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**(ELSEVIER EDITORS THIS TOOK QUITE A BIT OF EDITING  
SORRY HOPE I HELPED YOU MIKE SARR)**

**The location of the primary colon cancer has no impact in  
patients undergoing cytoreductive surgery for peritoneal  
metastasis**

**Running head:** impact of primary tumor location for colon cancer peritoneal  
metastasis

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## **Abstract**

### **Introduction**

The impact of the location of colorectal cancer (CRC) on patient outcomes has been demonstrated in several settings. The objective of this study was to assess the prognostic impact of the location of the primary colon cancer among patients with CRC peritoneal metastases undergoing complete cytoreductive surgery .

### **Methods**

We identified 796 patients treated by a complete CRS between January 2004 and January 2017 for CRC peritoneal metastases in 16 different institutions, in the prospectively maintained clinical and biological digestive peritoneal metastasis database of the BIG-RENAPE network. The two primary endpoints were overall survival (OS) and Progression-Free Survival (PFS). To evaluate the impact on OS and PFS of potential prognostic factors (including the location of the primary CRC), these factors were included in univariate and multivariate cox proportional hazard models.

### **Results**

Right-sided (RS) CRCs presented were more frequently BRAF-mutated and had microsatellite instability, while the frequency of RAS mutation was similar between RS and left-sided CRCs.

After a median follow-up time of 3.3 years, there was no significant difference in OS or PFS according to tumor side. The lack of effect of tumor location on OS and PFS was consistent across subgroups.

### **Conclusions**

Among patients undergoing a complete cytoreductive surgery for CRC peritoneal metastases, the site of the primary CRC was not associated with differences in

PFS or OS. Tumor side should not be used as a stratification factor in trials of CRC  
peritoneal metastases, and should not be used in the selection process of  
patients for cytoreductive surgery. ClinicalTrials.gov Identifier: NCT02823860)

**Keywords:** colorectal cancer; Peritoneal metastasis; prognostic; tumor side;  
retrospective Studies ; Survival Rate

ClinicalTrials.gov Identifier: NCT02823860

## **Introduction**

Colorectal cancers (CRCs) can be characterized by their primary location within the colon and rectum <sup>1</sup>Biologic characteristics of left-sided CRC (LC) and right-sided CRC (RC) differ substantially. Differences in the microbiome <sup>2</sup>, and carcinogenesis <sup>3</sup> have been reported according to tumor sidedness. As a consequence, RCs display more frequently mucinous histology, microsatellite instability (MSI) and activating mutations of KRAS, BRAF, and PIK3CA genes <sup>4,5</sup>, and less frequently NRAS and p53 mutations <sup>5,6</sup>.

The impact of CRC location on patient outcomes has been demonstrated in the settings of both localized and metastatic disease. Large population-based studies have shown that survival after resection of colon cancer differs by tumor location, patients with stage III RS colon cancers have a worse prognosis <sup>7-9</sup>. In the metastatic setting, LS CRCs are also associated with a significantly decreased risk of death <sup>10, 11</sup>.; these observations appear to be independent of the mutational spectrum within these CRCs <sup>11-14</sup>.

Some patients with CRC peritoneal metastases are candidates for surgery with the potential for long-term survival and cure <sup>15,16</sup>. The location of the primary CRC might be used as an aid in determining appropriate treatment strategies for patients with peritoneal metastasis secondary to CRC; however, the prognostic implication of the location of the primary CRC has not yet been examined in patients with resectable peritoneal metastases. The objective of this study was to assess the prognostic impact of the location of the primary CRC among patients with peritoneal metastases undergoing a complete cytoreductive surgery.

## **Material and methods**

### *Study design and patient selection*

A retrospective study of patients treated by a complete cytoreductive surgery between January 2004 and January 2017 for CRC peritoneal metastases was performed among 16 different institutions, 14 from the French national network of peritoneal surface malignancies (BIG-RENAPE), and 2 from Canada. The query was performed on September 2017 on the BIG-RENAPE hybrid clinical database on digestive peritoneal metastases <sup>17</sup>.

Inclusion criteria were histologically proven CRC, synchronous or metachronous peritoneal metastases at time of operation, and a first complete cytoreductive surgery defined as a completeness of cytoreduction (CC) score reported in the operative report of 0 or 1 <sup>18</sup>. Patients were excluded when the site of the CRC was not reported or located on transvers colon or mid and low rectum, when multiple primary

sites of CRC were reported, when the peritoneal carcinoma index (PCI) at the time of the cytoreductive surgery was 0 but there were non resectable, synchronous, extraperitoneal metastases.

### *Study protocol*

Detailed information was obtained on age, sex, site of the primary CRC, synchronicity between primary tumor and peritoneal metastases, RAS and BRAF mutational status, microsatellite instability (MSI), pathologic subtype, operative details such as duration of the operation and hyperthermic intraperitoneal chemotherapy (HIPEC), PCI <sup>18</sup>, and major surgical complications, history and type of perioperative chemotherapy, and operative details.

