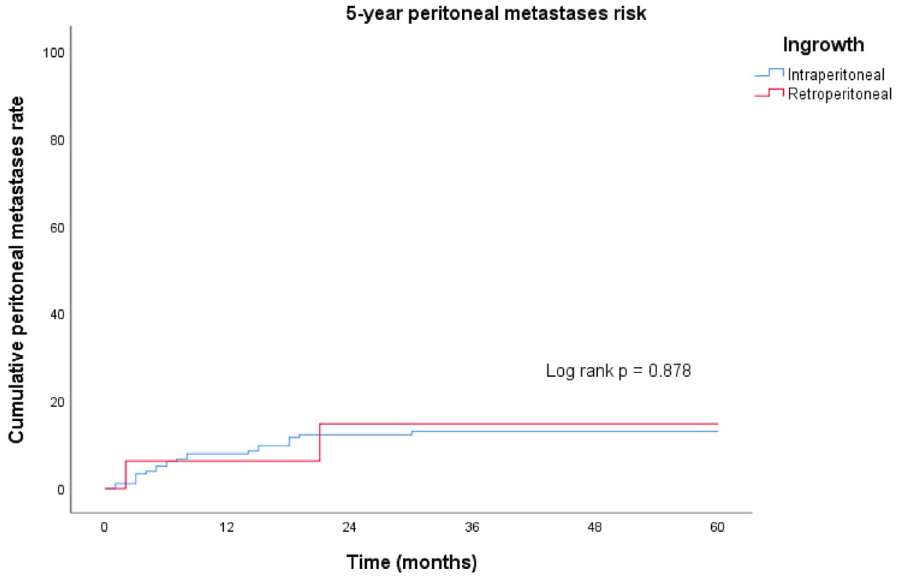
To our knowledge, this study is the first to evaluate the potential difference in the risk of mPM depending on the pT4b subtype (with and without extension across peritoneal adhesion). This might probably be explained by the rarity of only retroperitoneal invasion and the limited number of large existing cohorts of pT4 colon cancer with sufficient detail to analyze this phenomenon. Up till now, subgroups of pT4 colon cancer have only been analyzed according to the pT4a and pT4b categories of the AJCC staging system regarding the risk of mPM. [17,18] The question is whether the current criteria to discriminate pT4a from pT4b are of most clinical importance, and explorative analyses as performed in the present study might provide more insight into pathophysiological mechanisms with prognostic implications.

In a prior study by our group based on a smaller subset of patients, [11] different categories of multivisceral resections in 130 pT4b colon cancer patients and their correlation with 5-year intraperitoneal recurrence were evaluated. Intraperitoneal

Table 2
Details about invasion regarding number and type of involved structures and organs stratified by intra- and/or retroperitoneal invasion.

	Total (N = 198) No. (%)	Intra (N = 170) No. (%)	Intra + Retro (N = 12) No. (%)	Retro (N = 16) No. (%)	p-value
Number of organs with invasion					
1 organ	166 (83.8)	150 (88.2)	0 (0)	16 (100)	**<0.001**
>1 organ	32 (16.2)	20 (11.8)	12 (100)	0 (0)	
Invasion into abdominal wall					
Yes	32 (16.2)	30 (17.6)	1 (6.3)	1 (8.3)[a]	**0.538**
No	166 (83.8)	140 (82.4)	15 (93.8)	11 (91.7)	
Invasion into gastrointestinal organs					
Yes	94 (47.5)	80 (47.1)	8 (66.7)	6 (37.5)	0.311
No	104 (52.5)	90 (52.9)	4 (33.3)	10 (62.5)	
Invasion into urogenital organs					
Yes	73 (36.9)	57 (33.5)	8 (66.7)	8 (50.0)	**0.037**
No	125 (63.1)	113 (66.5)	4 (33.3)	8 (50.0)	

[a] This patient had invasion into the abdominal wall dorsal from the anterior peritoneal reflection. Intra: patients with intraperitoneal invasion only. Intra + retro: patients with intra- and retroperitoneal invasion. Retro: patients with retroperitoneal invasion only. Gastrointestinal organs included: small bowel, pancreas, spleen, liver, colon, appendix, or stomach. Urogenital organs included: uterus, bladder, kidney, ureter, vagina, cervix, ovary, tube, or spermatic cord.



