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Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy versus cytoreductive surgery alone for colorectal peritoneal metastases (PRODIGE 7): a multicentre, randomised, open-label, phase 3 trial

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1 **Hyperthermic Intraperitoneal Chemotherapy for Colorectal Peritoneal**
2 **Metastases: the phase 3, multicenter, randomized UNICANCER-**
3 **PRODIGE 7 study**

4

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Summary

48 **Background**

49 Cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) showed
50 encouraging results for selected patients with colorectal peritoneal metastases (PM) and eligible for
51 complete macroscopic resection but the specific role of HIPEC compared to CRS alone needs to be
52 evaluated.

53 **Methods**

54 A randomized phase 3 multicenter trial (ClinicalTrials.gov as NCT00769405) included patients of 18-
55 70 years with histologically proven isolated PM from 17 French centers. [Patients with performance](#)
56 [status 0/1 and a complete macroscopic resection \(R0/R1\) or surgical resection with residual tumor](#)
57 [tissue < 1 mm \(R2\) underwent central randomization with minimization by centre, completeness of](#)
58 [cytoreduction and number of previous systemic chemotherapy lines. Patients were](#) randomly (1:1)
59 assigned to CRS and HIPEC with oxaliplatin versus CRS alone. HIPEC was performed by closed or
60 open abdomen techniques. All individuals received systemic chemotherapy [with or without targeted](#)
61 [therapy before or after surgery, or both. The choice for chemotherapy regimens was at the](#)
62 [investigator's discretion](#). Primary endpoint was the overall survival (OS). The study was powered to
63 evaluate the median OS gain at 18 months with hazard ratio (HR) of 0.625 for which 264 patients
64 were necessary. [The primary analysis was done in the intention-to-treat population.](#)

65 **Findings**

66 Between from February 2008 and January 2014, 265 patients were included and assigned as HIPEC (n
67 = 132) and non-HIPEC arms (n = 133) with well-balanced baseline characteristics. After 63.8 months
68 median follow-up (IQR 53.0 - 77.1) the median OS were 41.2 months with 95% confidence interval
69 (CI) [35.2 - 49.7] in non-HIPEC arm and 41.7 months, 95% CI [36.2 - 53.8] in HIPEC arm (HR =
70 1.00, 95% CI [0.63 - 1.58], p = 0.997). The overall 30-day postoperative mortality rates were similar
71 in both arms (1.5%), but 60-days late complications rates were significantly higher in HIPEC vs non-
72 HIPEC arms (grade 3-5, rate of 25.9% vs 15.4%, p = 0.035, respectively).

73 **Interpretation**

74 Considering the absence additional 18-month survival advantage of CRS plus oxaliplatin-HIPEC
75 compared to CRS alone and more frequent postoperative late complications, these data reinforce the
76 concept that therapeutic curative management of colorectal PM by CRS alone is the cornerstone
77 treatment.

78 **Funding**

79 Institut National du Cancer (INCA), PHRC Cancer 2006 n°14 - 9 and Ligue Contre le Cancer.

80

RESEARCH IN CONTEXT

81

82 **Evidence before this study**

83 The subject was scrutinized in PubMed (MeSH terms used “cytoreduction surgical procedures”,
84 “peritoneum, “neoplasm metastasis”, “colorectal neoplasms”, “colorectal cancer”, “hyperthermia,
85 induced” and showed from 2000/01/01 to 2019/12/31 a number of 68 publications in English
86 (excluding other forms of cancer). There is only one randomized clinical trial in 2003. PM from
87 colorectal cancer are associated with a poorer prognosis than extra-peritoneal metastatic locations. The
88 median overall survival (OS) obtained after treatment of isolated PM with current systemic
89 chemotherapy is only 16 months. For patients eligible for complete surgical resection, combination of
90 CRS and HIPEC has been used for more than a decade. Many retrospective studies showed
91 encouraging median overall survival of 35-40 months for these patients amenable to macroscopically
92 complete PM resection. However, in these studies, CRS and HIPEC have always been used together.
93 The specific role of HIPEC on survival remains to be evaluated.

94

95 **Added value of this study**

96 This is the first study to address the question of specific role of HIPEC associated with CRS in PM
97 from colorectal cancer. We found that addition of oxaliplatin-HIPEC does not impact the overall OS
98 neither the relapse-free survival while post-operative complications were more frequent in CRS and
99 HIPEC group than CRS alone. With 5-year recurrence-free survival rates of almost 15% in both
100 groups, the curative management of PM from colorectal cancer by CRS alone, in association with
101 systemic chemotherapy, showed in specialized centers unexpected satisfactory survival results.

102

103 **Implications of all the available evidence**

104 Our data suggest that oxaliplatin-HIPEC administered at high dose and for short duration should be
105 left behind, while cytoreductive surgery should be considered as the fundament of PM treatment when

106 it is macroscopically complete. Consequently each colorectal cancer patient with PM should be
107 considered primarily for surgical resection. Such changes in the clinical practice would spare patients
108 with colorectal cancer from unnecessary intraperitoneal chemotherapy.

109

110

111

INTRODUCTION

112 Peritoneal metastases (PM) in colorectal cancer represent a clinical form of disease progression being
113 synchronous in approximately 7% of cases and as the first and only localization of metastases in more
114 than 4% of cases. In population-based studies, 5-years cumulative risk of metachronous PM reaches
115 6% of colorectal cancer cases.¹ The presence of PM in colorectal cancer is associated with shorter
116 overall survival (OS) and in 30 to 40% of cases with significantly worse prognosis compared to non-
117 peritoneal disease (16·3 months for PM and 19·1 months for liver-only and 24·6 months for lung-only
118 diseases).^{2,3} In isolated PM, contemporary systemic chemotherapeutic regimens – the unique treatment
119 available for patients with unresectable disease – provides short median overall survival of less than
120 18 months.³ Management of PM of colorectal origin has evolved profoundly in the last several years.
121 Worldwide, peritoneal surface malignancy teams have developed the concept of adding hyperthermic
122 intraperitoneal chemotherapy (HIPEC) to cytoreductive surgery (CRS). HIPEC achieves high local
123 concentrations of antineoplastic agents with enhanced cytotoxicity by hyperthermia. In patients
124 amenable to macroscopically complete resection, multiple retrospective studies showed encouraging
125 median OS, reaching 40 months in selected patients.⁴⁻⁶ A Dutch phase 3 controlled trial showed the
126 superiority of CRS plus HIPEC over systemic chemotherapy in patients in whom surgery was only
127 performed because of symptoms of bowel obstruction.⁸ In specialized centers, CRS plus HIPEC may
128 cure around 16% of selected patients.⁹ This combination of surgical resection and HIPEC entered now
129 in longstanding practice and are always used together. Consequently, the specific role of HIPEC
130 remained unexplored in prospective trials. To respond to this important question, we have conducted a
131 prospective multicenter randomized phase 3 trial to explore the specific role of HIPEC in addition to
132 CRS in patients with PM from colorectal origin.