The primary location of the CRC was determined by endoscopic, pathologic,



and/or operative reports. In order to be consistent with previous studies, primary CRCs located in cecum, ascending colon, and transverse colon were defined as RS CRCs, and those located in the splenic flexure, descending colon, sigmoid colon, and rectum were defined as LS CRCs<sup>19</sup>. RAS and BRAF mutation were tested in most patients since late 2008, according to French clinical practice <sup>20</sup>. The duration of the operation was defined as the time between the start of and the end of the cytoreduction, counting the time of HIPEC when performed using an open abdomen technique. Based on center protocol, HIPEC was performed either using an open (“coliseum”) or closed technique, with the goal of reaching an intraabdominal temperature of 43°C. The cytotoxic agents used were either oxaliplatin (360mg/m<sup>2</sup> for 30 min) or mitomycin C (35mg/m<sup>2</sup> for 90 min). PCI was scored during the cytoreductive surgery and extracted from the operative reports <sup>18</sup>. Post-operative morbidity and mortality was evaluated 90 days after cytoreductive surgery and graded by local investigators using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (NCI CTCAE). Major surgical complications were defined as any adverse event with a grade  $\geq 3$  according to NCI CTCAE. The type of perioperative chemotherapy was decided on by the center’s specialized multidisciplinary team meetings.

According to French guidelines, patients were followed with clinical examinations and surveillance imaging every 3 months for the first 3 years, then every 6 months for the next 2 years, and then annually <sup>21</sup>. Long-term outcomes were recorded, and the two primary endpoints were overall survival (OS) and Progression-Free Survival (PFS). OS was assessed from the date of cytoreductive surgery until death from any cause. PFS was assessed from the date of

cytoreductive surgery until death or relapse, whichever occurred first. Relapse was confirmed either on pathologic exams or on radiologic exams when peritoneal nodules appeared or increased in size. If relapse or death did not occur before the cutoff date, data were censored at the time of the last valid assessment. Progression was defined according to treating physicians in the 16 institutions.

#### *Data analysis*

Quantitative variables were expressed as median and 25th-75th percentiles. Categorical variables were summarized as number and percentages. The non-parametric Mann-Whitney U test or Fisher's exact test were used as appropriate to compare distributions of continuous and categorical variables between the two groups according to primary location of the CRC. OS and PFS were estimated by the Kaplan-Meier method and compared using the Log-Rank test according to primary location of the CRC.

To evaluate the impact on OS and PFS of potential prognostic factors (including primary location of the CRC), these factors were included in univariate Cox proportional hazard models. Continuous variables were modeled as binary using the most clinically relevant thresholds. The proportional hazards assumption was assessed using the scaled Schoenfeld residuals. Variables considered as clinically relevant or yielding p values less than 0.1 by univariate analysis were retained for multivariate model analysis. The objective of the multivariate analysis was to assess the independent effect of primary tumor side on survival outcomes. The added value of primary tumor side in the multivariate model was evaluated using a likelihood ratio test; the likelihood scores of the model

evaluated with and without primary tumor side were compared, considering that lesser likelihood scores indicate better fitting models. All testing was two-tailed with a  $p < 0.05$  considered to be statistically significant. Subgroup analyses were performed to assess the impact of primary tumor side on OS and PFS in subgroups defined according to age, date of cytoreductive surgery, synchronicity between primary tumor and peritoneal metastasis, RAS, BRAF, and microsatellite instability (MSI) status, CC score, HIPEC, PCI, duration of operation, major surgical complications, history and number of cycles of preoperative chemotherapy, and history of postoperative chemotherapy. Tests to determine interactions of the primary tumor side with covariates were used to identify predictive factors by assessing whether there was a significant difference in the primary tumor side effect on PFS and OS between subgroups.

Statistical analyses were performed with R software version 3.2.2.

## **Results**

### *Patient characteristics*

From January 2004 and January 2017, 1025 patients undergoing a cytoreductive surgery for CRC peritoneal metastasis were included in the BIG-RENAPE database. Sixty patients were excluded because of multiple tumors or an unknown primary site, 33 were excluded because the completeness of the cytoreductive surgery was insufficient (CC2) or not reported, 76 were excluded because the PCI was 0 or not scored, and 60 were excluded because the procedure was not the first complete cytoreductive surgery (Figure 1). Among the 796 patients included in the study, 306 had a right-sided RS CRC, and 490

had a LSCRC.

Patients with RS CRC were more likely to present with synchronous peritoneal metastases and to harbor signet cell pathology. RS CR also were more frequently harboring a BRAF mutation (22% vs 11%,  $P=0.018$ ), and MSI (23% vs 10%,  $P=0.0096$ ), while the frequency of RAS mutation was similar between RS and LS CRCs. There was no significant difference in PCI, CC score, HIPEC administration, or a history of preoperative chemotherapy and type between RS and LS tumors. The duration of cytoreductive surgery was somewhat greater among LS CRCs (median of 342 minutes vs 363 minutes,  $P=0.018$ ), while the administration of postoperative chemotherapy tended to be more frequent among RS CRCs (71% vs 63%,  $P=0.055$ ). The rate of missing data was low for covariates associated with patient characteristics and treatment strategy (age, sex, PCI, CC score, HIPEC, preoperative chemotherapy), but was more prevalent for tumor characteristics (35% for RAS status, 62% for BRAF status, 73% for MSI status, and 33% for pathologic subtype), and for administration of post-operative chemotherapy (28%) (Table 1).

