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ORIGINAL ARTICLE

Epidemiology, oncologic results and risk stratification model for metachronous peritoneal metastases after surgery for pT4 colon cancers: results from an observational retrospective multicentre long-term follow-up study

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Abstract

Purpose Metachronous peritoneal metastases (MPM) following a curative surgery procedure for pT4 colon cancer is a challenging condition. Current epidemiological studies on this topic are scarce.

Methods A retrospective multicentre trial was designed. All consecutive patients who underwent operations to treat pT4 cancers between 2015 and 2017 were reviewed. Demographic, clinical, operative, pathological and oncological follow-up variables were included. MPM were described as any oncological disease at the peritoneum, clearly different from a local recurrence. Univariate and multivariate Cox regression models were constructed. A risk stratification model was created on a cumulative factor basis. According to the calculated hazard ratio (HR), a scoring system was designed (HR < 3, 1 point; HR > 3, 2 points) and a scale from 0 to 6 was calculated for peritoneal disease-free rate (PDF-R). A risk stratification model was also created on the basis of these calculations.

Results Fifty different hospitals were involved, which included a total of 1356 patients. Incidence of MPM was 13.6% at 50 months median follow-up. The strongest independent risk factors for MPM were positive pN stage [HR 3.72 (95% CI 2.56–5.41; $p < 0.01$) for stage III disease], tumour perforation [HR 1.91 (95% CI 1.26–2.87; $p < 0.01$)], mucinous or signet ring cell histology [HR 1.68 (95% CI 1.1–2.58; $p = 0.02$)], poorly differentiated tumours [HR 1.54 (95% CI 1.1–2.2; $p = 0.02$)] and emergency surgery [HR 1.42 (95% CI 1.01–2.01; $p = 0.049$)]. In the absence of additional risk factors, pT4 tumours showed 98% and 96% PDF-R in 1-year and 5-year periods based on Kaplan–Meier curves.

Conclusions Cumulative MPM incidence was 13.6% at 5-year follow-up. The sole presence of a pT4 tumour resulted in high rates of PDF-R at 1-year and 5-year follow-up (98% and 96% respectively). Five additional risk factors different from pT4 status itself were identified as possible MPM indicators during follow-up.

Keywords Colon cancer · Metachronous peritoneal metastases · Second look · HIPEC · Risk stratification

Introduction

Metachronous peritoneal metastases (MPM) following curative colon cancer surgery have major implications, both in terms of patient survival and healthcare resource utilisation, with the need to centralise and ensure the specialisation of the treatment teams in order to optimise the outcomes in this context. Different strategies have been researched in recent years, which range from a proactive search for the disease in patients considered to be high risk by means of a second look procedure [1] to a more conservative policy limited

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Collaborating group for the study of metachronous peritoneal metastases of pT4 colon cancer members are listed in Acknowledgements section.

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to treating suspected disease when it appears [2]; however, conflicting results were obtained. There is also new ongoing research that aims to provide an answer to these questions [3]. All this conflicting evidence has motivated some authors to send a precautionary message regarding these second look strategies [4]. pT4 colon cancer has been advocated as one of the strongest predictors of MPM, with rates as high as 30% in certain series [5–8], which made it one of the indications for second look strategies [9]. However, some of the evidence supporting this behaviour is based on literature which is out of date [10], where treatment standards were probably different from today's standards, with very prolonged recruitment periods [11]. This makes it difficult for patients included in the same study to be considered comparable to old but recently published cohorts [6, 11], and where patients with colon cancer and rectal cancer are mixed together [12]. All these limitations make it reasonable to question the validity of these investigation initiatives at the present time.

Taking into account these concerns, a retrospective multicentre observational trial was designed to determine the epidemiology, chronology and potential risk factors for the development of MPM among the specific high-risk group of patients with pT4 colon cancer, after curative resection procedures. A secondary aim was to develop a risk stratification model for peritoneal carcinomatosis in patients with pT4 colon cancer who underwent operations with curative intent.

Materials and methods

Local Clinical Research Ethics Committee (CREC) approval was obtained (04/21-4398).

This study is registered with ClinicalTrials.gov, number NCT05300789.

Design, patients and variables

An observational retrospective multicentre trial was designed. A total of 50 different hospitals enrolled in the project. There was no limitation to participation in terms of type of hospital, level of care or degree of subspecialisation within the teams that treated the patients. This study was sponsored by the Spanish Surgical Society (Asociación Española de Cirujanos), both the Colorectal and Peritoneal Surgery subsections.

All consecutive patients operated on because of colon cancer with curative intent, both elective and emergency operations, with pathologic confirmation of pT4 stage adenocarcinoma, were included. Colon cancer was considered as tumours located in the large bowel 15 cm above the anal verge. The exclusion criteria were as follows: patients younger than 18 years of age, inability to achieve a whole tumour resection or palliative surgery (R2), synchronous peritoneal or systemic metastasis of any kind at the time of surgical intervention, pathological diagnosis of colon cancer other than adenocarcinoma, such as GIST, leiomyosarcomas, neuroendocrine tumours, or others, and a follow-up period of less than 6 months. Patients with missing information were also excluded from data analysis.