133

134

135

METHODS

136 TRIAL DESIGN AND PARTICIPANTS

137 This multicenter randomized open-label phase 3 trial (PRODIGE 7 – ACCORD 15; NCT00769405)
138 was conducted in 17 French centers (Supplementary Table S1). Independent local ethical committees
139 approved protocols and the study was conducted in accordance with Helsinki Declaration and Good
140 Clinical Practice requirements. Written informed consent was obtained for each patient before surgery.
141 Patients aged 18-70 years with histologically confirmed colorectal cancer and PM were eligible to
142 participate when Peritoneal Cancer Index (PCI) was ≤ 25 . In cases of complete macroscopic resection
143 (R0/R1) or surgical resection with residual tumor tissue < 1 mm (R2), inclusion was performed after
144 complete CRS in the operative room. *Any previous treatment was allowed. No washout period was*
145 *mandatory even if the majority of investigators operated on the patients after one month washout (6*
146 *weeks in case of using Bevacizumab).* Other inclusion criteria were World Health Organization
147 (WHO) performance status 0/1 and eligibility for 6-month systemic chemotherapy (adequate organ
148 function and life expectancy >12 weeks). *Patients needed to have haematological function defined as*
149 *neutrophil count $\geq 1.5 \times 10^9/L$, platelets count $\geq 100 \times 10^9/L$ and liver function as total bilirubin ≤ 1.5*
150 *times the upper limit of normal (ULN), SGOT and SGPT ≤ 3 times the ULN, alkaline phosphatase ≤ 3*
151 *times the ULN, plasma creatinine ≤ 1.25 times the ULN.* Main exclusion criteria were extra-peritoneal
152 metastasis, non-colorectal carcinomatosis, previous HIPEC treatment and peripheral neuropathy with
153 grade >3 (National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.
154 *Any co-morbidity was allowed as long as the patient was deemed operable.* PM response to pre-
155 operative chemotherapy was not considered for inclusion and *patients could be included whatever the*
156 *disease progression status.*

157 RANDOMISATION AND MASKING

158 Eligible patients were randomized peroperatively after complete CRS to receive HIPEC (HIPEC arm)
159 or not (non-HIPEC arm) using TenAlea software NKI (Amsterdam, NL) and performed by the study
160 statistician in the coordinating center. A minimization (1:1 ratio) using the Pocock and Simon method

161 was performed with any random factor, based on baseline prognostic variables. Minimization (with a
162 probability of 0.8) allowed an allocation in favour of the treatment that would minimize the
163 imbalance. To minimize the bias due to surgical unit, patients were stratified by the trial center based
164 on completeness of cytoreduction (complete macroscopic CRS [R0/R1] or minimal residual disease <
165 1 mm [R2]), number of previous systemic chemotherapy lines except for systemic preoperative
166 chemotherapy in the context of the protocol (first vs. second or later line) and preoperative character
167 of systemic chemotherapy (yes vs. no, *i.e.* post-operative).

168 **PROCEDURES**

169 Surgical procedures were the same in both arms and PCI was used to assess the spreading of PM. If
170 disease was too extensive (PCI > 25) complete macroscopic resection was ruled out (patients not
171 included) and if deemed resectable, every attempt was made to fully resect the macroscopically
172 resectable disease.

173 HIPEC was performed by closed or open abdomen techniques^{6,10} according to the choice of each
174 center. In both cases, systemic chemotherapy (5-fluorouracil 400 mg/m² and folinic acid 20 mg/m²)
175 was delivered intravenously 20 min before intraperitoneal oxaliplatin administration. The oxaliplatin
176 dose was 460 mg/m² (open technique) or 360 mg/m² (closed technique) in 2 L/m² of dextrose for
177 30 min at 43° C. No other drugs were allowed for HIPEC and no dose modification was possible. An
178 interruption of the HIPEC procedure could be conducted in case of important complication, but
179 without decreasing the doses of oxaliplatin. For systemic chemotherapy, the decision to reduce the
180 dose was left to the discretion of the investigator.

181 All patients received systemic chemotherapy with or without targeted therapy before or after surgery,
182 or both. The choice for chemotherapy and targeted therapy regimens were at the investigator's
183 discretion.

184

185 **OUTCOMES**

186 The primary endpoint was OS, defined as the interval between randomization and death from any
187 cause. Secondary endpoints were relapse-free survival (RFS) defined as the interval between
188 randomization and the first peritoneal or distant relapse or death from any cause, safety and
189 postoperative morbidity. Patients were followed up for 5 years, one month after surgery then every 3
190 months for the first 3 years and every 6 months up to 5 years. Tumor markers and albuminaemia were
191 assessed according to the same schedule. Blood count, ionograms, liver abd renal function tests, tumor
192 markers (CEA and CA 19-9), albuminaemia and pregnancy test were performed at baseline together
193 with comorbidity assessment. Disease evaluation was performed using clinical examination, tumor
194 markers and thoracic-abdominal – pelvic CT scan. PET and peritoneal MRI were completed at the
195 investigator discretion. Patients without events at the time of analysis were censored at their last
196 informative follow-up. Immediate postoperative morbidity was reported twice, for complications
197 observed between surgery and day 30 (30-day complication rate) and for complications observed
198 between days 31 and 60 (60-day complication rate). Adverse events were graded according to NCI-
199 CTCAE v3.0. Follow-up was performed every 3 months for 3 years and then every 6 months for 2
200 years.

201 **STATISTICAL ANALYSIS**

202 The study was powered to achieve a median OS gain from 30 to 48 months in the HIPEC arm with
203 hazard ratio [HR] of 0.625 and required 264 patients (132 per arm) as indicated by East v5 software.
204 To obtain 80% power and detect the difference between groups by two-sided log-rank test with
205 nominal 5% α level, 154 events (deaths) were required. The design was adaptive with two planned
206 intermediate analyses to test efficacy and futility using O'Brien-Fleming boundaries: at the 51st,
207 analysis would be significant for efficacy if $p \leq 0.0002$ and futile if $p > 0.965$, and at 10^{2nd} death (a
208 third of the total required events), analysis will be significant for efficacy if $p \leq 0.012$ and futile if $p >$
209 0.331. One planned interim analysis for primary endpoint was performed in April 2014, after
210 observation of 70 deaths in a sample of patients similar to the overall population in terms of clinical
211 characteristics. At the first interim analysis, inclusions were already completed and the Committee

212 recommended waiting for the complete database maturity to conclude on all the required events
213 (futility was not considered). The final analysis was planned at the 154th event with a significant level
214 of $p < 0.0463$ with adjusted CI.

215 All analyses were performed on intention-to-treat (ITT) basis. The ITT population was defined as all
216 randomized patients. The primary endpoint was also analyzed in the per-protocol (PP) population
217 defined as all randomized patients treated with CRS alone or CRS plus HIPEC, with no violation of
218 major inclusion or non-inclusion criteria but excluding patients treated for HIPEC for their recurrence
219 (cross-over patients). Qualitative variables were compared using chi-square or Fisher's exact tests
220 while quantitative variables by Kruskal-Wallis test. Survival rate estimates were calculated with
221 Kaplan-Meier method and compared with stratified log-rank test. A stratified Cox proportional-
222 hazards model was used to estimate HR with 95% CI and 95.37% for the primary endpoint. The
223 standard errors of the estimated HRs were adjusted to account for possible within-center correlation.
224 The proportional-hazards assumption was verified by the Schoenfeld residual method. Sensitivity
225 analyses using the inverse probability of censoring weighting (IPCW) method were performed on the
226 primary endpoint to take into account cross-over patients. A forest-plot was performed for different
227 subgroups. Post-hoc exploratory analyses were performed to assess the correlation between PCI and
228 time-to-event endpoints on ITT and PP populations. No imputation was used for missing data. All
229 analyses were performed using Stata, 13.0 (StataCorp LLC, College Station, TX, USA).