#### *Overall survival(OS)*

The median follow-up time was 3.3 years, (95% Confidence Interval (CI), 3.0 months to 3.7 years). There was no difference in duration of follow-up according to tumor side (median follow-up = 3.6 years in the RS group vs 3.2 years in the LS group,  $P=0.36$ ). The analysis of OS was based on 320 deaths (40% of patients), including 126 in the RS group (32%) and 194 in the LS group (40%). The median OS in the RS group was 3.5 years (95%CI, 3.0 years to 4.1 years) vs 4.0 years in the LS group (95%CI, 3.5 years to 4.4 years). The OS hazard ratio (HR)

was 0.99 (95%CI, 0.79 to 1.23,  $P=0.90$ ), Figure 2A.

In univariate analyses, patients recent date of cytoreductive surgery, BRAF wild-type status, score CC0, PCI  $\leq 14$ , duration of the cytoreductive surgery  $< 6$  hours, absence of major surgical complications, and history of postoperative chemotherapy were associated with a better OS (table 2). In the adjusted analysis using a multivariate Cox proportional hazard model, PCI  $\leq 14$  and absence of major surgical complications were independent factors associated with better OS. The side of the primary CRC was not associated with OS after adjustment on covariates (table 2).

No significant effect of tumor side on OS was seen across all subgroups. The duration of the operation was the only subgroup in which an impact of tumor side on OS was seen ( $<6$  hours: hazard ratio, 0.74 with 95% CI of 0.52 to 1.0, tending to  $P=0.096$  favor the LS tumor group ( $p=0.096$ );  $\geq 6$  hours: hazard ratio of 1.20; 95% CI, 0.82 to 1.75; but a  $P=0.35$ ); the interaction test, however, was not statistically significant ( $P=0.055$ ) (Supp Files)

#### *Progression-free survival(PFS)*

Follow-up imaging data were missing for 93 patients, and the PFS analysis was performed on the remaining population of 703 patients. The PFS analysis was based on 453 progressions or deaths (64% of patients), including 178 in the RS group (66%) and 275 in the LS group (63%). The median PFS in the RS group was 1.2 years (95%CI, 1.1 years to 1.5 years) vs 1.2 years in the LS group (95%CI, 1.1 years to 1.4 years). The PFS HR was 1.02 (95%CI, 0.85 to 1.23,  $P=0.84$ ), Figure 2B.

In univariate analyses, patients age  $> 60$  years, a more recent date of

cytoreductive surgery, CC score of 0, PCI  $\leq$  14, absence of a major surgical complication, number of preoperative chemotherapy cycles  $\leq$  6, and a history of postoperative chemotherapy were associated with a better PFS (table 3). In the adjusted analysis using a multivariate Cox proportional hazard models, a more recent date of cytoreductive surgery, PCI  $\leq$  14, absence of a major surgical complication, number of preoperative chemotherapy cycles  $\leq$  6, and history of postoperative chemotherapy were independent factors associated with better PFS. The side of the primary CRC was not associated with PFS after adjustment on covariates (table 3).

No significant effect of tumor side on PFS was seen across all subgroups (Supp Files).

## **Discussion**

This large, multicenter study of prospectively collected data showed that the side of the primary CRC had no impact on long-term outcomes for patients with peritoneal metastases undergoing a complete cytoreductive resection. In particular, there was no impact on OS and PFS, and this result was consistent across all subgroups. According to previous published evidence, RS CRCs were more frequently BRAF-mutated and had MSI than LS CRCs <sup>4</sup>. These different molecular features between RS and LS CRCs was observed also among the patients with peritoneal metastases included in this study.

For patients with stage IVCRC, RS CRCs have been associated consistently with worse outcome among patients treated with exclusive supportive care <sup>22</sup>, palliative chemotherapy <sup>10, 11, 23</sup>, and those undergoing curative resection of liver metastases <sup>24-26</sup>. The unfavorable outcomes of patients with RS CRCs has been

demonstrated among RAS wild type (WT) patients <sup>25,27</sup>. Moreover, for patients with RAS WT CRCs, the left side is also predictive of a greater efficacy of anti-EGFR treatment <sup>27,28</sup>. Despite these observations, the conclusions that can be driven from studies including mostly patients with liver and lung metastases cannot always be applied to patients with peritoneal metastasis. As an example, RAS mutations are associated with significantly worse outcomes among patients operated for liver metastasis <sup>29-31</sup>, but these same RS mutations do not affect outcomes among patients undergoing resection of CRC peritoneal metastasis <sup>29</sup>. In this study, we found no impact of side of the primary CRC on outcomes after complete cytoreductive surgery for a peritoneal metastases, whatever the status of RAS and BRAF mutation. Given the high rate of missing data regarding the type of perioperative chemotherapy and the low number of patients treated with anti-EGFR therapy, no formal recommendations can be offered from these data regarding the choice of the optimal perioperative chemotherapy.; We acknowledge that the general assumption that patients with RS, metastatic, RAS WT CRC may benefit more from initial treatment with bevacizumab in combination with chemotherapy and those with LS primary CRCs should receive first-line treatment with anti-EGFR therapies <sup>11, 19, 32, 33</sup> seems disputable in the context of peritoneal metastasis.