Considering a 3-year study period in order to ensure sufficient sample size, and a minimum 3-year follow-up period to analyse the oncological implications, 2015–2017 was the time span selected for the study.

Colon cancer location was categorised as proximal colon cancer (cecum, ascending colon, hepatic flexure and transverse colon) and distal colon cancer (splenic flexure, descending colon and sigmoid colon) according to what had been previously proposed elsewhere [13]. Free tumours were defined as those completely mobile without any adhesions identifiable to any adjacent viscera, nor abdominal wall nor retroperitoneum. Extended resections were defined as those in which any adjacent viscera, abdominal wall or retroperitoneal tissues over the anatomical resection planes were transected during surgery.

Data were recorded from two senior staff from each participant centre. Demographic, preoperative, operative, pathological analysis (based on the 8th edition of TNM classification) [14], admission and 30-day postoperative data, and oncological outcomes were recorded. All unfavourable histological characteristics, such as mucinous or signet ring cells, were grouped for data analysis concerning the histological pattern, since their frequency would be presumably low and hence analysing them separately would make it difficult to acquire statistical significance. Postoperative infectious complications, specifically surgical site infection (SSI) classification [15], anastomotic leak (AL) [16] or free purulent or faecal peritonitis data were collected. Complications were additionally classified according to the Clavien-Dindo classification for postoperative complications [17].

Adjuvant chemotherapy indication, regimen selection and follow-up schedule were evaluated in each single centre on the basis of the best clinical practice, in accordance with current guidelines and individualisation of patients' characteristics and wishes. Completion of adjuvant chemotherapy was defined as a minimum total dose of 80% of the pretreatment plan.

Peritoneal metastases were defined a priori in the study protocol as follows: presence of any oncological disease at the peritoneal level, either single or multifocal, both radiologically suspected or with pathological confirmation, and which was clearly recognisable and differentiated from other forms of locoregional recurrence of colon cancer such as anastomotic, mesenteric or lymph node recurrence and the retroperitoneal form [18]. Peritoneal metastases diagnosis was based on radiological studies such as

abdomen CT or PET-CT and/or histological samples, both percutaneous or surgically acquired samples.

Outcome measures

The main outcome of the study was the incidence of MPM after curative resection procedures for patients with confirmed pT4 colon cancer, and PDF-R, defined as the time period that is free of peritoneal recurrence (time from the date of the first surgical colon cancer resection until the date of onset of peritoneal recurrence).

Secondary outcomes were considered as local and systemic recurrence incidence, mid- to long-term oncological results in terms of disease-free survival (DFS) and overall survival (OS), analysis of associated factors with peritoneal recurrent disease and to create a stratification risk model for peritoneal recurrence based on this national multicentre cohort.

Statistical methods

Qualitative variables are presented with their frequency distribution. Quantitative variables are represented by their mean and standard deviation (SD) or median and interquartile range (IQR) in case of asymmetry.

Univariate analysis was performed to assess the association between the different independent variables with PDF-R. In order to correct for confounding factors, a multivariate analysis was performed using a Cox proportional hazard model. Variables that had a $p < 0.1$ in the univariate analysis were included in the multivariate analysis. The selection of the definitive model was carried out using the forward stepwise method with an inclusion value in the model of $p < 0.05$ and exclusion of $p > 0.10$. $p < 0.05$ was considered to indicate statistical significance (two-tailed test).

PDF-R was determined among the whole sample with Kaplan–Meier survival methods.

The following variables were analysed as potential risk factors for peritoneal metastases: patients' demographic data (sex, age), operative details (tumour location, elective vs. emergency surgery, preoperative stenting, type of resection, necessity for extended resection, laparoscopic vs. open approach), perioperative outcome (blood transfusions, SSI, anastomotic leak or peritonitis), and especially pathological findings (type of pT4 tumour, a or b, tumour differentiation, lymph node status, resection margin status, mucinous or signet ring cells histology and vascular, lymphatic or perineural microscopic invasion).

Risk model construction

The starting point for the risk model was the multivariate regression model for PDF-R that had previously been performed. Each of the variables included in the Cox regression model was assigned a score according to the obtained hazard ratio (HR): HR > 3 was assigned 2 points and HR < 3 was assigned 1 point. Data from every patient was analysed on the basis of these criteria: first, the presence or absence of associated variables, and then a definitive score was provided. A potential scale from 0 to 6 was established. Finally, PDF-R was analysed in relation to the score in the system, and groups with similar PDF-R rates were created.

Kaplan–Meier representation of the different groups was calculated after the explained model was created.