230 **ROLE OF THE FUNDING SOURCES AND ACCESS TO THE DATA**

231 The study was funded by INCA (PHRC cancer 2006 n°14-9) and by Ligue contre le Cancer. The
232 funder had no role in study design, collection, analysis or interpretation of data, writing of the report
233 or decision to submit the paper for publication. FQ, LR, HF had full access to all data and FQ was
234 responsible for the decision for publication.

RESULTS

235

236 Between February 11th 2008 and January 6th 2014, 265 patients from 17 French centers were randomly
237 assigned to receive CRS and HIPEC (n = 133) or CRS alone (n = 132). A number of 131 patients were
238 assessed before surgery but excluded before randomization mostly because of PCI > 25 or considered
239 non-resectable due to major visceral involvement (Figure 1). Baseline features, tumor characteristics
240 and previous treatments were similar in both arms (Table 1). The median age was 60 years (IQR 52-
241 65). The primary tumor was previously resected in 207/265 patients (78.1%), among which 128/265
242 patients (48.3%) were treated with systemic adjuvant chemotherapy. The complete macroscopic
243 resection rate was 89.5% (n = 119/133) in HIPEC arm and 91.7% (n = 121/132) in non-HIPEC arm.
244 The overall median PCI was 10 (IQR 5-16) without significant difference between two arms.

245 The median delay between PM diagnosis and CRS was 5.1 months (IQR 3.8-8.3). In 10% of patients,
246 a long delay was reported (5.9%, > 1 year) and in 4.1%, > 2 years). In 105 patients of 265 (39.8%)
247 the PM were synchronous with the primary tumor, among which 66/265 (24.9%) have previously
248 been treated by surgery and 39/265 (14.7%) and/or chemotherapy (Table 1). No significant difference
249 was observed between arms for previous PM surgery or chemotherapy. Sixteen patients/132 from the
250 non-HIPEC arm were crossed over and received HIPEC for treatment of first isolated PM relapse
251 (Figure 1). Most patients (95.5%, n = 253/265) received systemic chemotherapy for 6 months, either
252 preoperatively (19.6%, n = 52/265) or postoperatively (12.8%, n = 34/265) or both (63.0%, n =
253 167/265) in an interval strategy. Timing for chemotherapy and the median number of preoperative
254 chemotherapy cycles were similar between arms (Table 1). Patients received a median number of 6
255 cycles of preoperative chemotherapy (58.0% \geq 6 cycles, n = 127/219). Among all patients who
256 received preoperative chemotherapy, 94/219 (42.9%) received oxaliplatin-based treatment, including
257 patients (n = 50/127, 39.4%) with \geq 6 cycles (Supplementary Table S2). Taking into account systemic
258 regimens prior to trial inclusion, adjuvant treatment to surgery for primary tumor or for previous PM
259 treatment, a proportion of 73.2% of patients (n = 194/265) received oxaliplatin-based systemic
260 chemotherapy (cumulative oxaliplatin-based treatment, Supplementary Table S2). A number of
261 49/265 patients (18.5%) received chemotherapy with anti-EGFR (either pre- or post-operatively or

262 both) and 143/265 patients (54%) anti-VEGF treatment. Early discontinuation of preoperative
263 chemotherapy (61/219 patients treated preoperatively) was mostly due to toxicities (n = 24). Other
264 causes included disease progression (n = 1), patient's decision (n = 1), investigator's decision (n = 8)
265 and others (n = 27). Postoperatively, 68/201 patients discontinued chemotherapy, 37 for toxicities, 6
266 for progression, 3 for patient decision, 7 for investigator decision and 15 for other causes.

267 After a median follow-up of 63.8 months (IQR 53.0-77.1), 159 patients (60.0%) had died: 79 (59.4%)
268 in HIPEC arm and 80 (60.6%) in non-HIPEC arm and 221 (83.4%) patients either died or progressed.
269 There was no evidence for significant difference in median OS between the two groups. The median
270 OS was 41.7 months (95% CI: 36.2-53.8) in HIPEC arm and 41.2 months (95% CI: 35.1-49.7) in
271 non-HIPEC arm (HR = 1.00, 95.37% CI 0.63-1.58), stratified P = 0.99) (Figure 2A). One and 5-year
272 OS rates were 86.9% and 39.4% in HIPEC arm and 88.3% and 36.7% in non-HIPEC arm,
273 respectively.

274 Relapse occurrence was no significantly different between two arms. The median RFS was 13.1
275 months (95% CI 12.1-15.7) in HIPEC arm and 11.1 months (95% CI 9.0-12.7) in non-HIPEC arm
276 (HR = 0.908 with 95% CI 0.71-1.15, stratified with p = 0.43) (Figure 2B). RFS rates at 1 year were
277 59.0 and 46.1%, respectively while 5-year RFS rates were 14.8 and 13.1%, respectively. Peritoneal-
278 free survival was not significantly different between two arms (Supplementary Figure S1). The
279 recurrence patterns were also similar. Rates of PM recurrence were similar for both isolated PM
280 relapse (HIPEC 29.3% vs non-HIPEC 31.1%, respectively) and multiple metastatic recurrences.
281 These patients were treated with systemic chemotherapy (Supplementary Table S4)

282 Survival results in per-protocol population were similar to the ITT population (Supplementary Figure
283 S2). Supplementary Table S3 summarizes results of the survival analyses, including sensitivity
284 analyses.

285 In subgroup analysis, the post-hoc exploratory analyses showed that median OS was correlated with
286 the PCI, longer for patients with low PCI (<11) (Supplementary Figure S3). Forest plots for both OS
287 and RFS showed potential benefit of HIPEC in patients with a medium PCI (11-15) (**Figure 3,**

288 Supplementary Figures S4 and S5). In patients with medium PCI (n = 46), overall and relapse-free
289 survival were longer in HIPEC vs non-HIPEC arms (OS with HR = 0.437, 95% CI [0.21-0.90], p =
290 0.02, with a significant interaction test p = 0.0308 for PCI (11-15) vs other) as shown in
291 Supplementary Figure S4. A possible RFS benefit was reported in patients receiving exclusively
292 preoperative systemic chemotherapy (Supplementary Figure S5).

293 Concerning safety of the HIPEC procedure, the postoperative mortality rates at 30 days was 1.5% (n =
294 4, two in each arm) (Table 3) as result of cardiac failure, intra-peritoneal hemorrhage, septic shock and
295 massive pneumonia. At 60 days, three more deaths were reported (n = 2 in HIPEC arm) caused by
296 pulmonary embolism, acute respiratory distress and bilateral pneumonia. The overall mortality rate at
297 60 days was 2.6% (4 patients in HIPEC arm vs 3 patients in non-HIPEC arm).

298

299 The 30-days complication rate with severe (grade ≥ 3) complications was reported in 98/265 patients
300 (37.0%) (Table 3). For the entire population, the grade ≥ 3 intra-abdominal complications rate was
301 22.6% (n = 60/265) and for extra-abdominal 24.5% (n = 65/265). These rates were similar between
302 two arms.