Prognostic factors and scores have been developed to guide selection of patients for operative intervention based on favorable tumor biology <sup>34, 35</sup>. The independent prognostic value of the side of the primary CRC makes it an eligible biomarker for patient selection. Among selected patients undergoing liver resections for metastatic CRCs, tumor side impacted OS, but the observed cure rates were not different according to tumor side <sup>24, 36</sup> suggesting that the

location of the primary CRC should not change decision-making concerning resection of CRC liver metastases. Our results suggest that among selected patients undergoing a complete cytoreductive surgery for peritoneal metastases secondary to CRC, OS and cure rate are not different according to the side of the primary CRC. From our data, we maintain that there is no reason to include the side of the primary CR in the selection of patients for peritoneal cytoreductive surgery.

In the PRODIGE 7 phase III trial, patients were treated with cytoreductive surgery plus HIPEC with oxaliplatin or cytoreductive surgery alone, in association with systemic chemotherapy. There was no significant impact of HIPEC with oxaliplatin on long-term outcomes <sup>37</sup>. Most of the patients included in this series were treated before the presentation of the results of this trial and received HIPEC; however, given the absence of interaction between HIPEC and tumor side in this study and given the absence of any impact of HIPEC with oxaliplatin on long-term outcomes in the Prodiges 7 trial, it is unlikely that tumor side would impact the prognosis of patients treated with cytoreductive surgery without HIPEC.

The limitations of our study include the heterogeneity of patients in the RS and LS groups, a relatively uncontrolled selection of patients for cytoreductive surgery, and the high rate of missing data concerning biological tumor characteristics and perioperative treatment types. Nevertheless, the consistent lack of impact of the side of the primary CRC across all subgroups analyzed enhances our confidence in this result. Furthermore a consensus appears to exist on favoring classification of CRC based on molecular characteristics rather than



sidedness<sup>38</sup>. Given the present results, the impact on survival of this molecular classification should be further investigated in the setting of peritoneal metastases.

We want to point out that patients not amenable to cytoreductive surgery and patients with incomplete cytoreductive surgery were excluded from this survey, and thus the results cannot be applied to these patient populations.

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## **Figure legend**

### **Figure 1.**

Title: flow chart

Footnotes: PM = peritoneal metastases

### **Figure 2.**

Title: Survival of patients according to the side of the primary CRC

Footnotes: panel A : overall survival according to the side of the primary tumor ;  
panel B : progression-free survival according to primary tumor side

### **Supplementary file 1**

Title: Forest plot of the effect of the side of the primary CRC on overall survival across subgroups.

Footnotes : HR = Hazard ratio ; OS=overall survival ; CC=completeness of cytoreduction ; HIPEC = hyperthermic intraperitoneal chemotherapy ; P value for interaction test ; PCI = peritoneal cancer index

### **Supplementary file 2**

Title: Forest plot of the effect of the side of the primary CRC on progression-free survival across subgroups.

Footnotes : HR = Hazard ratio ; PFS=progression-free survival ;  
CC=completeness of cytoreduction ; HIPEC = hyperthermic intraperitoneal chemotherapy ; P value for interaction test ; PCI = peritoneal cancer index

## **Conflict of interest statement :**

None declared

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**ELSEVIER EDITORS PLEASE MAKE AN ADDITIONAL COLUMN IN THE TABLE BETWEEN “Variable” AND “All” called “Data not available” AND IN THAT COLUMN PUT THE NUMBER OF THE ABBREVIATION THEY USED CALLED NA  
FOR INSTANCE, FOR THE FIRST ROW “Age, years, median (25th-&5th)” THE VALUE WOULD BE 0 FOR THE THIRD ROW “Synchronous peritoneal metastases (%)” IT WOULD BE 37 THEN DELETE ALL THE “NA=x “IN THE FIRST COLUMN THANKS!**

**TABLE 1 Patient characteristics according to primary tumor location**

Variable	All (n=796)	Location of primry CRC		P
		Right-sided (n=306)	Left-sided (n = 490)	
Age, years, median (25 <sup>th</sup> -75 <sup>th</sup> ) NA=0	59 (51-65)	59 (51-65)	59 (51-65)	0.82
Sex male (%) NA=0	387 (49%)	147 (48%)	240 (49%)	0.85
Synchronous peritoneal metastases (%) NA=37	389 (51%)	162 (57%)	227 (48%)	0.017
Date of Cytoreductive surgery >=01/01/2012 (%) NA=0	427 (54%)	167 (55%)	260 (53%)	0.71
RAS mutation (%) NA=276	269 (52%)	110 (56%)	159 (49%)	0.15
BRAF mutation (%) NA=494	46 (15%)	24 (22%)	22 (11%)	0.018
MSI (%) NA=582	32 (15%)	19 (23%)	13 (10%)	0.0096
Signet-ring cells (%) NA=263	22 (4%)	14 (7%)	8 (2%)	0.011
Completeness of cytoreductive score (%) NA=60				0.94
CC0	702 (95%)	274 (95%)	428 (96%)	
CC1	34 (5%)	14 (5%)	20 (4%)	
HIPEC (%) NA=0	745 (94%)	284 (93%)	461 (94%)	0.57
PCI, median (25 <sup>th</sup> - 75 <sup>th</sup> ) NA=X	8 (4-13)	7 (4-14)	8 (4-13)	0.83
PCI>14 (%) NA=0	194 (24%)	82 (27%)	112 (23%)	0.23
Duration of	360 (282-450)	342 (262-	363 (300-	0.018

