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

Julien Peron, Frédéric Mercier, Jean-Jacques Tuech, Rami Younan, Lucas Sideris, Maximiliano Gelli, Frédéric Dumont, Bertrand Le Roy, Olivia Sgarbura, Réa Lo Dico, et al.

(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

J Péron, MD, PhD [1,2,3,4,5], F Mercier, MD [6], J.J Tuech, MD, PhD [5,7], R Younan, MD, PhD [6], L Sideris, MD, PhD [8], M Gelli, MD [5,9], F Dumont, MD, PhD [5,10], B Le Roy, MD [5,11], O Sgarbura, MD, PhD [5,12], R Lo Dico, MD, PhD [5,13,14], F Bibeau [15], O Glehen, MD, PhD [3,5,16,17], G Passot, MD, PhD [3,5,16,17], on behalf BIG RENAPE* working groups

[1] Hospices Civils de Lyon, Oncology department, Pierre-Benite, France.

[2] Hospices Civils de Lyon, Service de Biostatistique et Bioinformatique, Lyon, France.

[3] Université Lyon 1, Villeurbanne, France.

[4] CNRS, UMR 5558, Laboratoire de Biométrie et Biologie Evolutive, Equipe Biostatistique-Santé, Villeurbanne, France.

[5] BIG-RENAPE Working Group. All collaborators of BIG-RENAPE Working Group are listed at the end of the manuscript.

[6] Department of Surgical Oncology, Centre Hospitalier de l'Université de Montréal, Montreal, Quebec, Canada.

[7] Department of Surgery, Rouen University Hospital, Rouen, France.

[8] Department of Surgery, Hôpital Maisonneuve-Rosemont, Université de Montréal, Montreal, Quebec, Canada.

[9] Institut Gustave Roussy, Department of Surgical Oncology, Villejuif, France.

[10] ICO – Centre René Gauducheau, Department of Surgical Oncology, St Herblain, France.

[11] CHU Estaing, Department of Digestive Surgery, Clermont-Ferrand, France.

[12] Institut de Cancer Montpellier, Department of Surgical Oncology, Montpellier, France; University of Montpellier.

[13] Service de Chirurgie Digestive et Cancérologique Hôpital Lariboisière.

[14] Unité INSERM U965 / CART / Paris 7 Diderot Carcinose Angiogenèse et Recherche translationnelle ; Paris, France.

[15] Pathology Department, Caen University Hospital, Caen, France.

[16] Hospices Civils de Lyon, Department of General Surgery, Centre Hospitalier Lyon Sud, Pierre Bénite, France.

[17] EMR 3738, Lyon 1 University, Lyon, France.

Corresponding author:

Dr Julien Péron

Service d'Oncologie Médicale, Centre Hospitalier Lyon-Sud, Hospices Civils de Lyon, F-69310. 165, chemin du grand revoyet 69495 Pierre-Bénite, France

Tel: +33.(0)4.78.86.43.18

Fax: +33.(0)4.78.86.43.56

E-mail: julien.peron@chu-lyon.fr

Word count for text only: 2500

Declarations of interest: none

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 rilas 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 [1]Biologic characteristics of left-sided CRC (LC) and right-sided CRC (RC) differ substantially. Differences in the microbiome [2], and carcinogenesis [3] 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 [4, 5] ,and less frequently NRAS and p53 mutations [5, 6].

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 [7–9]. In the metastatic setting, LS CRCis also associated with a significantly decreased risk of death [10, 11].; these observations appear to be independent of the mutational spectrum within these CRCs [11–14].

Some patients with CRC peritoneal metastases are candidates for surgery with the potential for long-term survival and cure [15, 16]. 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 metstases [17].

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 [18]. Patients were excluded when the side 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 [18], 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[19]. RAS and BRAF mutation were tested in most patients since late 2008, according to French clinical practice [20]. 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 oxalipatin (360mg/m2 for 30 min) or mitomycin C (35mg/m2 for 90 min). PCI was scored during the cytoreductive surgery and extracted from the operative reports [18]. 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 ≥ 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 [21]. 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 ≤ 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 ≤ 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, 0.74with 95% CI of 0.52 to 1.0, tending to *P*=0.096 favor the LS tumor group (p=0.096); ≥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 ≤ 14, absence of a major surgical complication, number of preoperative chemotherapy cycles ≤ 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 ≤ 14, absence of a major surgical complication, number of preoperative chemotherapy cycles ≤ 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 [4]. 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 [22], palliative chemotherapy [10, 11, 23], and those undergoing curative resection of liver metastases [24–26]. The unfavorable outcomes of patients with RS CRCs has been

demonstrated among RAS wild type (WT) patients [25, 27]. Moreover, for patients with RAS WT CRCs, the left side is also predictive of a greater efficacy of anti-EGFR treatment [27, 28] . 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 [29–31], but these same RS mutations do not affect outcomes among patients undergoing resection of CRC peritoneal metastasis [29]. 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 [11, 19, 32, 33] 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 [34, 35]. 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 [24, 36] 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 [37]. 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 Prodige 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, r the consistent lack of impact of eh 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 [38]. 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, andthus the results cannot be applied to these patient populations.

.

Acknowledgments and funding

The BIG-RENAPE Biobank was established with the support of the French National Cancer Institute (INCa) - Grant for the constitution of clinical and biological databases nationwide in cancer (2013-195).

The authors thank Peggy Jourdan-Enfer for their expert help with data collection.

Collaborators (online version only)

* The collaborators of the BIG-RENAPE working group include:

Julio Abba, MD (Department of Digestive Surgery, Grenoble University Hospital, Grenoble, France); Karine Abboud, MD (Department of General Surgery, St Etienne University Hospital, St Etienne, France); Mourad Abdallah (Department of Pathology, Estaing University Hospital, Clermont-Ferrand, France); Mohammad Alyami, MD (Department of Digestive Surgery, Lyon-Sud University Hospital, Lyon, France); Catherine Arvieux, MD, PhD (Department of Digestive