The results are reported in accordance with the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) statement for observational studies [19].

All calculations were performed using Stata 13.1 (StataCorp, Texas, USA).

Results

Patients' description and operative data

A total of 50 different hospitals participated in the study with a total sample record of 2546 patients with pT4 colon cancer. After the inclusion and exclusion criteria were applied, a final population of 1356 patients was analysed (Fig. 1).

Mean age was age 70 (SD 12), and 57.2% were male patients.

Table 1 summarises demographic, preoperative and operative variables, and the most relevant postoperative outcomes.

Emergency surgery was performed on 308 patients (22.7%) of the sample, among which obstruction was the most frequent cause (in 204 patients). In addition, 76 endoluminal stents were used among the whole sample, which means a 5.6% rate.

A total of 379 patients required extended resection procedures during the intervention (28.9%).

Pathological tumour details

Table 2 presents the pathological and adjuvant treatment data of the whole sample.

Mean number of lymph nodes resected was 21.9, with 1175 (86.8%) patients with at least 12 nodes analysed.

In reference to pathological staging, T category was pT4a in 1055 patients (77.9%) and pT4b in 301 patients (22.1%); N0 category was present in 603 patients (44.5%), N1 in 474 patients (35%), and N2 in 279 patients (20.5%). Altogether,

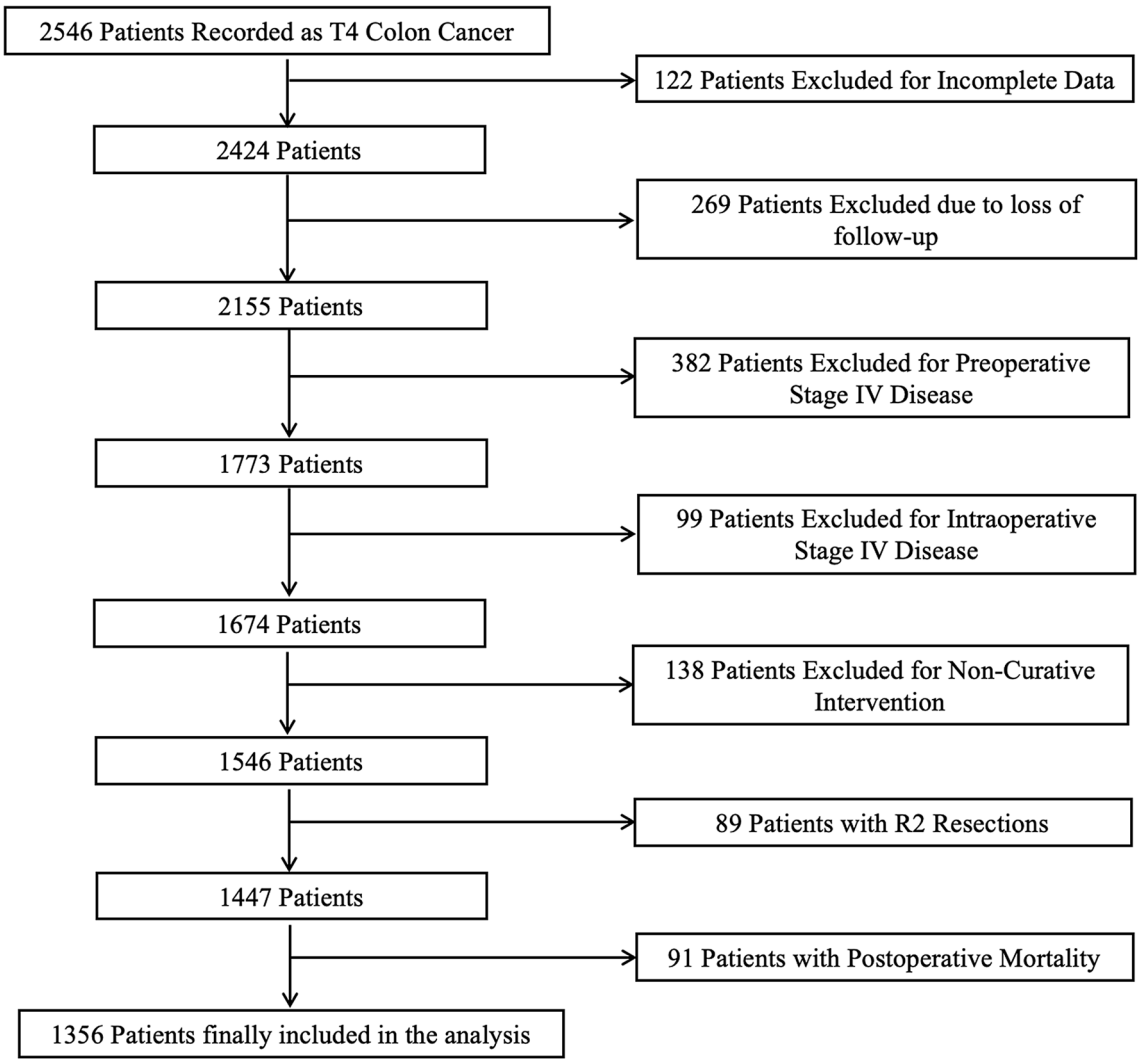

Fig. 1 Flowchart detailing the selection of the patients in this study

a total of 574 stage II patients (42.6%) and 773 stage III patients (57.4%) were recorded. Pathological tumour perforation was diagnosed in 253 cases (18.6%), and there were an additional 129 patients (9.5%) with affected surgical resection margin (R1).