<b>operation,median (25<sup>th</sup>-75<sup>th</sup>) NA=197</b>		449)	450)	
<b>Major surgical complication (%) NA=58</b>	351 (48%)	140 (49%)	211 (47%)	0.60
<b>Preoperative chemotherapy (%) NA=0</b>	709 (89%)	272 (89%)	437 (89%)	0.91
<b>&gt; 6 preoperative chemotherapy cycles (%) NA=144</b>	307 (47%)	103 (43%)	204 (49%)	0.12
Preop oxaliplatin (%) NA=282	249 (54%)	93 (53%)	156 (54%)	0.92
Preop irinotecan (%) NA=282	165 (32%)	65 (33%)	100 (32%)	0.85
Preop anti-EGFR (%) NA=282	31 (6%)	13 (7%)	18 (6%)	0.71
Preop antiangiogenic (%) NA=282	119 (23%)	43 (22%)	76 (24%)	0.52
<b>Post-operative chemotherapy (%) NA=223</b>	380 (66%)	152 (71%)	28 (63%)	0.055

CC = completeness of cytoreduction ; PCI = peritoneal cancer index ; EGFR = Epidermal growth factor receptor ; MSI = microsatellite instability ; HIPEC = hyperthermic intraperitoneal chemotherapy

**ELSEVEIER EDITORS AGAIN CAN YOU MAKE A COLUMN OF THE “DATA NOT AVAILIABLE” TO FOLLOW THE FIRST COLUMN AS IN TABLE 1**

**Table 2** Prognostic factors of overall survival (OS) in univariate and multivariate analysis (Cox model).

Cox proportional hazards regression for overall survival						
		Unadjusted analysis			Adjusted Analysis	
	N (%)	3-years OS rate (%) (95% CI)	HR (95%CI)	P	HR (95%CI)	P
<b>Tumor side NA=0</b>						
Right side	306 (38%)	57 (51-64)	REF	0.90	REF 0.8 (0.6-1.1)	0.21
Left side	490 (62%)	62 (57-68)	1.0 (0.8-1.2)			
<b>Age (years) NA=0</b>						
< 60	422 (53%)	57 (52-63)	REF	0.15	NI	NI
>=60	373 (47%)	64 (58-70)	0.8 (0.7-1.1)			
<b>Date of Cytoreductive surgery NA=0</b>						
< 2012	369 (46%)	57 (51-62)	REF	0.034	REF 0.7 (0.5-1.0)	0.051
>=2012	427 (54%)	66 (60-72)	0.8 (0.6-1.0)			
<b>Carcinomatosis NA=37</b>						
Metachronous	370 (49%)	62 (57-68)	REF	0.21	NI	NI
Synchronous	389 (51%)	61 (56-67)	1.2 (0.9-1.5)			
<b>Pathologic subtype NA=263</b>						
No signet-ring cells	511 (96%)	62 (57-67)	REF	0.28	NI	NI
Signet-ring cells	22 (4%)	56 (38-82)	1.4 (0.8-2.4)			
<b>Completeness of cytoreduction score NA=60</b>						
CC0	702 (95%)	61 (57-66)	REF	0.0034	REF 1.2 (0.7-2.2)	0.45
CC1	34 (5%)	39 (25-61)	1.9 (1.1-2.8)			
CC1						
<b>HIPEC NA=0</b>						
No	51 (6%)	60 (47-76)	REF	0.75	NI	NI
Yes	745 (94%)	60 (56-65)	1.1 (0.7-1.6)			
<b>PCI NA=0</b>						
≤14	602 (76%)	68 (63-72)	REF	<0.000	REF 2.0 (1.4-2.8)	0.0001
	194 (24%)	39 (32-48)	2.3 (1.8-2.9)	1		

>14						
<b>Duration of operation</b> <b>NA=197</b>						
< 6 hours	327 (55%)	64 (58-70)	REF	0.0054	REF	0.18
>= 6 hours	272 (45%)	49 (42-57)	1.4 (1.1-1.8)		1.3 (0.9-1.8)	
<b>Major surgical complication NA=58</b>						
No	387 (52%)	64 (58-70)	REF	0.0002	REF	0.042
Yes	351 (48%)	53 (47-60)	1.5 (1.2-1.9)	3	1.4 (1.0-1.9)	
<b>Preoperative chemotherapy NA=0</b>						
No	87 (11%)	60 (49-73)	REF	0.92	NI	NI
Yes	709 (89%)	60 (56-65)	1.0 (0.7-1.4)			
<b>No preoperative cycles NA=144</b>						
<=6	345 (53%)	59 (53-66)	REF	1.0	NI	NI
>6	307 (47%)	62 (56-68)	1.0 (0.8-1.3)			
<b>Postoperative chemotherapy NA=223</b>						
No	193 (34%)	58 (50-66)	REF	0.043	REF	0.35
Yes	380 (66%)	58 (52-65)	0.8 (0.6-1.0)		0.9 (0.6-1.2)	

HR=Hazard ration ; CI = confidence interval ; OS = overall survival ; MSI = microsatellite instability ; NI = Not included ; PCI = peritoneal carcinoma index ; HIPEC = hyperthermic intraperitoneal chemotherapy ; REF = Reference