Surgery, Grenoble University Hospital, Grenoble, France); Amani Asnacios, MD (Department of Gastoenterology, Curie Institute, Paris, France); Gerlinde Averous, MD (Department of Pathology, Hautepierre University Hospital, Strasbourg, France); Armelle Bardier, MD (Department of Pathology, La Pitié-Salpétrière University Hospital, Paris, France); Houda Ben Rejeb, MD (Department of Pathology, Bergonie Institute, Bordeaux, France); Jean-Marc Bereder, MD, PhD (Department of Digestive Surgery, Archet 2 University Hospital, Nice, France); Jean-Louis Bernard, MD (Department of Digestive Surgery, Archet 2 University Hospital, Nice, France); Frédéric Bibeau, MD, PhD (Department of Pathology, Caen University Hospital, Caen, France); Isabelle Bonnefoy (Department of Digestive Surgery, Lyon-Sud University Hospital, Lyon, France); Christophe Borg, MD, PhD (Department of Medical Oncology, Jean Minjoz University Hospital, Besançon, France); Nadia Bouarioua, MD (Department of Gastoenterology, St Etienne University Hospital, St Etienne, France); Olivier Bouche, MD, PhD (Department of Gastoenterology, Robert Debré University Hospital, Reims, France); Dominique Bouzard, MD, (Department of Digestive Surgery, Louis Mourier University Hospital, Colombes, France); Cécile Brigand, MD, PhD (Department of Digestive Surgery, Hautepierre University Hospital, Strasbourg, France); Wulfran Cacheux, MD (Department of Gastoenterology, Curie Institute, Paris, France); Olivier Capitain, MD (Department of Medical Oncology, ICO Paul Papin Cancer Center, Angers, France); Sébastien Carrère, MD (Department of Surgical Oncology, Val d'Aurelle Montpellier Cancer Center, Montpellier, France); Michel Carretier, MD, PhD (Department of Digestive Surgery, Poitiers University Hospital, Poitiers, France); Benjamin Castel, MD (Department of Digestive Surgery, Louis Mourier University

Hospital, Colombes, France); Marion Chauvenet, MD, PhD (Department of Gastoenterology, Lyon-Sud University Hospital, Lyon, France); Anne Chevallier, MD (Department of Pathology, Archet 2 University Hospital, Nice, France); Virginie Cloud (Department of Digestive Surgery, Lyon-Sud University Hospital, Lyon, France); Benoît Coffin, MD (Department of Gastoenterology, Louis Mourier University Hospital, Colombes, France); Cristina Costan, MD (Department of Medical Oncology, Grenoble University Hospital, Grenoble, France); Thomas Courvoisier, MD (Department of Digestive Surgery, Poitiers University Hospital, Poitiers, France); Laetitia Dahan, MD (Department of Medical Oncology, Timône University Hospital, Marseille, France); Peggy Dartigues, MD (Department of Pathology, Gustave Roussy Institute, Villejuif, France); Cécile De Chaisemartin, MD (Department of Surgical Oncology, Paoli Calmettes Institute, Marseille, France); Pierre Dechelotte, MD, PhD (Department of Pathology, Estaing University Hospital, Clermont-Ferrand, France); Sophie Deguelte-Lardière, MD (Department of Digestive Surgery, Robert Debré University Hospital, Reims, France); Jean-Robert Delpero, MD (Department of Surgical Oncology, Paoli Calmettes Institute, Marseille, France); Jean Del Grande, MD (Department of Pathology, Timône University Hospital, Marseille, France); Jean-Baptiste Delhorme, MD (Department of Digestive Surgery, Hautepierre University Hospital, Strasbourg, France); Martin Demarchi, MD (Department of Medical Oncology, Jean Minjoz University Hospital, Besançon, France); Emmanuel Desandes, MD (Department of Medical Oncology, Lorraine Cancer Institute, Vandoeuvre-les-Nancy France); Grégoire Desolneux, MD (Department of Surgical Oncology, Bergonie Institute, Bordeaux, France); Patrick Dufour, MD (Department of Medical Oncology, Paul Strauss Comprehensive Cancer Center,

Strasbourg, France); Sylvaine Durand-Fontanier, MD (Department of Visceral Surgery and Transplantation, Dupuytren University Hospital, Limoges, France); Clarisse Eveno, MD, PhD (Surgical Oncologic & Digestive Unit, Lariboisière University Hospital, Paris, France); Serge Evrard, MD, PhD (Department of Surgical Oncology, Bergonie Institute, Bordeaux, France); Olivier Facy, MD, PhD (Department of Digestive Surgical Oncology, University Hospital of Dijon, Dijon, France); Fereshteh Farkhondeh, MD (Department of Pathology, Curie Institute, Paris, France); Juliette Fontaine, MD (Department of Pathology, Lyon-Sud University Hospital, Lyon, France); Johan Gagniere, MD (Department of Digestive Surgery, Estaing University Hospital, Clermont-Ferrand, France); Marie-Pierre Galais, MD (Department of Medical Oncology, François Baclesse Comprehensive Cancer, Caen, France); Kelly Garbis (Hôpital Maisonneuve-Rosemont, Department of Surgery; Université de Montréal, Montreal, Quebec, Canada); Laurent Ghouti, MD (Department of Digestive Surgery, Purpan University Hospital, Toulouse, France); François-Noël Gilly, MD, PhD (Department of Digestive Surgery, Lyon-Sud University Hospital, Lyon, France); Nicolas Goasguen, MD (Department of General Surgery, Diaconesses Croix Saint Simon Group Hospital, Paris, France); Diane Goere, MD, PhD (Department of Surgical Oncology, Gustave Roussy Institute, Villejuif, France); Jean-Marc Gornet, MD, PhD (Department of Medical Oncology, Saint Louis University Hospital, Paris, France); Pierre Gourdiole, MD (Department of Digestive Surgery, Grenoble University Hospital, Grenoble, France); Caroline Gronnier, MD (Department of Surgical Oncology, CHRU Claude Huriez, Lille, France); Véronique Guerin-Meyer, MD (Department of Medical Oncology, ICO Paul Papin Cancer Center, Angers, France); Jean-Marc Guilloit, MD (Department of Surgical Oncology, François

Baclesse Comprehensive Cancer, Caen, France); Rosine Guimbaud, MD, PhD (Department of Medical Oncology, Rangueil University Hospital, Toulouse, France); Frédéric Guyon, MD (Department of Surgical Oncology, Bergonie Institute, Bordeaux, France); Bruno Heyd, MD, PhD (Department of Digestive Surgery, Jean Minjoz University Hospital, Besançon, France); Marie-Françoise Heymann, MD (Department of Pathology, Nantes University Hospital, Nantes, France); Sylvie Isaac, MD (Department of Pathology, Lyon-Sud University Hospital, Lyon, France); Pauline Jouet, MD (Department of Gastoenterology, Louis Mourier University Hospital, Colombes, France); Peggy Jourdan-Enfer (Department of Digestive Surgery, Lyon-Sud University Hospital, Lyon, France); Jean-Louis Jouve, MD (Department of Gastoenterology, University Hospital of Dijon, Dijon, France); Rachid Kaci, MD (Department of Pathology, Lariboisière University Hospital, Paris, France); Mehdi Karoui, MD, PhD (Department of Surgery, La Pitié-Salpétrière University Hospital, Paris, France); Reza Kianmanesh, MD, PhD (Department of Digestive Surgery, Robert Debré University Hospital, Reims, France); Sylvain Kirzin, MD, PhD (Department of Digestive Surgery, Purpan University Hospital, Toulouse, France); Jean-Emmanuel Kurtz, MD, PhD (Department of Medical Oncology, Hautepierre University Hospital, Strasbourg, France); François Labrousse, MD, PhD (Department of Pathology, Dupuytren University Hospital, Limoges, France); Valérie Lebrun-Ly, MD (Department of Medical Oncology, Dupuytren University Hospital, Limoges, France); Jérémie Lefevre, MD, PhD (Department of Digestive Surgery, University Hospital Saint Antoine, Paris, France); Bernard Lelong, MD (Department of Surgical Oncology, Paoli Calmettes Institute, Marseille, France); Anne-Elisabeth Lemaistre, MD (Department of Pathology, Léon Bérard