Adjuvant chemotherapy was administered to 1005 patients (74.1%).

Peritoneal metastases

The median follow-up time after colon cancer surgery was 50 months (Range 6–108). A total of 349 patients experienced some kind of recurrence (25.7%; median DFS of 45.8 months), of which 185 patients showed MPM (13.6%). Mean time for the onset of MPM was 14.7 months, with 64 patients developing MPM during the first year (4.7%) and 172 patients in the 3-year follow-up period (12.7%), which accordingly means 34.6% of MPM during the first year (64/185) and 93% in the 3-year period (172/185).

Regarding pT4a vs. pT4b status, MPM were observed in 146 pT4a patients (13.8%) and 39 pT4b patients (13.0%) ($p = 0.724$).

In the latest follow-up update, 106 of 185 (57.3%) patients with MPM showed some other kind of metastasic disease. Additionally, locoregional recurrence not related to MPM was observed in 38 (3.0%), 45 (3.6%) and 35 (2.8%) patients for perianastomotic, mesentery/nodal and retroperitoneal recurrence respectively.

The PDF-R of the whole sample calculated with Kaplan–Meier analysis as shown in Fig. 2, with 95.3% PDF-R during the 1-year period, 85.9% in the 3-year period and 84.3% in the 5-year period.

During follow-up, 362 (26.8%) patients died, with a median overall survival of 49.7 months.

Table 1 Demographic, preoperative, operative and postoperative outcome data for the whole group of patients, detailed for metachronous peritoneal metastases (MPM)

	No MPM $n=1171$	MPM $n=185$	Total $n=1356$	p
Age (years)	70.1 (12.1)	69.7 (12.3)	70 (±12.1)	0.65
Gender				
Male	682 (58.2)	94 (50.8)	776 (57.2)	0.058
Female	489 (41.8)	91 (49.2)	580 (42.8)	
ASA score				
I	48 (4.1)	9 (4.9)	57 (4.4)	0.64
II	572 (49.4)	92 (50.0)	664 (49.2)	
III	498 (43.0)	73 (39.7)	571 (42.3)	
IV	44 (3.8)	10 (5.4)	54 (4.1)	
BMI (kg/m^2)				
< 30	949 (81.0)	144 (77.8)	1093 (80.6)	0.24
> 30	222 (19.0)	41 (22.2)	263 (19.4)	
Presence of symptoms				
No	216 (18.4)	27 (14.6)	243 (17.9)	0.2
Yes	955 (81.6)	158 (85.4)	1113 (82.1)	
Main symptom				
Altered bowel habit	121 (12.7)	18 (11.4)	139 (12.5)	0.75
Obstruction	265 (27.7)	52 (32.9)	317 (28.5)	
Bleeding	261 (27.3)	40 (25.3)	301 (27)	
Cachexia	114 (11.9)	19 (12.0)	133 (12)	
Others	194 (20.3)	29 (18.4)	223 (20)	
Tumour location				
Proximal colon	579 (49.7)	108 (58.1)	687 (50.7)	0.04
Distal colon	587 (50.3)	78 (41.9)	665 (49.3)	
cT stage				
cT0/1	46 (4.5)	5 (3.2)	51 (4.3)	0.13
cT2	68 (6.6)	6 (3.8)	74 (6.3)	
cT3	359 (35.0)	46 (29.5)	405 (34.3)	
cT4	552 (53.9)	99 (63.5)	651 (55.1)	
cN stage				
cN0	531 (50.5)	68 (43.0)	599 (49.5)	0.06
cN1	382 (36.3)	59 (37.3)	441 (36.5)	
cN2	139 (13.2)	31 (19.6)	170 (14)	
Preoperative tumour stenting	66 (5.6)	10 (5.4)	76 (5.6)	0.89
Surgical scheduling				
Elective surgery	921 (78.7)	127 (68.6)	1048 (77.3)	< 0.01
Emergency surgery	250 (21.3)	58 (31.4)	308 (22.7)	
Free tumour				
Yes	741 (65.5)	118 (65.2)	859 (65.4)	0.94
No	391 (34.5)	63 (34.8)	454 (34.6)	
Type of surgery				
Right hemicolectomy	476 (40.8)	84 (45.4)	560 (41.5)	< 0.01
Left hemicolectomy	143 (12.3)	18 (9.7)	161 (11.9)	
Sigmoidectomy	369 (31.6)	37 (2.0)	406 (30)	
Hartmann	58 (5.0)	22 (11.9)	80 (5.9)	
Others	120 (10.3)	24 (13.0)	144 (10.7)	
Extended resection	332 (29.4)	47 (26.1)	379 (28.9)	0.37
Surgical approach				
Open surgery	700 (59.8)	119 (64.3)	819 (60.4)	0.24
MIS	471 (40.2)	66 (35.7)	537 (39.6)	