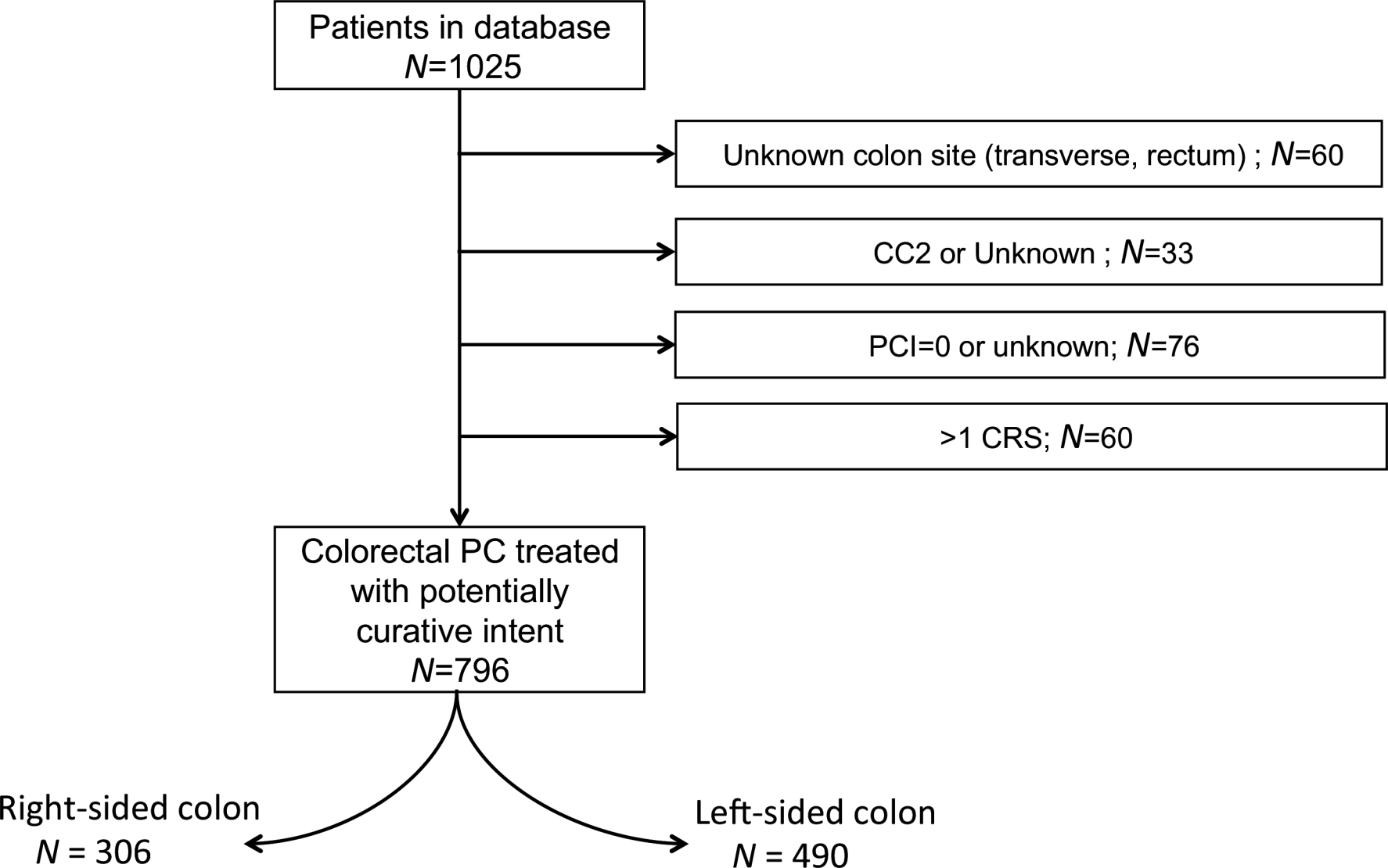
**ELSEVIER EDITORS AGAIN ADD A COLUMN AFTER m(%) CALLED “Data not available” AS IN TABLES 1 AND 2**