303 Main intra-abdominal complications were digestive fistulae (8.7%, n = 23/265) and abscesses (4.2%,
304 n = 11/265) (Supplementary Table S5). Among patients with severe complications at day 30, a
305 proportion of 41.1% (n = 39/95) also presented severe complications at day 60. The 60-days grade ≥ 3
306 complications rate was 20.7% (n = 54/261) in all population. As shown in Table 3, the complications
307 rate was higher in HIPEC arm (25.9%, n = 34/131) than in non-HIPEC arm (15.4%, n = 20/130) with
308 p = 0.035. The most frequent complications (17.6%, n = 46/261) were extra-abdominal. Of note, the
309 neurotoxicity rate was very low (1.9%, n = 5/261). The median duration of hospital stay was
310 significantly longer in HIPEC (18 days, IQR: 14-27) than in non-HIPEC arm (13 days, IQR: 11-20, p
311 < 0.001) (Table 1). Similarly, the median interval between surgery and food intake was 7.5 days (IQR
312 5-10) in HIPEC arm and 6.0 days (IQR 4-8) in non-HIPEC arm (p < 0.001). In case of interval or
313 exclusively postoperative systemic chemotherapy, the median time between discharge after surgery
314 and the start of a new chemotherapy cycle was longer in the HIPEC arm: 67 days (IQR 50-85) vs 56

315 days (IQR 45-68), $p = 0.004$). Among patients with 60-days complications, 75% ($n = 41$) already had
316 one complication in the first 30 days.

317

DISCUSSION

318 In this Prodiges 7 trial we present evidence for no benefit for HIPEC plus CRS compared to CRS alone.
319 After a decade of encouraging survival results of this combined strategy, this trial is to our knowledge
320 the first study to question the specific role of HIPEC. Indeed, in colorectal PM, the complete CRS is
321 aimed to remove macroscopic lesions while HIPEC is meant to treat remaining microscopic disease.
322 However, previous retrospective or prospective studies evaluating the survival benefits have always
323 assessed CRS and HIPEC together, missing a CRS arm alone^{6, 7, 11}. These data are crucial in the
324 clinical practice indicating that with this particular HIPEC regimen, this procedure has no specific
325 benefit compared to CRS alone.

326 The primary endpoint – an OS benefit through the addition of HIPEC with oxaliplatin to CRS – was
327 not reached. In the non-HIPEC arm, median OS was 41 months, a very high and unexpected rate,
328 which probably represents the most important result meaning that complete CRS is the determining
329 factor for prolonged OS in patients. Completeness of CRS is confirmed as the most important factor
330 determining survival after surgical treatment of colorectal PM, a well-established result for PM of any
331 origin.^{7,8,12} The OS rate for the non-HIPEC arm in our trial was almost twofold higher than seen in the
332 phase 3 Dutch trial, which reported a R0/R1 rate of 36% in the HIPEC arm.⁸ Fifteen years later, the
333 ability of expert centers to achieve a higher complete resection rate for such a demanding procedure
334 strongly affects survival. Because radical resection was a prerequisite for patients inclusion, the
335 resection rate was almost 90% in our multicenter trial, which grouped centers with extensive
336 experience (71% patients were included in the three main study centers, which had performed more
337 than 500 procedures at the time of the study) or less experience, allowing such survival results in the
338 two arms. No statistically significant difference was reported for RFS between the two treatment arms.
339 The 1-year RFS rates revealed 13% difference between the two arms, suggesting that addition of
340 HIPEC may delay recurrence of peritoneal disease. However, the patterns of recurrence showed that
341 adding HIPEC to CRS did not affect the peritoneal recurrence rate, a strong argument against the
342 effectiveness of oxaliplatin HIPEC as a local treatment. The proportion of patients considered cured
343 was close to 15% in both arms, results comparable to that of previously published data.⁹ Interestingly,

344 the RFS curve leveled off after 24 months, which probably shows that the number of patients alive
345 without recurrence might in fact be higher.

346

347 In a subgroup analysis, we observed that OS and RFS differed according to patients' PCI. Patients
348 with a medium (11-15) PCI benefited from the addition of HIPEC. Although this was a post-hoc
349 subgroup analysis, which was not initially planned, this result may serve as a basis for future research
350 in patients with quite extensive PM in whom CRS cannot achieve good survival results as in patients
351 with low PCI.

352 The 30-day mortality rate was of 1·5% and the grade ≥ 3 morbidity rate of 37%, 42·1% in the HIPEC
353 arm and 31·8% in the non-HIPEC arm. These numbers are comparable to those published by other
354 specialized institutions.^{6,7,13} Recently, Foster et al.¹³ used data from the American College of Surgeons
355 National Surgical Quality Improvement Project database to compare perioperative and 30-day
356 postoperative morbidity and mortality rates for CRS and HIPEC with other high-risk surgical
357 oncology procedures.¹⁴ They showed that CRS and HIPEC had lower or comparable morbidity rates
358 than pancreatoduodenectomy or oesophagectomy.¹⁴ In our study, adding HIPEC with oxaliplatin to
359 CRS did not significantly increase the overall rate of early postoperative complications at 30 days and
360 resulted in a mortality rate similar to that of CRS alone. Grade ≥ 3 digestive fistulae occurred in
361 10·5% of patients vs. 6·8% for patients treated with CRS alone, rates which were not significantly
362 different between the two arms and remained close to those reported by single- and multicenter
363 studies.^{6,7,8} We did not report a statistical significant different for extra-abdominal complications, but
364 hematologic toxicity was higher in the HIPEC group. We used the protocol of bi-directional
365 chemotherapy¹⁵ and allowed HIPEC to be performed with either open or closed techniques, as no clear
366 difference has been demonstrated between these two procedures.^{10,16,17} However, oxaliplatin-HIPEC
367 significantly increased the 60-day grade ≥ 3 complications rate. This suggests that HIPEC may extend
368 the time during which patients are at risk of developing postoperative complications, resulting in a 5-
369 day longer hospital stay and a longer time to resume postoperative systemic chemotherapy in the

370 HIPEC arm vs. the non-HIPEC arm. It should be noted that very few intra-abdominal complications
371 were reported at 60 days, showing that severe complications were fairly different from those recorded
372 in the early postoperative period with a large majority of general complications such as pulmonary and
373 infectious complications, undernutrition or anemia.

374 Our results bring into question the benefit for efficacy of HIPEC itself. Unlike systemic results,
375 HIPEC intensification with irinotecan did not improve survival.⁶ Two recent randomized phase 3
376 studies in prophylactic settings using the same HIPEC regimen did not demonstrate its superiority in
377 preventing the occurrence of PM, thus raising questions about its effectiveness.^{18,19}

378 The duration of peritoneal oxaliplatin exposure may improve HIPEC efficacy. In our study, oxaliplatin
379 HIPEC was administered for only 30 minutes. Other protocols reported HIPEC administration for up
380 to 120 minutes.²⁰ In patients with ovarian cancer, cisplatin HIPEC administered for 90 minutes
381 showed a significant survival benefit.²¹ Since the beginning of this trial, other experimental studies
382 have shown that response to local oxaliplatin is related to duration of exposure.^{22,23} It is possible that
383 future studies regarding both dose and duration of oxaliplatin-HIPEC may revise the results of our
384 study.