Comprehensive Cancer Center, Lyon, France); Agnès Leroux-Broussier, MD (Department of Pathology, Lorraine Institute of Oncology, Vandoeuvre-les-Nancy, France); Pierre Levillain, MD, PhD (Department of Pathology, Poitiers University Hospital, Poitiers, France); Benjamin Linot, MD (Department of Medical Oncology, ICO Paul Papin Cancer Center, Angers, France); Valéria Loi, MD (Department of Digestive Surgery, Tenon University Hospital, Paris, France); Gérard Lorimier, MD (Department of Digestive Surgery, University Hospital, Angers, France); Abakar Mahammat, MD (Department of Medical Oncology, Archet 2 University Hospital, Nice, France); David Malka, MD (Department of Medical Oncology, Gustave Roussy Institute, Villejuif, France); Frédéric Marchal, MD, PhD (Department of Surgical Oncology, Lorraine Cancer Institute, Vandoeuvre-les-Nancy France); Antoine Mariani, MD (Department of Surgery, La Pitié-Salpétrière University Hospital, Paris, France); Pascale Mariani, MD (Department of Surgical Oncology, Curie Institute, Paris, France); Laurent Martin, MD, PhD (Department of Pathology, University Hospital of Dijon, Dijon, France); Pierre Meeus, MD (Department of Surgery, Léon Bérard Comprehensive Cancer Center, Lyon, France); Jean-Luc Meffert, MD (Department of Digestive Surgery, Robert Debré University Hospital, Reims, France); Mathieu Messager, MD, PhD (Department of Digestive and Oncological Surgery, University Hospital Claude Huriez, Lille, France); Pierre Michel, MD, PhD (Department of Gastroenterology, Charles Nicolle University Hospital, Rouen, France); Simon Msika, MD, PhD (Department of Digestive Surgery, Louis Mourier University Hospital, Colombes, France); Thierry Muron, MD (Department of Medical Oncology, Cancer Loire Cancer Institute, Saint Priest-en-Jarez, France); Georges Noel, MD (Department of Medical Oncology, Paul Strauss Comprehensive Cancer Center, Strasbourg,

France); Pablo Ortega-Deballon, MD, PhD (Department of Digestive Surgical Oncology, University Hospital of Dijon, Dijon, France); Brice Paquette, MD (Department of Digestive Surgery, Jean Minjoz University Hospital, Besançon, France); Caroline Petorin, MD (Department of Digestive Surgery, Estaing University Hospital, Clermont-Ferrand, France); Patrice Peyrat, MD (Department of Surgery, Léon Bérard Comprehensive Cancer Center, Lyon, France); Denis Pezet, MD, PhD (Department of Digestive Surgery, Estaing University Hospital, Clermont-Ferrand, France); Guillaume Piessen, MD, PhD (Department of Digestive and Oncological Surgery, University Hospital Claude Huriez, Lille, France); Nicolas Pirro, MD, PhD (Department of Digestive Surgery, Timône University Hospital, Marseille, France); Marc Pocard, MD, PhD (Surgical Oncologic & Digestive Unit, Lariboisière University Hospital, Paris, France); Flora Poizat, MD (Department of Pathology, Paoli Calmettes Institute, Marseille, France); Jack Porcheron, MD, PhD (Department of Digestive Surgery, St Etienne University Hospital, St Etienne, France); Fabienne Portales, MD (Department of Medical Oncology, Montpellier Cancer Institute, Montpellier, France); Justine Prost a la Denise, MD (Department of Digestive Surgery, Georges Pompidou University Hospital, Paris, France); François Quenet, MD (Department of Surgical Oncology, Montpellier Cancer Institute, Montpellier, France); Patrick Rat, MD, PhD (Department of Digestive Surgical Oncology, University Hospital of Dijon, Dijon, France); Christine Rebischung, MD, PhD (Department of Medical Oncology, Grenoble University Hospital, Grenoble, France); Jean-Marc Regimbeau, MD, PhD (Department of Digestive Surgery, University Hospital of Amiens, Amiens, France); Romain Rivoirard, MD (Department of Medical Oncology, Cancer Loire Cancer Institute, Saint Priest-en-Jarez, France); Samuel Rodriguez-Qizilbash

(Hôpital Maisonneuve-Rosemont, Department of Surgery; Université de Montréal, Montreal, Quebec, Canada); Serge Rohr, MD, PhD (Department of Digestive Surgery, Hautepierre University Hospital, Strasbourg, France); Philippe Rougier, MD, PhD (Department of Medical Oncology, Georges Pompidou University Hospital, Paris, France); Pierre Rousselot, MD (Department of Pathology, Francois Baclesse Comprehensive Cancer Center, Caen, France); Léa Saban-Roche, MD (Department of Medical Oncology, Cancer Loire Cancer Institute, Saint Priest-en-Jarez, France); Jean-Marc Sabate, MD, PhD (Department of Gastroenterology, Louis Mourier University Hospital, Colombes, France); Charles Sabbagh, MD (Department of Digestive Surgery, University Hospital of Amiens, Amiens, France); Jean-Christophe Sabourin, MD, PhD (Department of Pathology, Charles Nicolle University Hospital, Rouen, France); Emmanuelle Samalin-Scalzi, MD (Department of Medical Oncology, Montpellier Cancer Institute, Montpellier, France); Lilian Schwarz, MD, PhD (Department of Digestive Surgery, Charles Nicolle University Hospital, Rouen, France); Jean-François Seitz, MD, PhD (Department of Digestive Surgery, Timône University Hospital, Marseille, France); Janick Selves, MD, PhD (Department of Pathology, Toulouse University Hospital, Toulouse, France); Helène Senellart, MD (Department of Medical Oncology, ICO René Gauducheau Cancer Center, Saint-Herblain, France); Martine Serrano (Department of Digestive Surgery, Lyon-Sud University Hospital, Lyon, France); Igor Sielezneff, MD, PhD (Department of Digestive Surgery, Timône University Hospital, Marseille, France); Magali Svrcek, MD, PhD (Department of Pathology, Saint Antoine University Hospital, Paris, France); Abdelkader Taibi, MD (Department of Visceral Surgery and Transplantation, Dupuytren University Hospital, Limoges, France); Julien Taieb,