**Table 3** Prognostic factors of progression-free survival in univariate and multivariate analysis (Cox model).

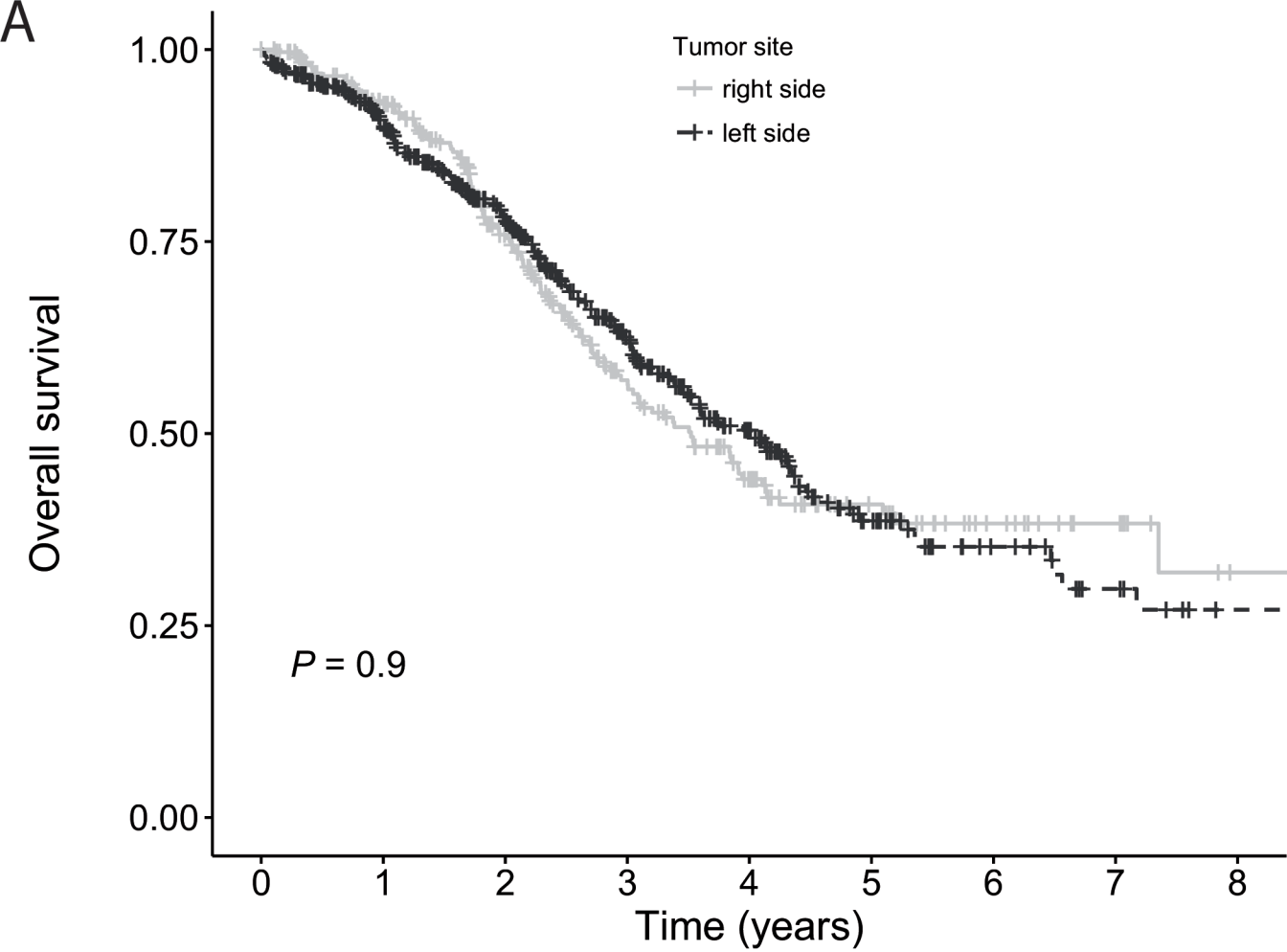
Cox proportional hazards regression for progression-free survival						
			Unadjusted analysis		Adjusted Analysis	
	N (%)	3-years PFS rate (%) (95% CI)	HR (95%CI)	P	HR (95%CI)	P
<b>Tumor side NA=0</b>						
Right side	306 (38%)	26 (20-32)	REF	0.84	REF	0.24
Left side	490 (62%)	24 (20-30)	1.0 (0.8-1.2)			
<b>Age (years) NA=0</b>						
< 60	422 (53%)	23 (19-29)	REF	0.036	REF	0.26
>=60	373 (47%)	27 (22-34)	0.8 (0.7-1.0)			
<b>Date of Cytoreductive surgery NA=0</b>						
< 2012	369 (46%)	21 (16-26)	REF	0.019	REF	0.021
>=2012	427 (54%)	31 (25-37)	0.8 (0.7-1.0)			
<b>Carcinomatosis NA=37</b>						
Metachronous	370 (49%)	28 (22-34)	REF	0.15	NI	NI
Synchronous	389 (51%)	24 (19-29)	1.1 (1.0-1.4)			
<b>Pathological subtype NA=263</b>						
No signet-ring cells	511 (96%)	27 (23-33)	REF	0.56	NI	NI
Signet-ring cells	22 (4%)	20 (8-48)	1.1 (0.7-1.8)			
<b>Completeness of cytoreduction score NA=60</b>						
CC0	702 (95%)	24 (21-29)	REF	0.018	REF	0.40
CC1	34 (5%)	7 (2-26)	1.6 (1.1-2.4)			
CC1						
<b>HIPEC NA=0</b>						
No	51 (6%)	20 (11-35)	REF	0.94	NI	NI
Yes	745 (94%)	26 (22-30)	1.0 (0.7-1.4)			
<b>PCI NA=0</b>						
≤14	602 (76%)	30 (25-35)	REF	<0.000	REF	<0.000