385 At the time of the study design, the choice of oxaliplatin appeared appropriate based on good survival
386 results obtained with CRS and oxaliplatin HIPEC in selected patients.^{3,7} Its efficacy in the systemic
387 treatment of adjuvant or metastatic colorectal cancer had been widely demonstrated.^{24,25}

388 A very large number of HIPEC regimens have been described worldwide²⁶ for PM from colorectal
389 cancer, but the majority of them are based on two molecules, oxaliplatin or mitomycin C. Even if no
390 meaningful comparison could be made regarding results from retrospective studies, oxaliplatin HIPEC
391 has shown survival results equivalent to that of the Dutch series by Hompes *et al.*²⁷, and superior to
392 those of mitomycin C in the Italian comparative study²⁸ using mitomycin C and cisplatin, or to those
393 of a monocentric Australian study by Leung *et al.*²⁹ Interestingly, consistent with our results in the last
394 two studies, subgroup analyses revealed a survival advantage in patients with a PCI between 10 and
395 15.^{28,29}

396 In a large retrospective study³⁰ no significant difference was found in survival comparing oxaliplatin
397 and mitomycin C, although mitomycin C was superior in patients with low tumor burden. It is
398 important to note that the oxaliplatin regimen used in these studies was the same as in our trial. This
399 explains why it would be difficult to believe that mitomycin C will show in the future much higher
400 efficacy than oxaliplatin, even if the results of these retrospective studies are conflicting. However, our
401 data cannot be extrapolated to other HIPEC regimens and further studies with different HIPEC
402 protocols would be needed before the additional benefit of HIPEC can be abandoned.

403 This HIPEC regimen – short duration and high oxaliplatin dose – had shown a peritoneal oxaliplatin
404 concentration 25-fold higher than that seen in plasma.¹⁵ The intra-tumoral oxaliplatin penetration was
405 also 17-fold higher than that in non-bathed tissues. Intravenous 5-FU administration in our protocol
406 could be questioned; a short single intraoperative injection may not allow reaching synergy between
407 oxaliplatin and 5-FU. Indeed, intravenous oxaliplatin administered as monotherapy was shown to have
408 limited effect in metastatic colorectal cancer patients because a single injection of a short infusion of
409 5FU at the time of surgery may not be the best way to achieve synergy between 5FU and oxaliplatin,
410 and oxaliplatin IV monotherapy has only moderate activity in metastatic colorectal cancer³¹. Since
411 2002, this particular HIPEC regimen has been adopted by many teams worldwide with comparable
412 results.^{5,27}

413 The population of patients with PM in our study was indeed a selected population. The main criterion
414 for inclusion in the trial was the possibility of reaching a complete resection of the peritoneal lesions,
415 regardless of the treatments and number of chemotherapy lines previously received. This means that
416 these survival figures reflect the outcome of patients referred to the surgical teams, when resection
417 was deemed feasible whatever the history of their management after the diagnosis of peritoneal
418 carcinomatosis. We wanted only to focus on patients amenable to complete resection. Moreover, we
419 intended to select as few as possible the population of the study by not imposing any obligation as to
420 the nature of the systemic chemotherapy received and the extent of the peritoneal disease (PCI < 25).
421 Operating on such patients in expert centers with a relatively small number of expert surgeons may
422 have generated an unexpectedly high survival rate in the CRS alone group. As such, the additional

423 HIPEC may have had very little room to demonstrate any additional benefit. However, our results
424 reflect what we believe should be the currently optimal treatment for these patients. Surgery for PM is
425 a highly specialized procedure, which, in our opinion, should be performed by experts in specialized
426 centers. Despite this, our study groups remained homogeneous since the median time between PM
427 diagnosis and surgery was 5 months in both arms. Only 5% of the patients underwent surgery more
428 than 1 year after PM diagnosis, and another 5% within 2 years. On the other hand, all patients were
429 heavily treated with systemic chemotherapy, either in adjuvant setting to primary tumor resection, as
430 previous PM treatment or as part of the systemic chemotherapy regimen of the trial. It is important to
431 note that among these different chemotherapy regimens, 73% were oxaliplatin-based. Finally, the
432 majority of patients received the trial systemic treatment in a pre-operative setting, either completely
433 or in an interval strategy. Considering colorectal PM as a metastatic condition, we required that all
434 patients to receive systemic chemotherapy and, if possible, pre and post-operative chemotherapy,
435 using an interval strategy. This may explain the quite low median PCI reported. Patients who
436 underwent CRS may have been good responders to neoadjuvant chemotherapy and thus presented
437 with less extensive residual PM. Otherwise, the advances in both systemic chemotherapies and
438 targeted therapies have OS of metastatic colorectal cancer patients, a possible explanation for our
439 results better than expected in both arms. The extensive use of systemic oxaliplatin prior to HIPEC in
440 our study may also have increased the number of somatic gene mutations responsible for resistance to
441 oxaliplatin resulting in a poorer survival, as shown in patients with colorectal liver metastases by the
442 Andreou *et al.* study.³² The authors showed that a higher number of RAS mutations in patients treated
443 with an adjuvant oxaliplatin chemotherapy regimen resulted in lower DFS rates than in patients treated
444 with 5-FU or no chemotherapy³². In the MOSAIC trial, the median time from relapse to death was
445 shorter in the FOLFOX group than in the 5FU group.²⁴ Although the number of cycles received and
446 the neoadjuvant nature of chemotherapy were stratification factors all these points may of course have
447 selected "long-survivor" patients and modified the efficacy of HIPEC.

448 This randomized trial has several limitations. Beside the high dose of oxaliplatin and the short
449 duration of HIPEC discussed above, our hypothesis-generating the sample size may be criticized for

450 two main reasons. Firstly, at the time of the trial design, no survival data were available in the
451 literature in patients treated with CRS alone. The 18-month difference awaited between the arms was
452 probably over estimated, which may explain the similarity between the two arms. Secondly, we chose
453 OS as a primary endpoint, which may introduce bias due to patients who were crossed-over from CRS
454 alone to HIPEC at first recurrence of PM. However, it should be noted that only 16 patients were
455 crossed-over and the sensitivity analyses indicated no outcome differences between the two arms.
456 Another limitation was the inability to collect data on RAS/Braf mutations, as such analyses did not
457 exist in the early stages of the study. In addition, uncertainty regarding the collection of data on the
458 location of transverse colon tumors limited us to present results according only to "right colon vs.
459 others" pattern.

460 In conclusion, this study did not show additional 18-month survival advantage with CRS plus
461 oxaliplatin-HIPEC whilst the curative management of PM from colorectal cancer by CRS alone
462 revealed unexpectedly satisfactory survival results.

463

464

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470

471

DECLARATION OF INTEREST

472 The authors declared no conflicts of interest

473

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485

DATA SHARING STATEMENT

486 Unicancer will share anonymized individual data under the following conditions: data shared will be
487 limited to that required for independent mandated verification of published results; the reviewer will

488 need authorization from Unicancer for personal access; data would be transferred only after signing of
489 a data access agreement. Decision concerning other study documents sharing, including protocol and
490 statistical analysis plan, will be examined upon request. Unicancer will consider access to data upon
491 written detailed request sent to c-jouffroy@unicancer.fr from 6 months to 5 years after the publication
492 of the present article.

493

494 **AUTHORS' CONTRIBUTIONS**

495 Conception and design: FQ, DE, LR, OG

496 Study coordination and funding: FQ, BJ

497 Data collection: FQ, DE, DG, LG, MP, OF, CA, GL, DP, FM, VL, PM, JP, OG

498 Data analysis and interpretation: FQ, LR, HF, OG

499 Drafting of the manuscript: FQ, LR, HF

500 Critical revision of the manuscript: FQ, LR, DG, MP, HF, OG

501 Final approval: FQ, DE, LR, DG, LG, MP, OF, CA, GL, DP, FM, VL, PM, BJ, HF, JP, OG

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605 patients undergoing hepatectomy for metachronous liver metastases. *Ann Surg* 2012; **256**:
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- 607

608

FIGURE LEGENDS**609 Figure 1. Randomization and treatment of the patients**

610 HIPEC denotes hyperthermic intraperitoneal chemotherapy, PCI Peritoneal Carcinomatosis Index, ITT
611 intention-to-treat population, and PP per-protocol population.