MD, PhD (Department of Medical Oncology, Georges Pompidou University Hospital, Paris, France); Emilie Thibaudeau, MD (Department of Surgical Oncology, ICO René Gauducheau Cancer Center, Saint-Herblain, France); David Tougeron, MD (Department of Gastroenterology, Poitiers University Hospital, Poitiers, France); Jean-Jacques Tuech, MD, PhD (Department of Digestive Surgery, Charles Nicolle University Hospital, Rouen, France); Séverine Valmary-Degano, MD, PhD (Department of Pathology, Jean Minjoz University Hospital, Besançon, France); Delphine Vaudoyer, MD (Department of Digestive Surgery, Lyon-Sud University Hospital, Lyon, France); Véronique Verriele-Beurrier, MD (Department of Pathology, ICO Paul Papin Cancer Center, Angers, France); Laurent Villeneuve (Hospices Civils de Lyon, Pôle Information Médicale Evaluation Recherche, Unité de Recherche Clinique, Lyon, France); Julien Volet, MD (Department of Gastroenterology, Robert Debré University Hospital, Reims, France); Romuald Wernert, MD (Department of Surgical Oncology, ICO Paul Papin Cancer Center, Angers, France); Marc Ychou, MD, PhD (Department of Medical Oncology, Montpellier Cancer Institute, Montpellier, France); Benoît You, MD, PhD (Department of Medical Oncology, Lyon-Sud University Hospital, Lyon, France); Aziz Zaanan, MD (Department of Medical Oncology, Georges Pompidou University Hospital, Paris, France); Franck Zinzindohoue, MD, PhD (Department of Digestive Surgery, Georges Pompidou University Hospital, Paris, France);

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.

Foornotes : 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 CRCon progression-free survival across subgroups.

Foornotes : 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

References

1. Bufill JA: Colorectal cancer: evidence for distinct genetic categories based on proximal or distal tumor location. [Internet]. Ann Intern Med 113:779–88, 1990[cited 2017 Dec 7] Available from: http://www.ncbi.nlm.nih.gov/pubmed/2240880

2. Gao Z, Guo B, Gao R, et al: Microbiota disbiosis is associated with colorectal cancer [Internet]. Front Microbiol 6:20, 2015[cited 2017 Dec 7] Available from: http://www.ncbi.nlm.nih.gov/pubmed/25699023

3. Yamauchi M, Morikawa T, Kuchiba A, et al: Assessment of colorectal cancer molecular features along bowel subsites challenges the conception of distinct dichotomy of proximal versus distal colorectum [Internet]. Gut 61:847–854, 2012[cited 2017 Dec 7] Available from: http://www.ncbi.nlm.nih.gov/pubmed/22427238

4. Sinicrope FA, Mahoney MR, Yoon HH, et al: Analysis of Molecular Markers by Anatomic Tumor Site in Stage III Colon Carcinomas from Adjuvant Chemotherapy Trial NCCTG N0147 (Alliance) [Internet]. Clin Cancer Res 21:5294–5304, 2015[cited 2017 Dec 7] Available from: http://www.ncbi.nlm.nih.gov/pubmed/26187617

5. Loree JM, Pereira A AL, Lam M, et al: Classifying colorectal cancer by tumor location rather than sidedness highlights a continuum in mutation profiles and Consensus Molecular Subtypes [Internet]. Clin Cancer Res clincanres.2484.2017, 2017[cited 2017 Dec 8] Available from: http://www.ncbi.nlm.nih.gov/pubmed/29180604

6. Soong R, Powell B, Elsaleh H, et al: Prognostic significance of TP53 gene mutation in 995 cases of colorectal carcinoma. Influence of tumour site, stage,

adjuvant chemotherapy and type of mutation. [Internet]. Eur J Cancer 36:2053–60, 2000[cited 2017 Dec 7] Available from: http://www.ncbi.nlm.nih.gov/pubmed/11044641

7. Weiss JM, Pfau PR, O'Connor ES, et al: Mortality by Stage for Right- Versus Left-Sided Colon Cancer: Analysis of Surveillance, Epidemiology, and End Results–Medicare Data [Internet]. J Clin Oncol 29:4401–4409, 2011[cited 2017 Dec 7] Available from: http://www.ncbi.nlm.nih.gov/pubmed/21969498

8. Benedix F, Kube R, Meyer F, et al: Comparison of 17,641 Patients With Right- and Left-Sided Colon Cancer: Differences in Epidemiology, Perioperative Course, Histology, and Survival [Internet]. Dis Colon Rectum 53:57–64, 2010[cited 2017 Dec 7] Available from: http://www.ncbi.nlm.nih.gov/pubmed/20010352

9. Brungs D, Aghmesheh M, de Souza P, et al: Sidedness is prognostic in locoregional colon cancer: an analysis of 9509 Australian patients. [Internet]. BMC Cancer 17:251, 2017[cited 2017 Dec 7] Available from: http://bmccancer.biomedcentral.com/articles/10.1186/s12885-017-3255-z

10. Petrelli F, Tomasello G, Borgonovo K, et al: Prognostic Survival Associated With Left-Sided vs Right-Sided Colon Cancer [Internet]. JAMA Oncol 3:211, 2017[cited 2017 Dec 7] Available from: http://www.ncbi.nlm.nih.gov/pubmed/27787550

11. Alan P. Venook, Donna Niedzwiecki, Federico Innocenti, Briant Fruth, Claire Greene BHO: Impact of primary (1^{o}) tumor location on overall survival (OS) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): Analysis of CALGB/SWOG 80405 (Alliance) [Internet]. ASCO Annu Meet J Clin Oncol 34:3504–3504, 2016[cited 2017 Dec 28] Available from: https://www.researchgate.net/publication/309050962_Impact_of_primary_1_tu

mor_location_on_overall_survival_OS_and_progression-free_survival_PFS_in_patients_pts_with_metastatic_colorectal_cancer_mCRC_Analysis_of_CALGBSWOG_80405_Alliance

12. Boeckx N, Koukakis R, Op de Beeck K, et al: Primary tumor sidedness has an impact on prognosis and treatment outcome in metastatic colorectal cancer: results from two randomized first-line panitumumab studies. [Internet]. Ann Oncol Off J Eur Soc Med Oncol 28:1862–1868, 2017[cited 2017 Dec 7] Available from: http://academic.oup.com/annonc/article/28/8/1862/3752514/Primary-tumor-sidedness-has-an-impact-on-prognosis