>14	194 (24%)	13 (8-20)	1.8 (1.5-2.2)		1.7 (1.3-2.2)	1
<b>Duration of operation</b> <i>NA=197</i>	327 (55%)	25 (20-31)	REF	0.57	NI	NI
< 6 hours	272 (45%)	30 (24-39)	0.9 (0.7-1.2)			
>= 6 hours						
<b>Major surgical complication</b> <i>NA=58</i>	387 (52%)	30 (25-36)	REF	0.0002	REF	0.012
No	351 (48%)	19 (14-26)	1.4 (1.2-1.8)	7	1.3 (1.1-1.7)	
Yes						
<b>Preoperative chemotherapy</b> <i>NA=0</i>	87 (11%)	24 (16-37)	REF	0.99	NI	NI
No	709 (89%)	25 (22-30)	1.0 (0.8-1.3)			
Yes						
<b>No preoperative cycles</b> <i>NA=144</i>	345 (53%)	28 (22-35)	REF	0.014	REF	0.015
<=6	307 (47%)	23 (18-29)	1.3 (1.1-1.6)		1.3 (1.1-1.7)	
>6						
<b>Postoperative chemotherapy</b> <i>NA=223</i>	193 (34%)	25 (19-33)	REF	0.0027	REF	0.010
No	380 (66%)	25 (20-32)	0.7 (0.6-0.9)		0.7 (0.6-0.9)	
Yes						

HR=Hazard ration ; CI = confidence interval ; PFS = progression-free survival ; MSI = microsatellite instability ; NI = Not included ; PCI = peritoneal carcinoma index ; HIPEC = hyperthermic intraperitoneal chemotherapy ; REF = Reference



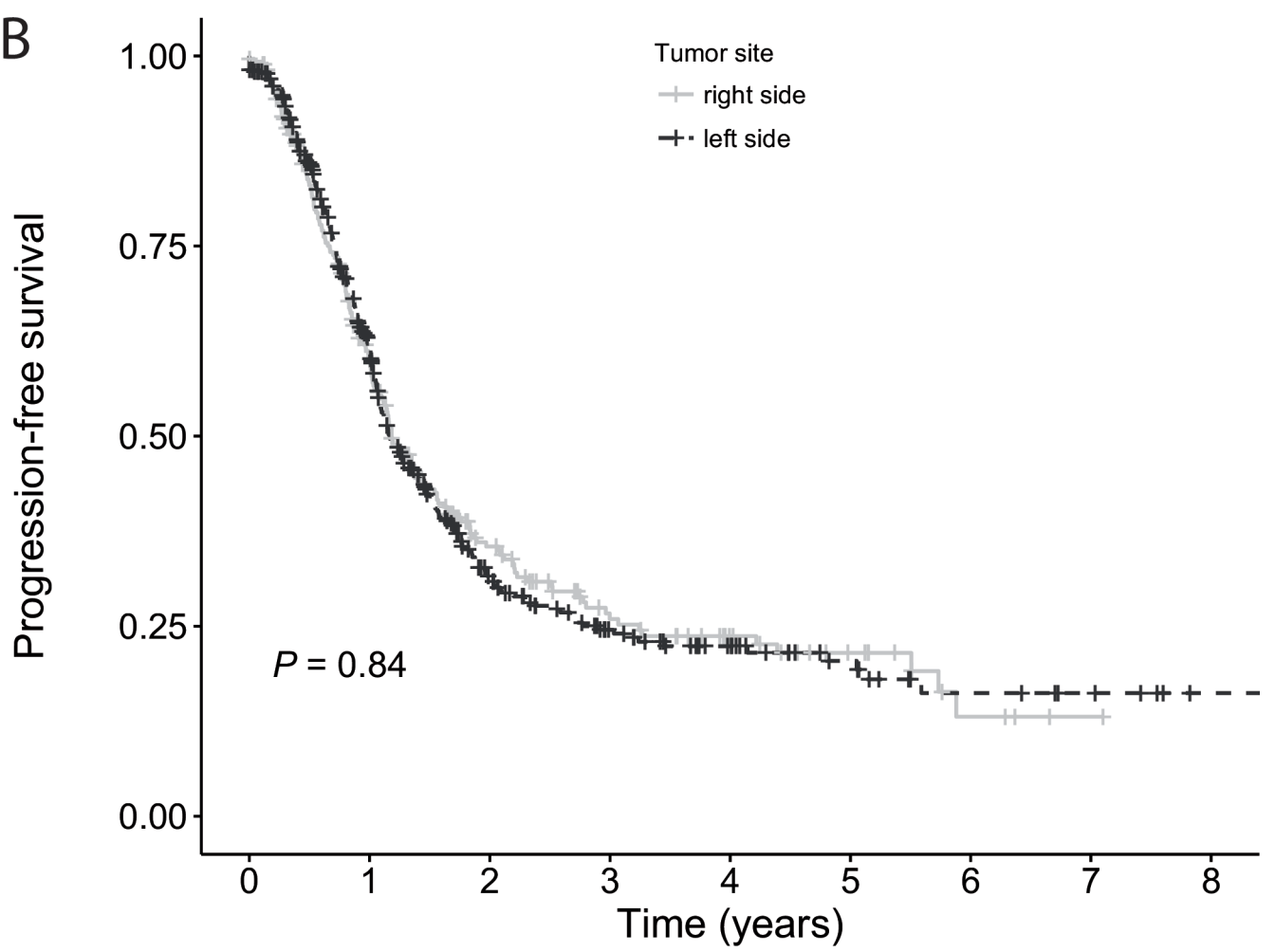




Number at risk

Time (years)	0	1	2	3	4	5	6	7	8
right side	306	247	164	95	60	35	19	11	3
left side	490	383	267	163	94	44	23	13	6

Tumor site



Number at risk

Time (years)	0	1	2	3	4	5	6	7	8
right side	269	143	64	35	23	13	4	1	0
left side	434	222	85	48	31	18	9	6	1

Tumor site