612

**613 Figure 2. Kaplan-Meier estimates of (A) OS and (B) RFS in the Intention-to-Treat Population,
614 According to treatment Group**

615 OS denotes overall survival and RFS relapse-free survival. Overall survival is present with 95.37%
616 confidence intervals due to interim analyses planned

617

618

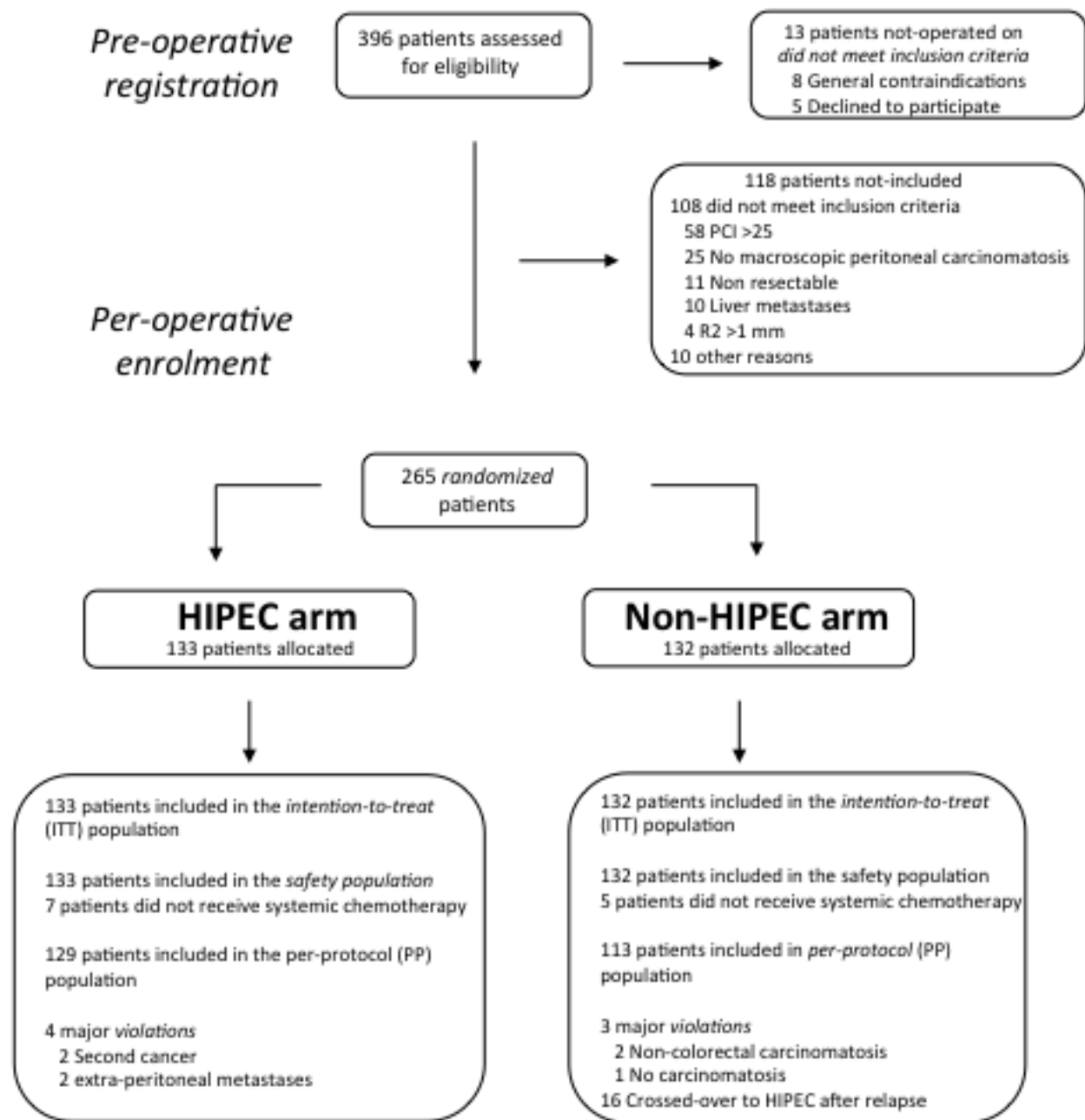
619 Figure 3. Forest Plot of HIPEC Effect on Overall Survival in subgroup analyses.

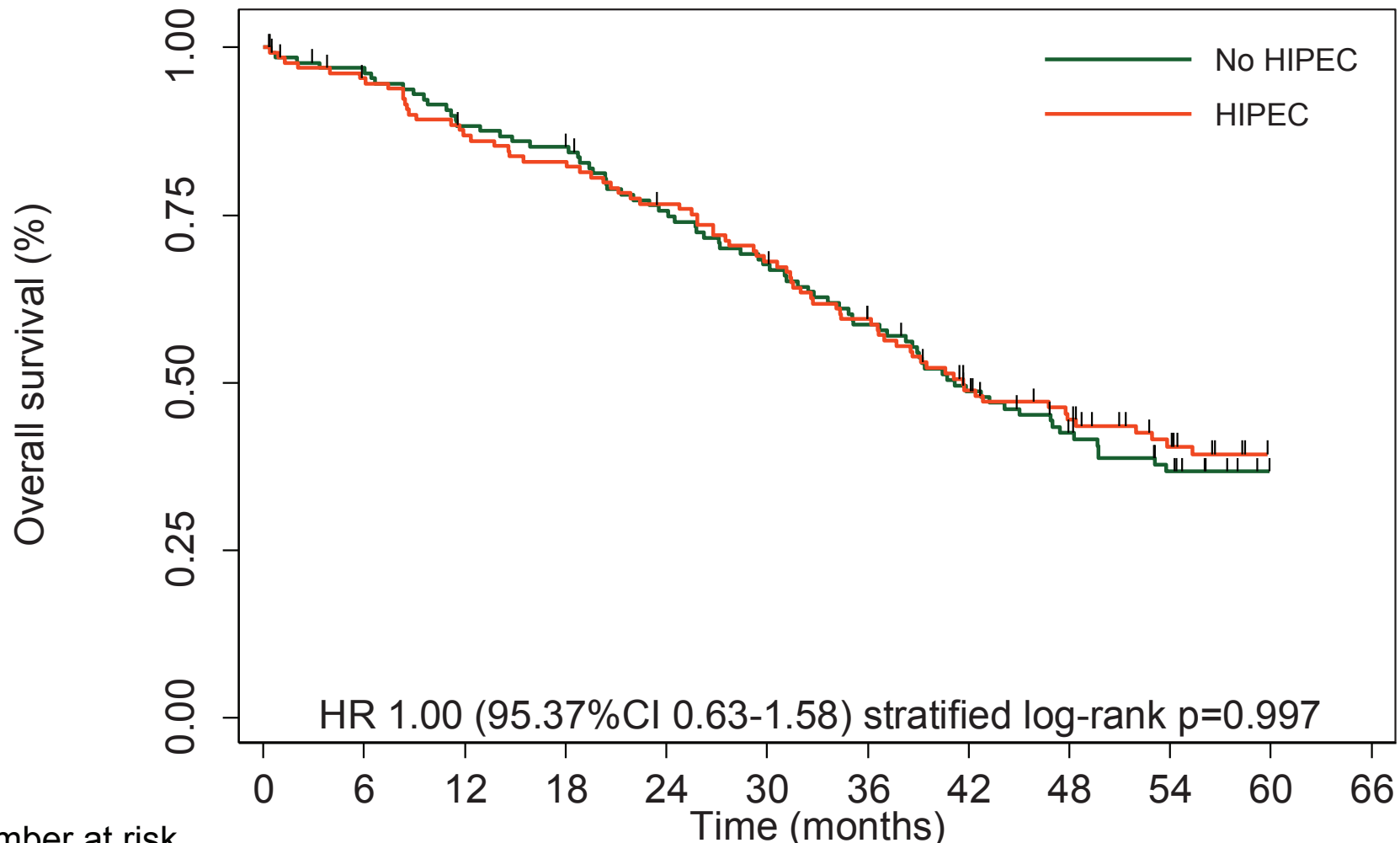
620 CI denotes confidence interval, CT chemotherapy, HIPEC hyperthermic intraperitoneal chemotherapy,
621 HR hazard ratio, LN lymph node, PCI Peritoneal Carcinomatosis Index. The position of each square
622 represents the point estimate of the treatment effect, and error bars represent 95% CI. The sizes of the
623 squares are proportional to the precision of the estimates. The diamond represents the overall point
624 estimate of the treatment effect, with the lateral points indicating the 95% CI. The vertical line
625 indicates a hazard ratio of 1.0, which was the null hypothesis value. Data refers to a number of 265
626 patients except for lymph nodes (LN) subgroup for which data were missing for 16 patients (n = 249)
627 and the preoperative nutrition subgroup (n = 261), which did not consider such data for 4 deaths.