13. von Einem JC, Heinemann V, von Weikersthal LF, et al: Left-sided primary tumors are associated with favorable prognosis in patients with KRAS codon 12/13 wild-type metastatic colorectal cancer treated with cetuximab plus chemotherapy: an analysis of the AIO KRK-0104 trial [Internet]. J Cancer Res Clin Oncol 140:1607–1614, 2014[cited 2017 Dec 7] Available from: http://www.ncbi.nlm.nih.gov/pubmed/24816724

14. Tejpar S, Stintzing S, Ciardiello F, et al: Prognostic and Predictive Relevance of Primary Tumor Location in Patients With *RAS* Wild-Type Metastatic Colorectal Cancer [Internet]. JAMA Oncol 3:194, 2017[cited 2017 Dec 7] Available from: http://www.ncbi.nlm.nih.gov/pubmed/27722750

15. Shida D, Tsukamoto S, Ochiai H, et al: Long-Term Outcomes After R0 Resection of Synchronous Peritoneal Metastasis from Colorectal Cancer Without Cytoreductive Surgery or Hyperthermic Intraperitoneal Chemotherapy. [Internet]. Ann Surg Oncol , 2017[cited 2017 Dec 7] Available from: http://link.springer.com/10.1245/s10434-017-6133-7

16. Goéré D, Malka D, Tzanis D, et al: Is There a Possibility of a Cure in Patients

With Colorectal Peritoneal Carcinomatosis Amenable to Complete Cytoreductive Surgery and Intraperitoneal Chemotherapy? [Internet]. Ann Surg 257:1065–1071, 2013[cited 2017 Dec 11] Available from: http://www.ncbi.nlm.nih.gov/pubmed/23299520

17. Villeneuve L, Jourdan-Enfer P, Bibeau F, et al: Biobank-based research on digestive peritoneal carcinomatosis (the BIG-RENAPE Biobank) [Internet]. J Peritoneum (and other serosal surfaces) 1, 2016[cited 2018 Jan 3] Available from: http://www.jperitoneum.org/index.php/joper/article/view/12

18. Jacquet P, Sugarbaker PH: Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. [Internet]. Cancer Treat Res 82:359–74, 1996[cited 2017 Dec 7] Available from: http://www.ncbi.nlm.nih.gov/pubmed/8849962

19. Stintzing S, Tejpar S, Gibbs P, et al: Understanding the role of primary tumour localisation in colorectal cancer treatment and outcomes [Internet]. Eur J Cancer 84:69–80, 2017[cited 2017 Dec 7] Available from: http://www.ncbi.nlm.nih.gov/pubmed/28787661

20. commission de la transparence H: Avis sur l'Erbitux, cetuximab [Internet], 2009[cited 2017 Dec 7] Available from: https://www.has-sante.fr/portail/upload/docs/application/pdf/2009-09/erbitux_-_ct-6366.pdf

21. Cancer colorectal métastatique | SNFGE.org - Société savante médicale française d'hépato-gastroentérologie et d'oncologie digestive [Internet][cited 2017 Dec 7] Available from: https://www.snfge.org/content/4-cancer-colorectal-metastatique

22. Price TJ, Beeke C, Ullah S, et al: Does the primary site of colorectal cancer impact outcomes for patients with metastatic disease? [Internet]. Cancer

121:830–835, 2015[cited 2017 Dec 7] Available from: http://www.ncbi.nlm.nih.gov/pubmed/25377235

23. Loupakis F, Yang D, Yau L, et al: Primary Tumor Location as a Prognostic Factor in Metastatic Colorectal Cancer [Internet]. JNCI J Natl Cancer Inst 107, 2015[cited 2017 Dec 7] Available from: http://www.ncbi.nlm.nih.gov/pubmed/25713148

24. Creasy JM, Sadot E, Koerkamp BG, et al: The Impact of Primary Tumor Location on Long-Term Survival in Patients Undergoing Hepatic Resection for Metastatic Colon Cancer [Internet]. Ann Surg Oncol , 2017[cited 2017 Dec 7] Available from: http://www.ncbi.nlm.nih.gov/pubmed/29181680

25. Sasaki K, Andreatos N, Margonis GA, et al: The prognostic implications of primary colorectal tumor location on recurrence and overall survival in patients undergoing resection for colorectal liver metastasis [Internet]. J Surg Oncol 114:803–809, 2016[cited 2017 Dec 7] Available from: http://www.ncbi.nlm.nih.gov/pubmed/27792291

26. Yamashita S, Brudvik KW, Kopetz SE, et al: Embryonic Origin of Primary Colon Cancer Predicts Pathologic Response and Survival in Patients Undergoing Resection for Colon Cancer Liver Metastases. [Internet]. Ann Surg 1, 2016[cited 2017 Dec 11] Available from: http://insights.ovid.com/crossref?an=00000658-900000000-96290

27. Arnold D, Lueza B, Douillard J-Y, et al: Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials† [Internet]. Ann Oncol 28:1713–1729, 2017[cited 2017 Dec 7] Available from: http://www.ncbi.nlm.nih.gov/pubmed/28407110

28. Brulé SY, Jonker DJ, Karapetis CS, et al: Location of colon cancer (right-sided versus left-sided) as a prognostic factor and a predictor of benefit from cetuximab in NCIC CO.17 [Internet]. Eur J Cancer 51:1405–1414, 2015[cited 2017 Dec 7] Available from: http://www.ncbi.nlm.nih.gov/pubmed/25979833

29. Passot G, Kim BJ, Glehen O, et al: Impact of RAS Mutations in Metastatic Colorectal Cancer After Potentially Curative Resection: Does Site of Metastases Matter? [Internet]. Ann Surg Oncol , 2017[cited 2017 Dec 7] Available from: http://www.ncbi.nlm.nih.gov/pubmed/29071660

30. Lièvre A, Bachet J-B, Le Corre D, et al: KRAS mutation status is predictive of response to cetuximab therapy in colorectal cancer. [Internet]. Cancer Res 66:3992–5, 2006[cited 2017 Dec 7] Available from: http://cancerres.aacrjournals.org/lookup/doi/10.1158/0008-5472.CAN-06-0191

31. Vauthey J-N, Zimmitti G, Kopetz SE, et al: RAS Mutation Status Predicts Survival and Patterns of Recurrence in Patients Undergoing Hepatectomy for Colorectal Liver Metastases [Internet]. Ann Surg 258:619–627, 2013[cited 2017 Dec 7] Available from: http://www.ncbi.nlm.nih.gov/pubmed/24018645

32. Holch JW, Ricard I, Stintzing S, et al: The relevance of primary tumour location in patients with metastatic colorectal cancer: A meta-analysis of first-line clinical trials [Internet]. Eur J Cancer 70:87–98, 2017[cited 2017 Dec 7] Available from: http://www.ncbi.nlm.nih.gov/pubmed/27907852