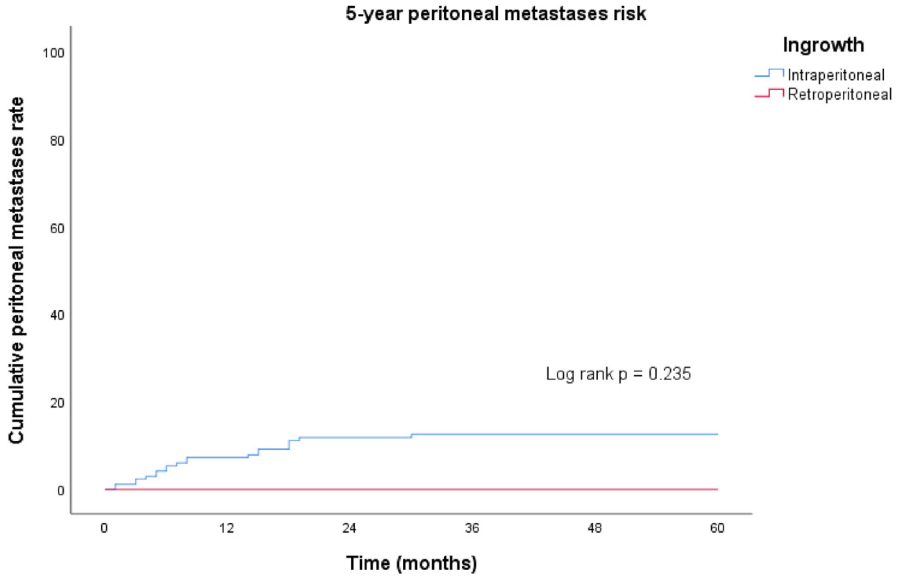
At risk	0	12	24	36	28	60
Intraperitoneal	182	154	132	108	85	59
Retroperitoneal	16	13	9	6	5	4

Fig. 2A. 5-year risk of peritoneal metastases in pT4b colon cancer patients with intraperitoneal versus retroperitoneal invasion.

recurrence was defined as any potential site of outgrowth of free intraperitoneal cancer cells including incisional, local recurrence, ovarian, omental and peritoneal metastases. The different categories of multivisceral resection included gastrointestinal organs, urologic organs, solid organs (i.e. spleen, kidney, liver, pancreas and uterus) and the abdominal wall, omentum or ovaries. We found that a multivisceral resection of the abdominal wall, omentum and ovaries was independently associated with an increased risk of intra-abdominal recurrence (HR 7.8, 95% CI 1.0–57.8), and already concluded that multivisceral resection for pT4b colon cancer is a heterogeneous procedure with regard to surgical as well as oncological risk profiles.

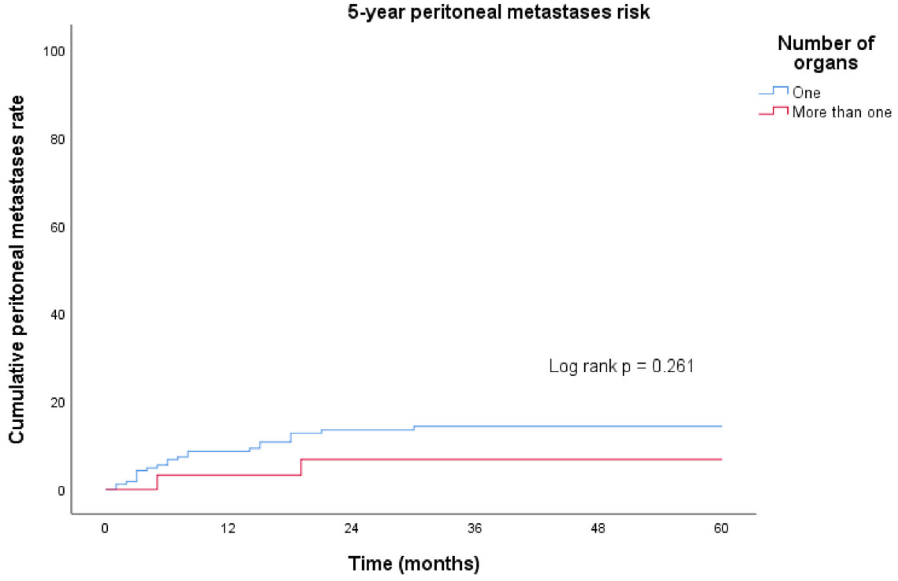
In the present larger dataset with a slightly different primary outcome parameter, we confirm our previous findings of substantial differences in the risk of developing mPM, with the highest risk in patients with tumor invasion into the abdominal wall. An explanation for the higher risk of mPM in tumors that had grown into the abdominal wall compared to other structures could be that these tumors might have peritoneal penetration first, accompanied with intraperitoneal seeding of tumor cells. As the abdominal wall is more rigid, full coverage of the site of peritoneal penetration by complete adherence to the abdominal wall might take longer than coverage by intraperitoneal organs which have more mobility and pliability to cover the tumor site. It might be even the case that intraperitoneal organs, such as small bowel loops, first adhere to the site of colon cancer by inflammatory adhesions before peritoneal penetration by the tumor, thereby completely preventing intraperitoneal spread.