Table 1 (continued)

	No MPM $n=1171$	MPM $n=185$	Total $n=1356$	p
Any complication	535 (46.8)	81 (44.0)	616 (46.4)	0.48
Major complication (CD ≥ 3)	131 (11.5)	26 (14.1)	157 (11.8)	0.3
Surgical infectious complication				
Organ/space	65 (26.0)	11 (21.6)	76 (6.2)	0.8
Anastomotic leak	48 (19.2)	11 (21.6)	59 (5.5)	0.15
Any	137 (54.8)	29 (56.9)	166 (12.7)	0.16
Perioperative transfusion	174 (18.3)	29 (18.6)	203 (18.3)	0.9

Data are expressed as number of patients (%), except age data which are mean and standard deviation (SD)
Organ/space infection is defined according to the previous definition published by Horan et al. [15]

Table 2 Pathological data for the whole group of patients, detailed for metachronous peritoneal metastases (MPM)

	No MPM $n=1171$	MPM $n=185$	Total $n=1356$	p
Positive peroperative cytology	20 (1.7)	4 (2.2)	24 (1.8)	0.4
Histologic type				
Adenocarcinoma	1052 (90.2)	148 (80.0)	1200 (88.8)	< 0.01
Mucinous or signet ring cell	115 (9.9)	37 (20.0)	152 (11.2)	
Differentiation grade				
Low grade	968 (84.7)	132 (75.4)	1100 (83.5)	< 0.01
High grade	175 (15.3)	43 (24.6)	218 (16.5)	
pT stage				
pT4a	909 (77.8)	146 (78.1)	1055 (77.9)	0.7
pT4b	260 (22.2)	39 (21.9)	299 (22.1)	
Lymph node count				
< 12	154 (13.2)	25 (13.5)	179 (13.2)	0.7
> 12	1017 (86.8)	160 (86.5)	1177 (86.8)	
pN stage				
pN0	566 (48.3)	37 (37.8)	603 (44.5)	< 0.01
pN1	396 (33.8)	78 (42.2)	474 (35)	
pN2	209 (17.9)	70 (37.8)	279 (20.5)	
pTNM stage				
Stage II	537 (46.2)	37 (20.0)	574 (42.6)	< 0.01
Stage III	625 (53.8)	148 (80.0)	773 (57.4)	
Microscopic invasion				
Lymphatic invasion	427 (37.0)	106 (58.2)	533 (39.3)	< 0.01
Vascular invasion	397 (34.5)	96 (53.0)	493 (36.3)	< 0.01
Perineural invasion	332 (28.9)	75 (41.2)	407 (30.0)	< 0.01
Any type of invasion	610 (53.1)	128 (70.0)	738 (54.4)	< 0.01
Pathologic tumour perforation	205 (17.6)	48 (26.0)	253 (18.6)	< 0.01
Surgical resection margin				
R0	1061 (90.6)	166 (89.7)	1227 (90.5)	0.7
R1	110 (9.4)	19 (10.3)	129 (9.5)	
Adjuvant chemotherapy				
Yes	853 (72.8)	152 (82.2)	1005 (74.1)	< 0.01
No	318 (27.2)	33 (17.8)	351 (25.9)	

TNM TNM classification of malignant tumours

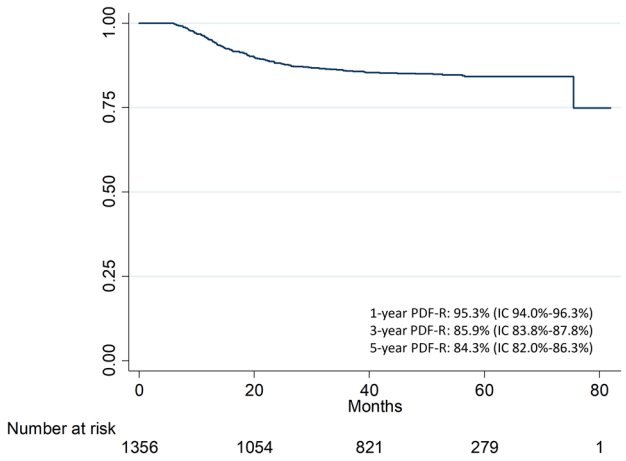

Fig. 2 Kaplan–Meier curve for PDF-R among the studied sample

Univariate and multivariate analysis for MPM

The results from the univariate and multivariate analysis are shown in Table 3.