33. Venook AP, Niedzwiecki D, Lenz H-J, et al: Effect of First-Line Chemotherapy Combined With Cetuximab or Bevacizumab on Overall Survival in Patients With *KRAS* Wild-Type Advanced or Metastatic Colorectal Cancer [Internet]. JAMA 317:2392, 2017[cited 2017 Dec 28] Available from:

http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2017.7105

34. Fong Y, Fortner J, Sun RL, et al: Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. [Internet]. Ann Surg 230:309-18; discussion 318-21, 1999[cited 2017 Dec 7] Available from: http://www.ncbi.nlm.nih.gov/pubmed/10493478

35. Brudvik KW, Jones RP, Giuliante F, et al: RAS Mutation Clinical Risk Score to Predict Survival After Resection of Colorectal Liver Metastases [Internet]. Ann Surg 1, 2017[cited 2017 Dec 7] Available from: http://www.ncbi.nlm.nih.gov/pubmed/28549012

36. Dupré A, Malik HZ, Jones RP, et al: Influence of the primary tumour location in patients undergoing surgery for colorectal liver metastases [Internet]. Eur J Surg Oncol , 2017[cited 2017 Dec 8] Available from: http://www.ncbi.nlm.nih.gov/pubmed/29183640

37. Quenet F, Elias D, Roca L, et al: A UNICANCER phase III trial of hyperthermic intra-peritoneal chemotherapy (HIPEC) for colorectal peritoneal carcinomatosis (PC): PRODIGE 7. [Internet]. J Clin Oncol 36:LBA3503-LBA3503, 2018[cited 2018 Jul 17] Available from: http://ascopubs.org/doi/10.1200/JCO.2018.36.18_suppl.LBA3503

38. Guinney J, Dienstmann R, Wang X, et al: The consensus molecular subtypes of colorectal cancer [Internet]. Nat Med 21:1350–1356, 2015[cited 2017 Dec 29] Available from: http://www.ncbi.nlm.nih.gov/pubmed/26457759

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 (25th-75th) ***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 (25th-75th) ***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

operation,median (25th-75th) ***NA=197***		449)	450)	
Major surgical complication *(%)* *NA=58*	351 (48%)	140 (49%)	211 (47%)	0.60
Preoperative chemotherapy *(%)* *NA=0*	709 (89%)	272 (89%)	437 (89%)	0.91
> 6 preoperative chemotherapy cycles *(%) NA=144*	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
Post-operative chemotherapy *(%)* *NA=223*	380 (66%)	152 (71%)	28 (63%)	0.055

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

ELSEVEIER EDITORS AGAIN CAN YOU MAKE A COLUMN OF THE "DATA NOT AVALIABLE" 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*
Tumor side NA=0						
Right side	306 (38%)	57 (51-64)	REF	0.90	REF	0.21
Left side	490 (62%)	62 (57-68)	1.0 (0.8-1.2)		0.8 (0.6-1.1)	
Age (years) *NA=0*						
< 60	422 (53%)	57 (52-63)	REF	0.15	NI	NI
>=60	373 (47%)	64 (58-70)	0.8 (0.7-1.1)			
Date of Cytoreductive surgery *NA=0*						
< 2012	369 (46%)	57 (51-62)	REF	0.034	REF	0.051
>=2012	427 (54%)	66 (60-72)	0.8 (0.6-1.0)		0.7 (0.5-1.0)	
Carcinomatosis *NA=37*						
Metachronous	370 (49%)	62 (57-68)	REF	0.21	NI	NI
Synchronous	389 (51%)	61 (56-67)	1.2 (0.9-1.5)			
Pathologic subtype *NA=263*						
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)			
Completeness of cytoreduction score *NA=60*						
CC0	702 (95%)	61 (57-66)	REF	0.0034	REF	0.45
CC1	34 (5%)	39 (25-61)	1.9 (1.1-2.8)		1.2 (0.7-2.2)	
HIPEC *NA=0*						
No	51 (6%)	60 (47-76)	REF	0.75	NI	NI
Yes	745 (94%)	60 (56-65)	1.1 (0.7-1.6)			
PCI *NA=0*						
≤14	602 (76%)	68 (63-72)	REF	<0.0001	REF	0.00012
	194 (24%)	39 (32-48)	2.3 (1.8-2.9)		2.0 (1.4-2.8)	

>14						
Duration of operation ***NA=197*** < 6 hours >= 6 hours	327 (55%) 272 (45%)	64 (58-70) 49 (42-57)	REF 1.4 (1.1-1.8)	0.0054	REF 1.3 (0.9-1.8)	0.18
Major surgical complication ***NA=58*** No Yes	387 (52%) 351 (48%)	64 (58-70) 53 (47-60)	REF 1.5 (1.2-1.9)	0.00023	REF 1.4 (1.0-1.9)	0.042
Preoperative chemotherapy ***NA=0*** No Yes	87 (11%) 709 (89%)	60 (49-73) 60 (56-65)	REF 1.0 (0.7-1.4)	0.92	NI	NI
No preoperative cycles ***NA=144*** <=6 >6	345 (53%) 307 (47%)	59 (53-66) 62 (56-68)	REF 1.0 (0.8-1.3)	1.0	NI	NI
Postoperative chemotherapy ***NA=223*** No Yes	193 (34%) 380 (66%)	58 (50-66) 58 (52-65)	REF 0.8 (0.6-1.0)	0.043	REF 0.9 (0.6-1.2)	0.35