A possible clinical implication of our findings could be that patients with radically resected pT4b colon cancer with retroperitoneal invasion do not need intensive follow-up schedules, whereas patients with pT4b colon cancer and invasion into the abdominal wall should be considered having similar prognosis and requiring similar intensive follow-up as pT4a tumors. Patient selection for



Time (months)	0	12	24	36	48	60
Intraperitoneal	172	147	126	103	80	56
Retroperitoneal	12	11	9	6	5	4

Fig. 2B. 5-year risk of peritoneal metastases in pT4b colon cancer patients with a R0 resection (n = 184), with intraperitoneal versus retroperitoneal invasion.

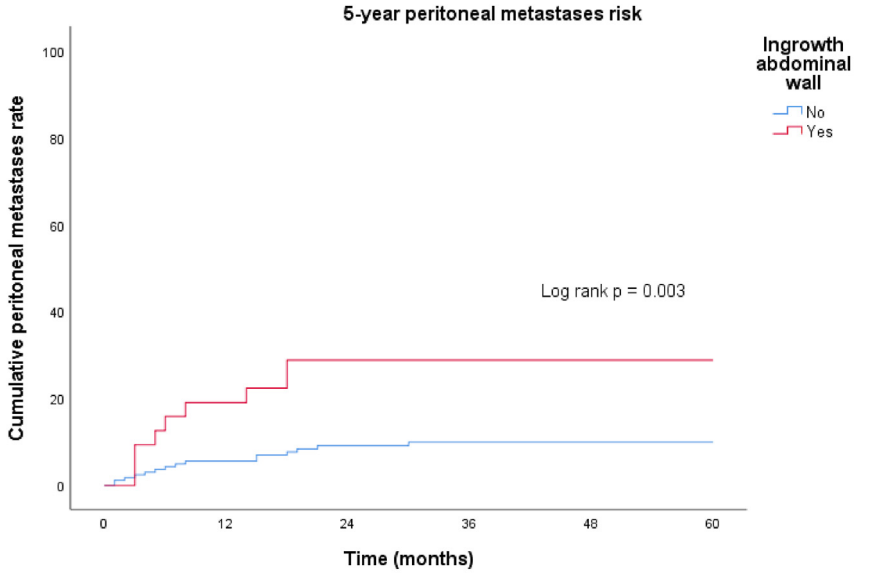


Time (months)	0	12	24	36	48	60
One organ	166	139	117	93	76	54
> one organ	32	28	25	21	14	9

Fig. 3. 5-year risk of peritoneal metastases in patients with invasion in one organ versus more than one organ.

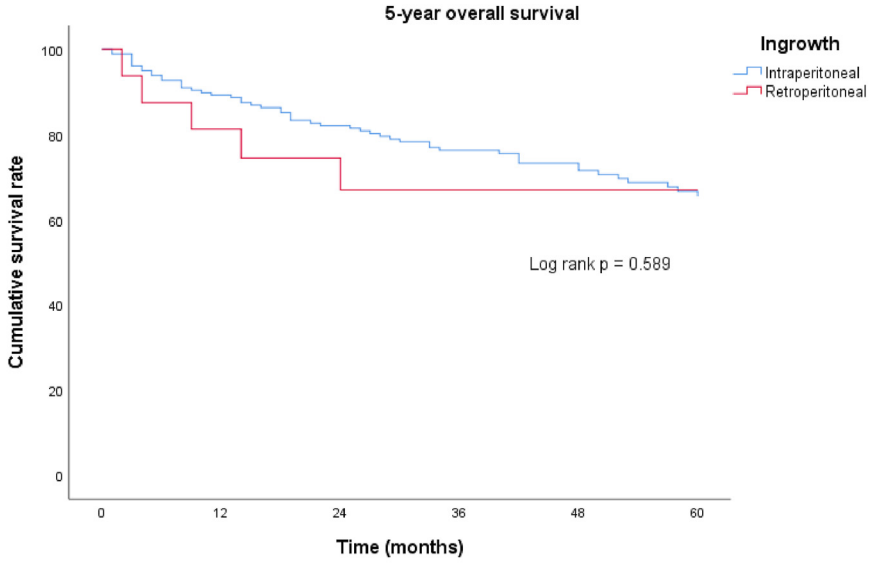
certain follow-up schedules is becoming more and more relevant, since the focus of treatment of mPM mainly is on early detection rather than prevention of mPM. [13] As of today, no preventive therapy, like adjuvant HIPEC, has proven its effectiveness. Therefore, the COLOPEC-2 trial is investigating the added value of second or even third look surgery for early detection of mPM, to increase the part of patients that is still eligible for curative treatment of mPM. [19]