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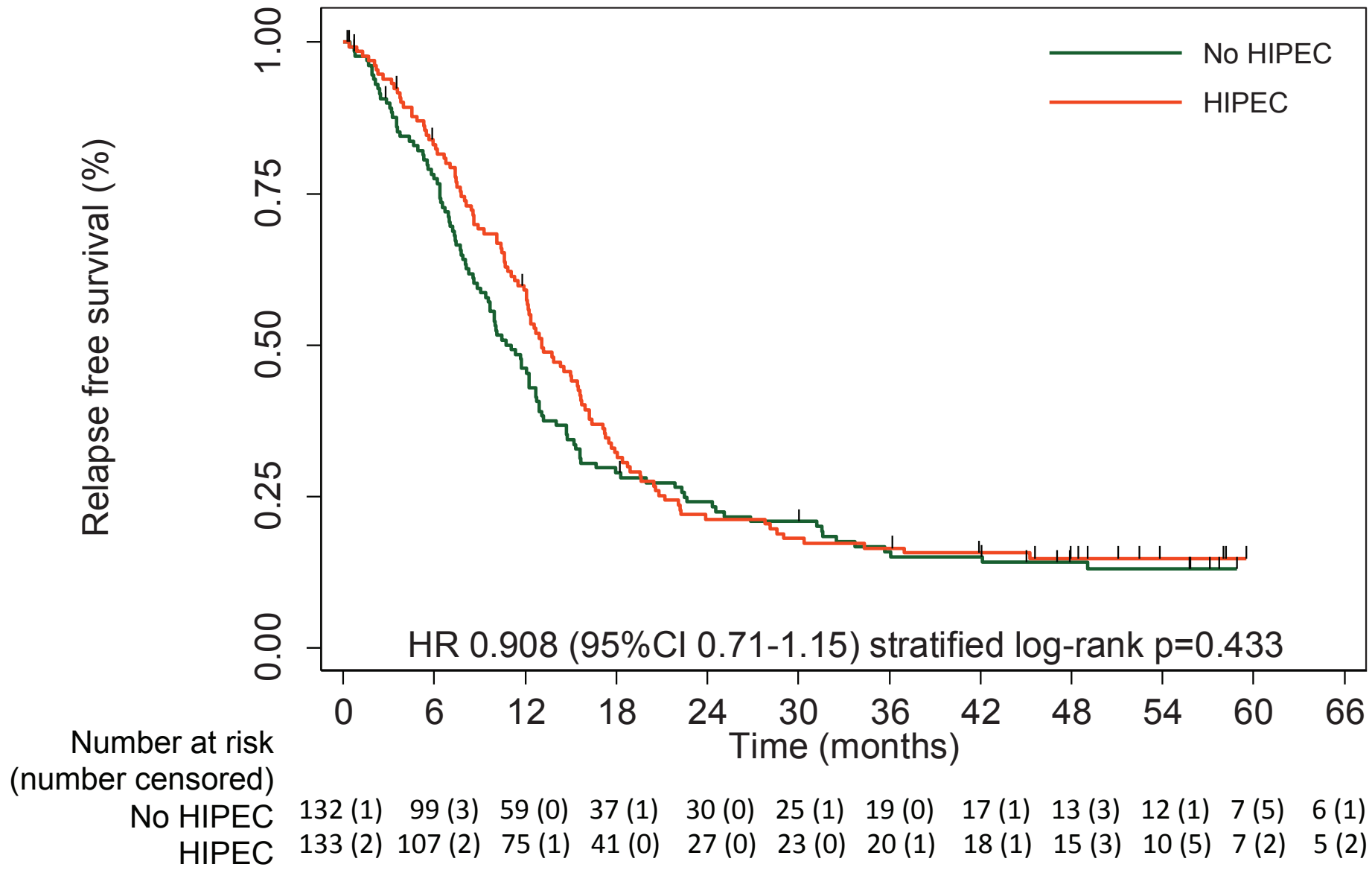
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Number at risk
(number censored)

No HIPEC	132 (1)	124 (3)	113 (0)	109 (1)	94 (2)	83 (1)	72 (0)	56 (4)	45 (4)	36 (4)	27 (9)	22 (5)
HIPEC	133 (2)	123 (2)	111 (1)	106 (0)	98 (0)	87 (0)	74 (2)	58 (4)	49 (3)	37 (8)	37 (5)	22 (6)