Subsequent to univariate analysis, the following variables were included in multivariate analysis (p value < 0.1): gender, tumour location, emergency operation, tumour perforation, histological type, grade of differentiation, pN stage, lymph node ratio (LNR) and the presence of any type of microscopic invasion. After the forward stepwise process, the variables of the definitive Cox model were pN stage, tumour perforation, histological type, differentiation grade and emergency operation. The strongest independent risk factors for MPM were pN stage (HR 3.72), tumour perforation (HR 1.91), mucinous or signet ring cell histology (HR 1.68), high grade of differentiation tumours (HR 1.54) and emergency surgery (HR 1.42). There was a total of 320

Table 3 Univariate and multivariate analysis of possible factors influencing postoperative peritoneal recurrence

	Metachronous peritoneal metastases (MPM)				
	Univariate		Multivariate		
	n (%)	*p*	HR	*p*	95% CI
Gender					
Male	94 (50.8)	1	–	–	–
Female	91 (49.2)	0.085			
Surgical scheduling					
Elective	127 (68.7)	< 0.01	1		
Emergency	58 (31.4)		1.42	0.049	1.01–2.01
Tumour location					
Proximal colon	108 (58.1)	0.04	–	–	–
Distal colon	78 (41.9)				
Tumour perforation	38 (20.5)	< 0.01	1.91	0.002	1.26–2.87
Histologic type					
Adenocarcinoma	148 (80.0)	< 0.01	1		
Mucinous or signet ring cell	37 (20.0)		1.68	0.02	1.1–2.58
Differentiation grade					
Low grade	132 (75.4)	< 0.01	1		
High grade	43 (24.6)		1.54	0.022	1.1–2.2
pN stage					
pN0	37 (20.0)	< 0.01	1		
pN1	78 (42.2)		3.72	< 0.01	2.56–5.41
pN2	70 (37.8)				
Microscopic lymphatic invasion	106 (58.2)	< 0.01	–	–	–
Microscopic vascular invasion	96 (53.0)	< 0.01	–	–	–
Microscopic perineural invasion	75 (41.2)	< 0.01	–	–	–
Adjuvant chemotherapy	152 (82.2)	< 0.01	–	–	–

MPM metachronous peritoneal metastases, *HR* hazard ratio, *95% CI* 95% confidence interval