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

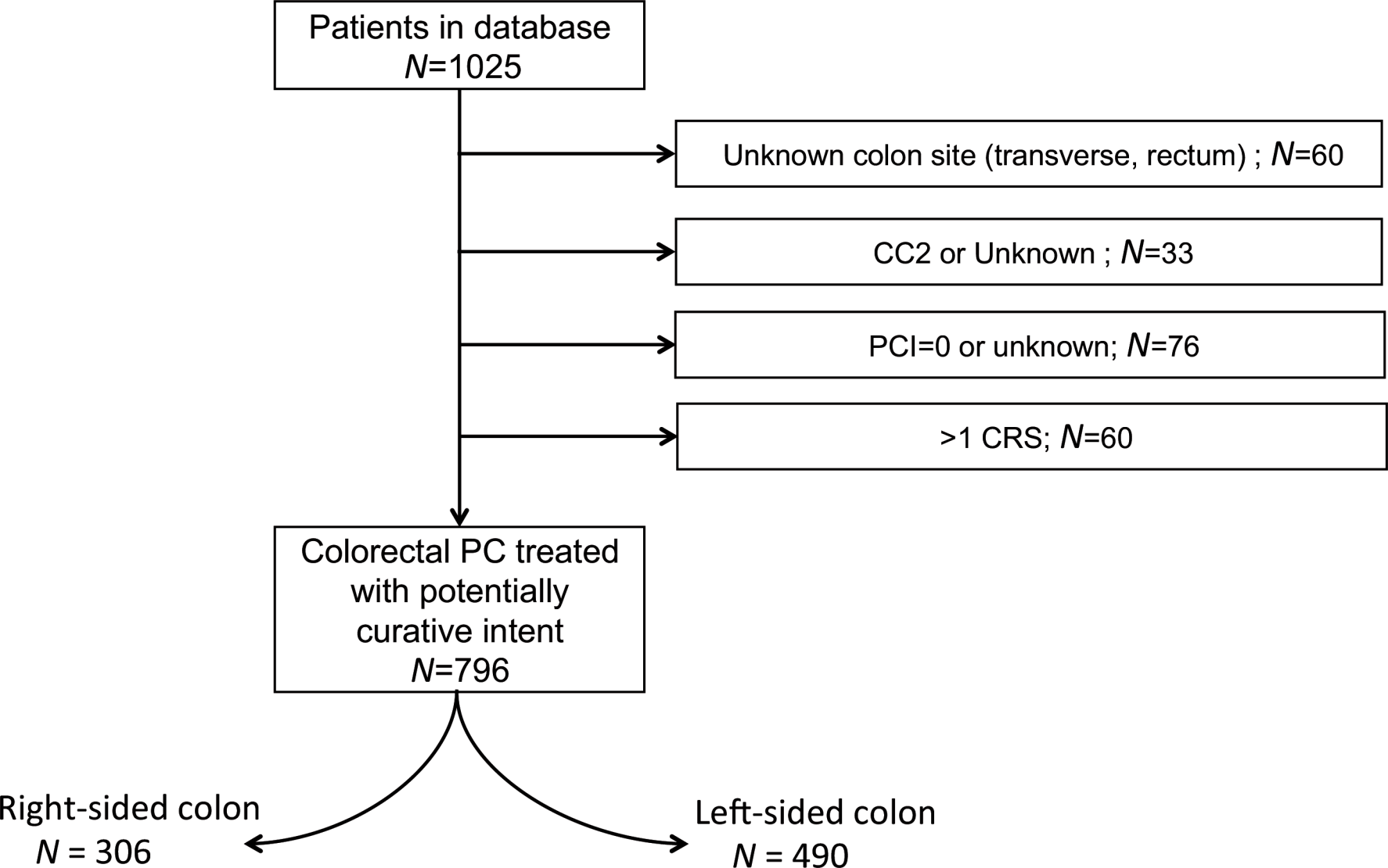
ELSEVVIER EDITORS AGAIN ADD A COLUMN AFTER m(%) CALLED "Data not available" AS IN TABLES 1 AND 2

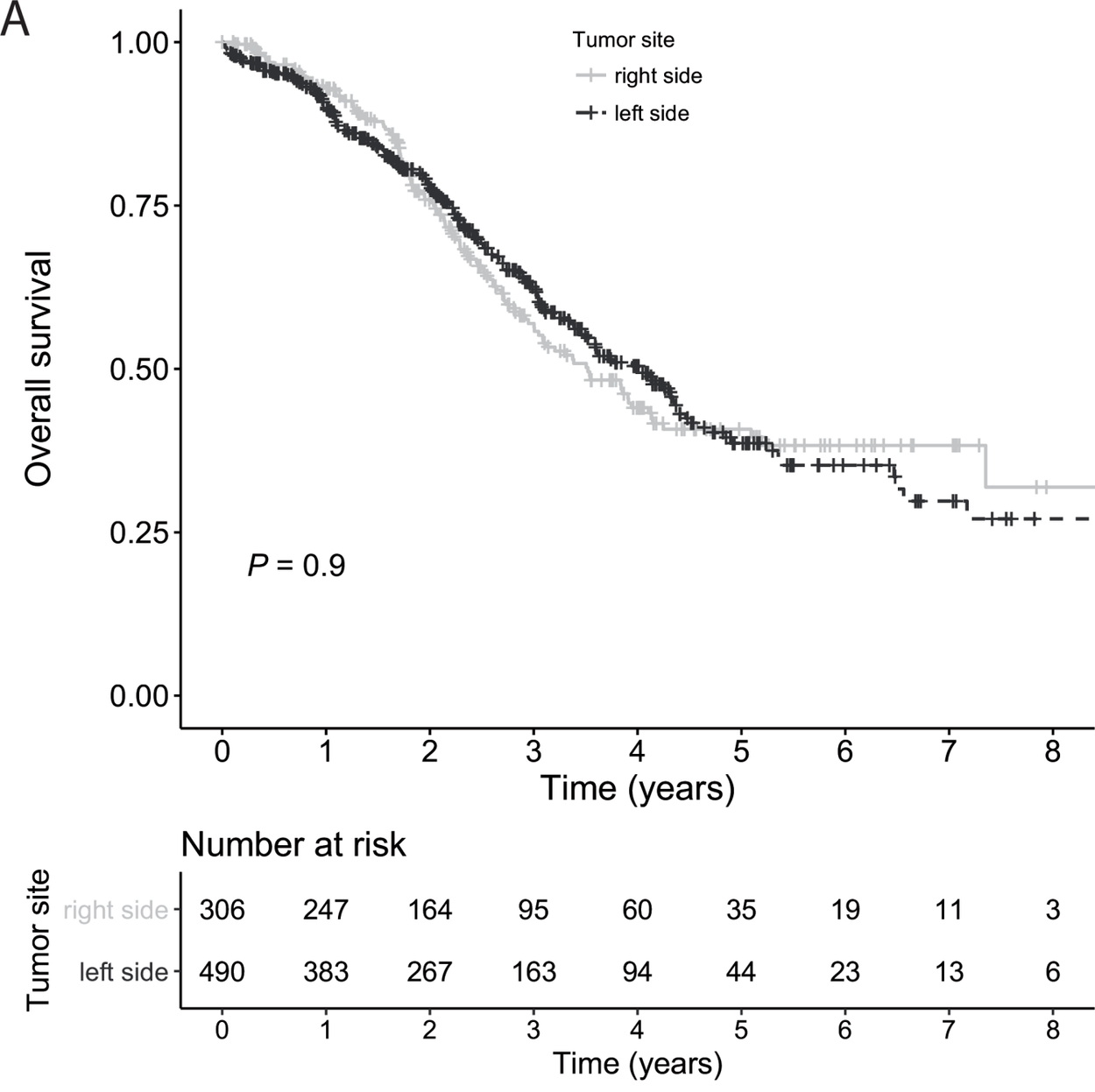
Table 3 Prognostic factors of progression-free survival in univariate and multivariate analysis (Cox model).