Some limitations of the current study require further debate. First, subgroup analyses were based on small patient samples with inherent methodological shortcomings, and the current results should therefore be interpreted with caution. Validation in a larger



Time (months)	0	12	24	36	48	60
No	166	142	121	96	77	52
Yes	32	25	21	18	13	11

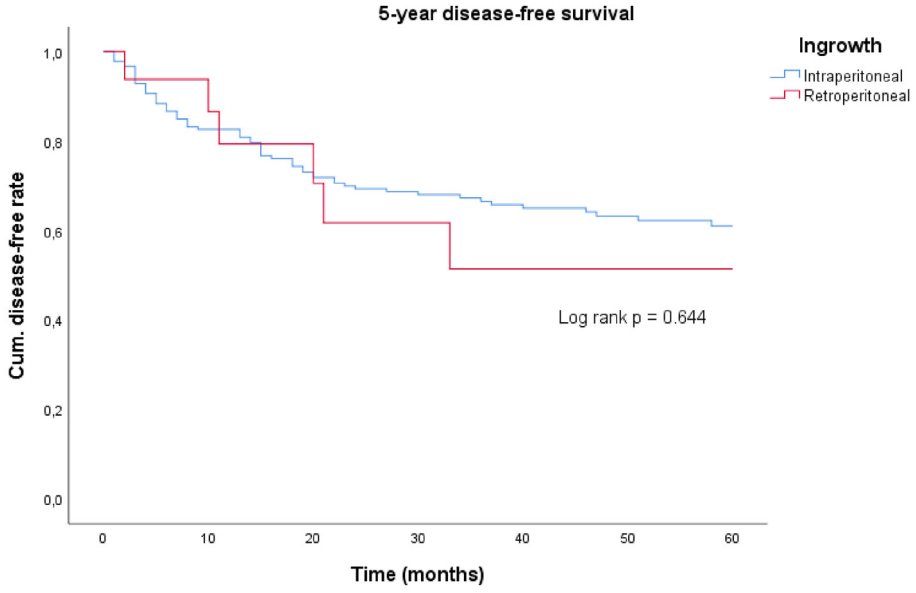
Fig. 4. 5-year metachronous peritoneal metastases risk in patients with pT4b tumour invasion into the abdominal wall.



Time (months)	0	12	24	36	48	60
Intraperitoneal	182	154	132	108	85	59
Retroperitoneal	16	13	9	6	5	4

Fig. 5A. 5-year overall survival of pT4b colon cancer patients with intraperitoneal versus retroperitoneal invasion.

patient cohort is required. However, one might debate the importance and feasibility of studying the risk of mPM between patients with intraperitoneal and retroperitoneal invasion, as it comprises a very small subset of colon cancer patients, given the fact that only 16 patients with retroperitoneal invasion were recruited in this international multicenter study over a period of more than 20 years. Secondly, the retrospective nature of the current study is inherent to the occurrence of biases. Patients were diagnosed and treated in different time periods and hospitals, with no standardized diagnostic tools or treatment options and a possible wide range of interobserver variability in histopathological assessment of the tumor. Another limitation might be the issues that occur during sampling. Uncertainty remains whether tumors had both pT4a and pT4b present. A prior study of Snaebjornsson et al., [20]



Time (months)	0	12	24	36	48	60
Intraperitoneal	182	142	110	89	69	49
Retroperitoneal	16	11	7	5	4	3

Fig. 5B. 5-year disease-free survival of pT4b colon cancer patients with intraperitoneal versus retroperitoneal invasion.

showed that 29% of the included pT4b tumors in their cohort also contained areas with penetration to the free peritoneal surface (pT4a). Another limitation is that there was no information available on how mPM were detected.

Main strengths of the present study include the innovative research question in this particular patient group. Further, with almost 200 pT4b patients, this seems to be the largest study up till now investigating pT4b colon cancer patients that provides detailed information on the several pT4b types of invasion. Finally, the multicenter design of the current study increases external validity.

In conclusion, this international, multicenter study investigated different types of pT4b among pT4bN0-2M0 colon cancer patients, with specific focus on exclusive retroperitoneal invasion. It was demonstrated that exclusive retroperitoneal invasion is rare, and seemingly associated with a negligible risk of mPM over time if radically resected. We confirmed previous findings that tumor invasion into the abdominal wall carries the highest risk of mPM. In our view, this study provides additional information for tailored follow-up in pT4N0-2M0 colon cancer patients regarding the risk of peritoneal recurrence.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2022.05.028.

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