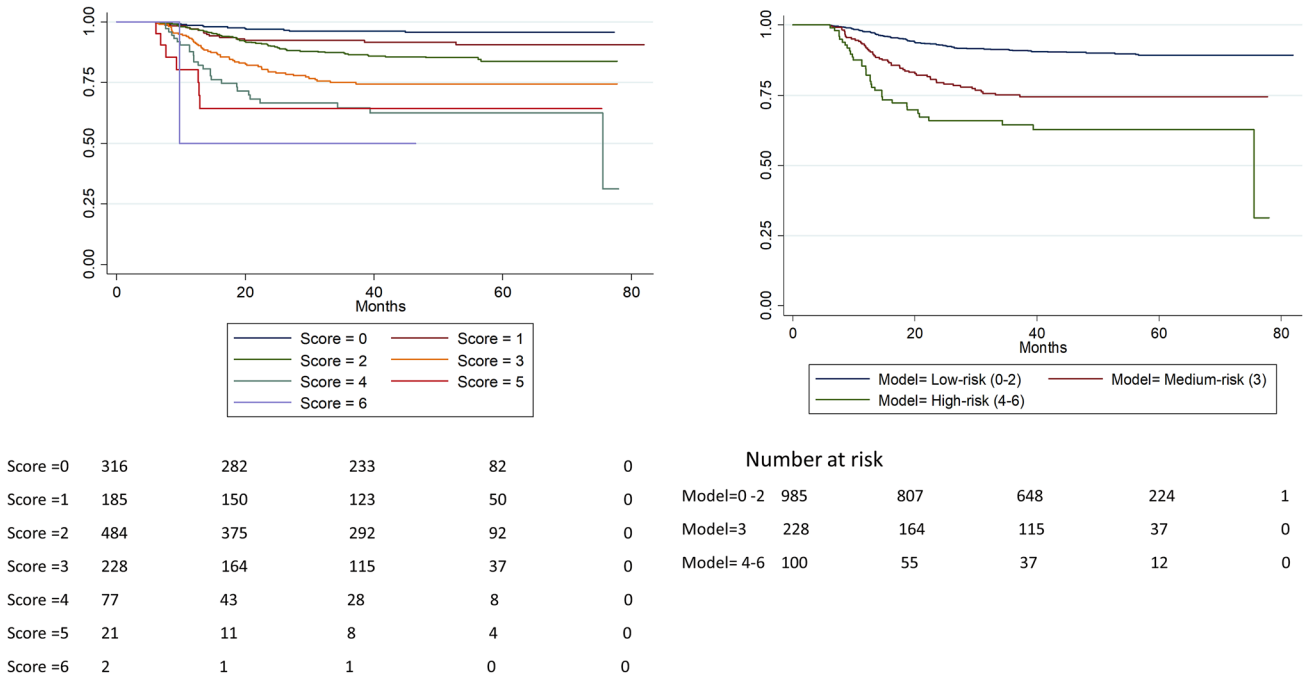

Fig. 3 Kaplan–Meier curve for the stratification model for MPM created on the basis o the multivariate Cox regression model

patients with pT4 tumours with no additional risk factors (23.6%) present. pT4 subclassification itself, pT4a vs. pT4b, showed no association with peritoneal metastases development in our sample (13.8% vs. 13%; $p=0.7$). The distribution of the variables related to MPM in the two subgroups is shown in supplementary material 1.

Risk stratification model

According to the results of multivariate analysis, the variables that were included in the model were nodal stage (N0 vs. N+), tumour perforation, histologic type, differentiation grade and surgical scheduling. Each risk factor added 1 point, but positive nodes added 2 points.

Table 4 Peritoneal recurrence function data for PDF-R at 1, 3 and 5 years for each score from 0 to 6 based on the multivariate Cox regression model generated

Risk model	1 year				3 years				5 years			
	n-exp	Fail	PDFR-F	95% CI	n-exp	Fail	PDFR-F	95% CI	n-exp	Fail	PDFR-F	95% CI
0 points	298	4	0.98	0.97–0.99	250	11	0.96	0.94–0.98	83	12	0.96	0.93–0.98
1 point	169	5	0.97	0.93–0.99	135	13	0.92	0.87–0.96	51	15	0.91	0.85–0.94
2 points	432	14	0.97	0.95–0.98	313	56	0.87	0.93–0.90	93	62	0.84	0.8–0.87
3 points	198	18	0.92	0.87–0.95	128	51	0.75	0.69–0.80	39	52	0.74	0.68–0.8
4 points	62	12	0.83	0.73–0.9	33	24	0.65	0.52–0.75	9	25	0.62	0–49-0.73
5 points	17	4	0.8	0.56–0.92	9	7	0.64	0.39–0.81	5	7	0.64	0.39–0.81
6 points	2	1	0.5	0.1–0.91	2	1	0.5	0.01–0.91	1	1	–	–
Model 2	1 year				3 years				5 years			
	n-exp	Fail	PDF-R	95% CI	n-exp	Fail	PDF-R	95% CI	n-exp	Fail	PDF-R	95% CI
Low risk (0–2)	896	23	0.97	0.96–0.98	696	80	0.91	0.89–0.93	226	89	0.89	0.87–0.91
Medium risk (3)	198	18	0.92	0.87–0.95	128	51	0.75	0.69–0.80	39	52	0.74	0.68–0.8
High risk (4–6)	79	17	0.82	0.73–0.88	42	32	0.64	0.53–0.73	13	33	0.63	0.51–0.72

n-exp number of patients exposed, *PDFS-F* peritoneal disease-free survival function, *95% CI* 95% confidence interval

Figure 3 and Table 4 respectively show the Kaplan–Meier curve and the stratification risk model created for PDF-R in 1-, 3- and 5-year periods.

According to this model, the score 0 group showed 98% PDF-R during the 1-year period, and 96% PDF-R in 3- and 5-year periods. An additional stratification model was constructed to create three different risk categories for MPM in patients: low, intermediate and high. The medium- and high-risk groups had a lower PDF-R than the low-risk group (HR 2.8 (2.0–3.9), $p < 0.001$ for medium-risk group, and HR 4.9 (3.3–7.3), $p < 0.001$ for high-risk group).

Supplementary materials 2 and 3 respectively show the Kaplan–Meier curves for PDF-R and the PDF-R in the 1-, 3- and 5-year period according to the presence of the specific risk factors resulting from the multivariate Cox regression model.

Discussion

This study analyses the prevalence of MPM in patients following an operation for T4 colon cancer with curative intent. The obtained incidence of 13.6% is slightly lower than that of another recently published study (18.3%) [20].

T4 colon cancer tumours have acquired a growing relevance because they are related to a substantially worse oncological prognosis, mainly based on the risk of MPM. In such settings, different therapeutic options have arisen and might be discussed, such as cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS HIPEC) [21] or neoadjuvant chemotherapy [22].