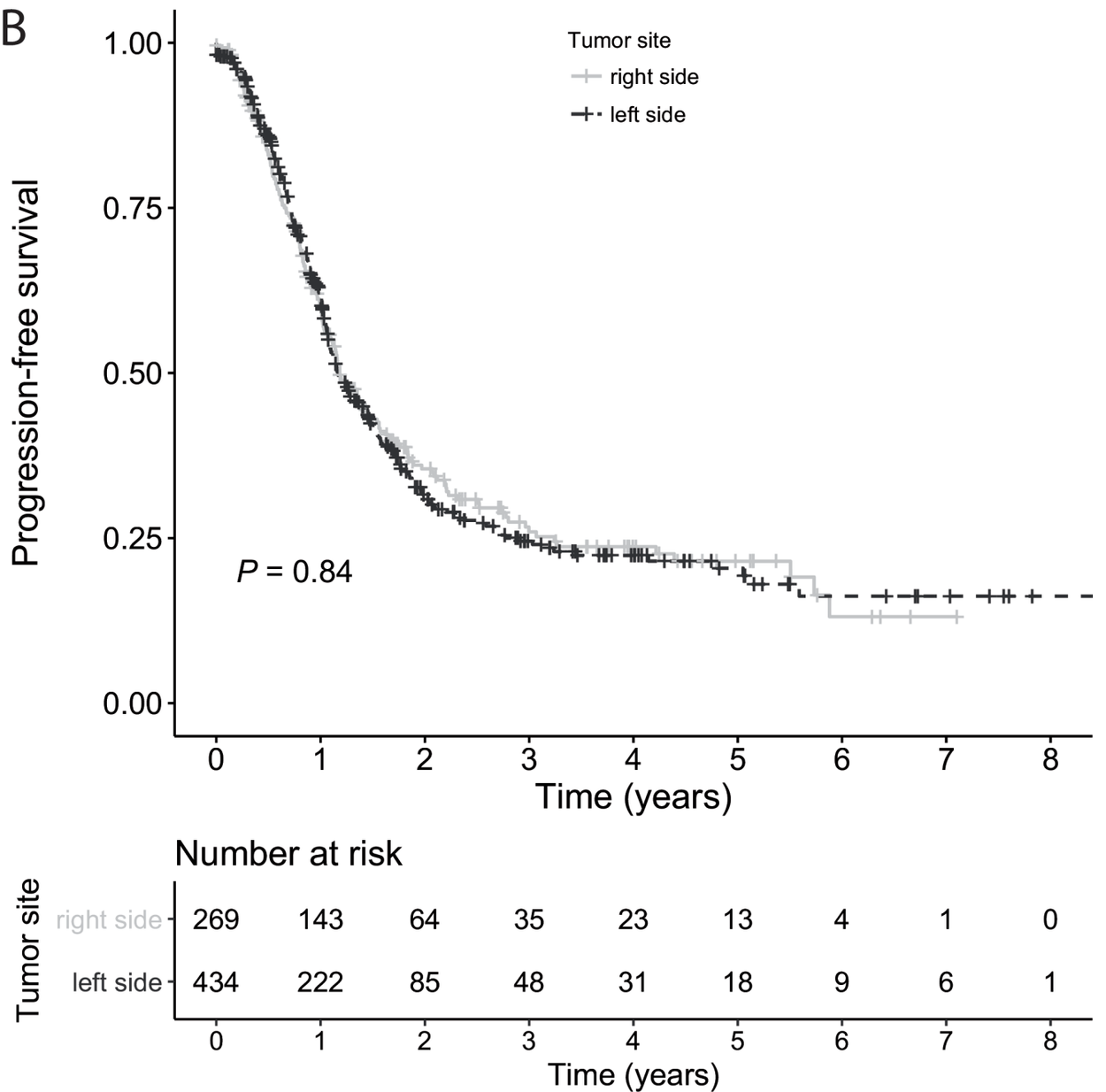
			Cox proportional hazards regression for progression-free survival			
			Unadjusted analysis		Adjusted Analysis	
	N (%)	3-years PFS rate (%) (95% CI)	HR (95%CI)	*P*	HR (95%CI)	*P*
Tumor side NA=0						
Right side	306 (38%)	26 (20-32)	REF	0.84	REF	0.24
Left side	490 (62%)	24 (20-30)	1.0 (0.8-1.2)		0.9 (0.7-1.1)	
Age (years) *NA=0*						
< 60	422 (53%)	23 (19-29)	REF	0.036	REF	0.26
>=60	373 (47%)	27 (22-34)	0.8 (0.7-1.0)		0.9 (0.7-1.1)	
Date of Cytoreductive surgery *NA=0*						
< 2012	369 (46%)	21 (16-26)	REF	0.019	REF	0.021
>=2012	427 (54%)	31 (25-37)	0.8 (0.7-1.0)		0.8 (0.6-1.0)	
Carcinomatosis *NA=37*						
Metachronous	370 (49%)	28 (22-34)	REF	0.15	NI	NI
Synchronous	389 (51%)	24 (19-29)	1.1 (1.0-1.4)			
Pathological subtype *NA=263*						
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)			
Completeness of cytoreduction score *NA=60*						
CC0	702 (95%)	24 (21-29)	REF	0.018	REF	0.40
CC1	34 (5%)	7 (2-26)	1.6 (1.1-2.4)		1.2 (0.8-2.0)	
HIPEC *NA=0*						
No	51 (6%)	20 (11-35)	REF	0.94	NI	NI
Yes	745 (94%)	26 (22-30)	1.0 (0.7-1.4)			
PCI *NA=0*				<0.000		
≤14	602 (76%)	30 (25-35)	REF	1	REF	<0.000

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

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


Patients in database
N=1025
Unknown colon site (transverse, rectum) ; N=60
CC2 or Unknown ; N=33
PCI=0 or unknown; N=76
>1 CRS; N=60
Colorectal PC treated with potentially curative intent
N=796
Right-sided colon
N = 306
Left-sided colon
N = 490


A
Tumor site
right side
left side
Overall survival
1.00
0.75
0.50
0.25
0.00
P = 0.9
0
1
2
3
4
5
6
7
8
Time (years)
Number at risk
Tumor site
right side 306 247 164 95 60 35 19 11 3
left side 490 383 267 163 94 44 23 13 6
Time (years)


B
Tumor site
right side
left side
Progression-free survival
1.00
0.75
0.50
0.25
0.00
P = 0.84
0
1
2
3
4
5
6
7
8
Time (years)
Number at risk
Tumor site
right side 269 143 64 35 23 13 4 1 0
left side 434 222 85 48 31 18 9 6 1
Time (years)