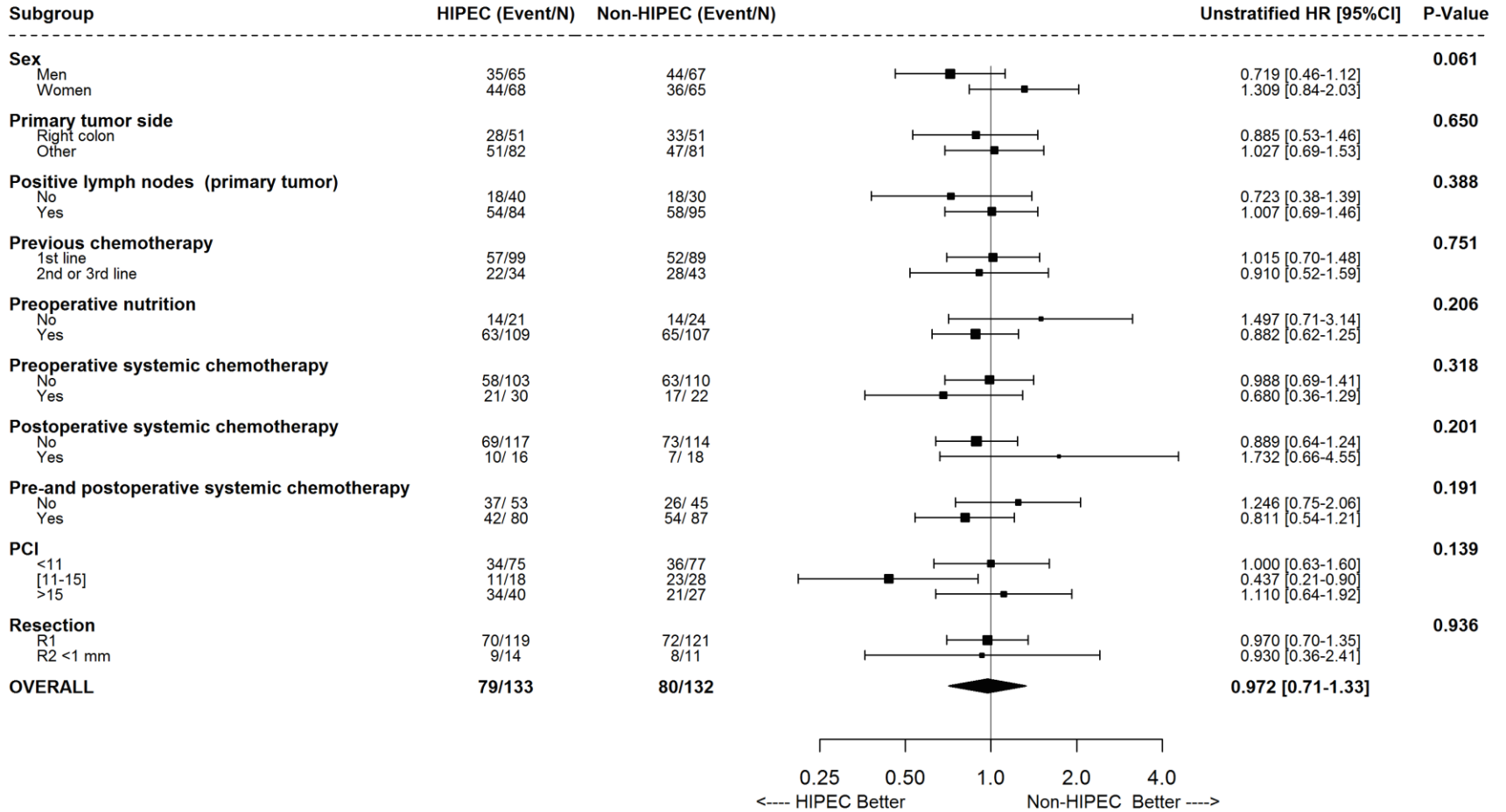


Table 1: Patient characteristics of the intention-to-treat (ITT) population

	HIPEC (n = 133)		No HIPEC (n = 132)	
Baseline Characteristics				
Age				
Median age, years (IQR)	60.0	(53-64)	61.0	(52-66)
≥65 — no. (%)	33	(24.8)	43	(32.6)
Male gender — no. (%)	65	(48.9)	67	(50.8)
WHO performance status — no. (%)†				
0	105	(79.5)	100	(76.9)
1	26	(19.7)	30	(23.1)
2	1	(0.8)	0	(0)
Primary tumor localization — no. (%)				
Right colon	51	(38.3)	51	(38.6)
Transverse colon	10	(7.5)	8	(6.1)
Left colon	61	(45.9)	64	(48.5)
Rectum	13	(9.8)	14	(10.6)
Colon (with no further information)	1	(0.8)	4	(3.0)
Previous surgery for primary tumor — no. (%)	107	(80.5)	100	(75.8)
Previous chemotherapy for primary tumor — no. (%)	65	(48.9)	63	(47.7)
Oxaliplatin for treatment of primary tumor or PM — no. (%)	59	(44.4)	58	(43.9)
Synchronous PM — no. (%)‡	51	(38.6)	54	(40.9)
Previous surgery for PM — no. (%)	29	(21.8)	37	(28.0)
Previous chemotherapy for PM — no. (%)	19	(14.3)	20	(15.2)
Systemic chemotherapy§ — no. (%)¶				
No chemotherapy	7	(5.3)	5	(3.8)
Preoperative	30	(22.6)	22	(16.7)
Postoperative	16	(12.0)	18	(13.6)
Both	80	(60.2)	87	(65.9)
Median number of preoperative chemotherapy cycles (IQR)¶	6	(4-7)	6	(4-8)
Median carcinoembryonic antigen (CEA), IU/mL (IQR)	3.8	(1.9-6)	3	(1.5-8)

*Data are n (%) unless otherwise indicated, HIPEC = hyperthermic intraperitoneal chemotherapy; PM = peritoneal metastases; PCI = Peritoneal Carcinomatosis Index; WHO = World Health Organization. There were no significant differences between the trial groups in any characteristic (nonparametric Kruskal-Wallis test).

† Data were available for 132 patients in HIPEC arm and for 130 patients in non-HIPEC arm.

‡ Data available for 132 patients in HIPEC arm.

§ Systemic chemotherapy proposed in the protocol,

¶ Patients received systemic chemotherapy for 6 months, either preoperatively, postoperatively or both.

¶ The median is given for patients who received preoperative chemotherapy, including patients in interval strategy (n = 253).

Table 2. Treatment characteristics in the intention-to-treat population, according to the treatment groups*

	HIPEC (n=133)	No HIPEC (n=132)	P value
Treatment characteristics			
Completeness of cytoreduction — no. (%)			
Complete macroscopic cytoreduction (R0/R1)**	119 (89.5)	121 (91.7)	0.541
Residual disease < 1 mm (R2)	14 (10.5)	11 (8.3)	-
Median PCI (IQR)	10 (5-16)	9 (5-14.5)	0.499
PCI — no. (%)			
<11	77 (58.3)	75 (56.4)	0.094
11–15	28 (21.2)	18 (13.5)	-
>15	27 (20.5)	40 (30.1)	-
Median time from PM diagnosis to CRS – days (IQR)	149 (112-230)	163.5 (117-259.5)	0.386
Median number of affected regions by PM (IQR)§	5.0 (3-9)	5.5 (3-9)	0.071
Median number of resected organs (IQR)	2.0 (1-3)	2.0 (1-3)	0.946
Median number of anastomoses during surgery (IQR) (n=197)	1 (1-2)	1 (1-2)	0.889
Median duration of surgery (IQR) — min††	365 (280-460)	300 (240-360)	<0.001
Median duration of hospitalization (IQR) — days‡‡	18 (14-27)	13 (11-20)	<0.001
Median duration of intensive care unit stay – days (IQR) (n=129)	2.5 (1-7.5)	3 (1-7)	0.575
Median interval between surgery and food intake (IQR) — days §§	7.5 (5-10)	6 (4-8)	<0.001
Median number of surgical reintervention (IQR) (n=46)	1 (1-2)	0 (1-1.5)	0.268

*HIPEC, hyperthermic intraperitoneal chemotherapy.

** Cytoreduction was described as R0/R1: complete macroscopic resection or R2: surgical resection with residual tumor tissue ≤ 1 mm.

§ Data available for 128 patients in the non-HIPEC arm.

†† Data were available for 131 patients in the HIPEC arm and 128 patients in the non-HIPEC arm.

‡‡ Data available for 131 patients in the non-HIPEC arm.

§§ Data were available for 112 patients in the HIPEC arm and 110 patients in the non-HIPEC arm.