Despite this growing interest, epidemiological studies in this subject are scarce. In addition, highly variable methodology has been used, including major limitations such as long-term periods for inclusion [6, 20], different time periods analysed [20], big administrative databases which can omit relevant clinical details [5], and studies in which patients with colon cancer and rectal cancer are merged together [12]. Considering all these limitations, it is unclear in the context of changing treatment regimens whether or not these populations are comparable to each other and, evidently, the information from such old cohorts is doubtfully useful for making management decisions at the present time. In addition, there is no unanimous consensus regarding who should be considered as high-risk patients [23]. Some of these previously mentioned factors include right colon tumours [5], patients with peritoneal tumour implants discovered during primary tumour surgery, even in the event of complete resection [24], ovarian metastases [24, 25], advanced pN stage [5, 26], pT4 tumours [5, 8, 10, 26], perforated or obstructive tumours [5, 27] or patients with intraoperative positive cytological study [28].

On the basis of data from a retrospective study [7], pT4 tumours have been upgraded to the category of high-risk tumours for developing MPM [23, 29]. However, some important data such as tumour perforation, microscopic prognostic factors like lymphatic, vascular or perineural invasion, surgical resection status, or even lymph node staging were not considered in the multivariate analysis. All these aspects should make the evidence and the recommendations based on it subject to debate; in the present work, some of these variables were absolutely key to the development of peritoneal metastases, even in the event of a higher rate of administered chemotherapy.

As a result of the observed relationship between T stage and MPM, a second-look and CRS ± HIPEC therapeutic strategy has been proposed for high-risk patients [29]. However, recent evidence based on two different randomised clinical trials [1, 30] showed agreement in both their results, denying any benefits of prophylactic HIPEC in very high-risk and high-risk patients respectively, in the PROPHYLOCHIP-PRODIGE 15 and COLOPEC trials. In line with the suggestions of these recent publications, in the present study, we detected a PDF-R of 98% in the 1-year period and 96% in the 3- and 5-year periods for patients with pT4 tumours as the single risk factor.

In the context of patients with pT4 colon cancer, five risk factors have been identified: emergency surgery, tumour perforation, high-grade differentiation tumours, presence of mucinous or signet ring cell histology, or positive lymph node isolation. Regarding the pT stage, several authors have described significant differences in MPM rates when monitoring pT4a tumours in comparison with pT4b tumours [20]. In the cases of pT4a tumours, it has been hypothesized that detached tumour cells in contact with the visceral peritoneum, not adhering to any other neighbouring organ and lacking an inflammatory reaction around them, might finally implant at any location along the peritoneal surface. In the cases of pT4b tumours, this inflammatory reaction may prevent peritoneal spreading and, with adequate oncological en bloc resections, better oncological outcomes can be achieved.

In the present series, contrary to what has been previously published (24.7% and 12.2% for pT4a and pT4b) [20], no significant differences were found between pT4a vs. pT4b tumours. The distribution of the remaining identified risk factors between both groups was more or less equivalent and high rates of adjuvant chemotherapy were similarly used in both groups. These results differ from another recent publication [20] in which pN+ patients and neoadjuvant treatments were clearly asymmetrically distributed in favour of pT4b tumours.

In this study, a new model for stratification MPM risk after pT4 colon cancer is presented, similar to that previously developed by Segelman et al. [12], although with

different statistical methodology. Our proposed model is intended to be easier to use and to decide an overall strategy in the presence of certain threatening oncological conditions. This model combines the two criteria that perhaps should be judged as the most important: HR and incidence of the event. The combination of this information will allow each group to determine the best strategies to adopt depending on both factors, although this is just the initial proposal and further research for validation remains to be done. On the basis of the patients' characteristics and risk, we could suggest an individualized strategy. Patients with a score of >4, whose estimated PDF-R in a 1-year period is 83%, could be candidates for a cytoreductive surgery and HIPEC program, while patients in the low-risk group, should be recommended to be only included in intensive follow-up programs.

This study has some limitations such as its retrospective design, which has missing detailed information about the adjuvant chemotherapy regimens used or the fact that certain high-risk patients were excluded from the study, such as resected peritoneal metastases or ovarian metastasis during the primary tumour intervention, because these groups were considered stage IV disease at the time of initial diagnosis, and the lack of validation of the risk stratification model presented. The study also has several strengths such as its multicentre nature, with the enrolment of 50 different national hospitals with distinct levels, its large sample, and a recent brief inclusion period, which enhances the comparisons among patients. Furthermore, the development of the stratification risk model shows PDF-R in 1-, 3- and 5-year follow-up periods, based on the existence of five different identified risk factors in the context of patients with pT4 colon cancer.

Conclusion

This large multicentre study based on patients with a histological diagnosis of pT4 colon cancer treated with curative intent showed a lower incidence of MPM compared to that previously reported in the literature. Additionally, five risk factors were related to the development of MPM. A risk stratification model was proposed showing a straightforward correlation with the expectation of MPM.

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Declarations

Conflict of interest The authors of the article do not have any commercial association that might pose a conflict of interest in relation to this article.

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