



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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François Quénet, Dominique Elias, Lise Roca, Diane Goéré, Laurent Ghouti, et al.. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy versus cytoreductive surgery alone for colorectal peritoneal metastases (PRODIGE 7): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncology, 2021, 22 (2), pp.256-266. 10.1016/s1470-2045(20)30599-4 . hal-03220825

HAL Id: hal-03220825

<https://hal.science/hal-03220825>

Submitted on 13 Feb 2023

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

François Quénet, Dominique Elias, Lise Roca, Diane Goéré, Laurent Ghouti, Marc Pocard, Olivier Facy, Catherine Arvieux, Gérard Lorimier, Denis Pezet, Frédéric Marchal, Valeria Loi, Pierre Meeus, Beata Juzyna, Hélène de Forges, Jacques Paineau, Olivier Glehen, UNICANCER-GI Group and French “BIG-Renape” Group

Surgical Oncology Department, Institut du Cancer de Montpellier (ICM), University of Montpellier, Montpellier, France (F Quénet MD)

Surgery Department, Gustave Roussy, Villejuif, France (Prof D Elias MD and Prof D Goéré MD);

Biometrics Unit, Institut du Cancer de Montpellier (ICM), University of Montpellier, Montpellier, France (L Roca MSc)

Surgery Department, Centre Hospitalier Purpan, Toulouse , France (L Ghouti MD);

Surgical Oncological and Digestive Unit, Paris University, U1275 CAP Paris-Tech, Paris, France (Prof M Pocard MD);

Digestive Surgery and Oncology Department, Centre Hospitalier Universitaire du Bocage, Dijon, France (Prof O Facy MD);

Oncologic Surgery Department, Centre Hospitalier Universitaire Grenoble, La Tronche, France (Prof C Arvieux MD);

Surgery Department, Centre Paul Papin, Angers, France (G Lorimier MD);

24 **Digestive and Hepatobiliary Surgery Department, Hôtel Dieu, Clermont-Ferrand, France** (Prof
25 D Pezet MD);

26 **Oncologic Surgery Department, Institut de Cancérologie de Lorraine, Vandoeuvre-Lès-Nancy,**
27 **France** (Prof F Marchal MD);

28 **Digestive and Visceral Surgery Department, Hôpital Tenon, Paris, France** (V Loi MD);

29 **Oncologic Surgery Department, Centre Léon Bérard, Lyon, France** (P Meeus MD);

30 **R&D UNICANCER Department, Paris, France** (B Juzyna, Eng);

31 **Clinical Research and Innovation Department, Institut du Cancer de Montpellier (ICM),**
32 **University of Montpellier, Montpellier, France** (H de Forges PhD);

33 **Surgery Department, Institut de Cancérologie de l'Ouest, Saint Herblain, France** (Prof J
34 Paineau MD);

35 **Digestive Surgery Department, Centre Hospitalier Lyon Sud, Pierre Bénite, France** (Prof O
36 Glehen MD);

37 **Correspondence to :**

38 Dr François Quénet

39 Department of Surgical Oncology

40 Institut du Cancer de Montpellier (ICM)

41 208 avenue des Apothicaires

42 34298 Montpellier

43 France

44 Email: francois.quenet@icm.unicancer.fr

45 Phone: +33 4 67 61 30 15

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Summary

Background

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

Methods

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

Findings

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

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RESEARCH IN CONTEXT

Evidence before this study

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

Added value of this study

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

Implications of all the available evidence

Our data suggest that oxaliplatin-HIPEC administered at high dose and for short duration should be 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.

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INTRODUCTION

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

METHODS

TRIAL DESIGN AND PARTICIPANTS

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

RANDOMISATION AND MASKING

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

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

PROCEDURES

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

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

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

OUTCOMES

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

STATISTICAL ANALYSIS

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

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

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

ROLE OF THE FUNDING SOURCES AND ACCESS TO THE DATA

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

RESULTS

Between February 11th 2008 and January 6th 2014, 265 patients from 17 French centers were randomly assigned to receive CRS and HIPEC (n = 133) or CRS alone (n = 132). A number of 131 patients were assessed before surgery but excluded before randomization mostly because of PCI > 25 or considered non-resectable due to major visceral involvement (Figure 1). Baseline features, tumor characteristics and previous treatments were similar in both arms (Table 1). The median age was 60 years (IQR 52-65). The primary tumor was previously resected in 207/265 patients (78.1%), among which 128/265 patients (48.3%) were treated with systemic adjuvant chemotherapy. The complete macroscopic resection rate was 89.5% (n = 119/133) in HIPEC arm and 91.7% (n = 121/132) in non-HIPEC arm. The overall median PCI was 10 (IQR 5-16) without significant difference between two arms. The median delay between PM diagnosis and CRS was 5.1 months (IQR 3.8-8.3). In 10% of patients, a long delay was reported (5.9%, > 1 year) and in 4.1%, > 2 years). In 105 patients of 265 (39.8%) the PM were synchronous with the primary tumor, among which 66/265 (24.9%) have previously been treated by surgery and 39/265 (14.7%) and/or chemotherapy (Table 1). No significant difference was observed between arms for previous PM surgery or chemotherapy. Sixteen patients/132 from the non-HIPEC arm were crossed over and received HIPEC for treatment of first isolated PM relapse (Figure 1). Most patients (95.5%, n = 253/265) received systemic chemotherapy for 6 months, either preoperatively (19.6%, n = 52/265) or postoperatively (12.8%, n = 34/265) or both (63.0%, n = 167/265) in an interval strategy. Timing for chemotherapy and the median number of preoperative chemotherapy cycles were similar between arms (Table 1). Patients received a median number of 6 cycles of preoperative chemotherapy (58.0% \geq 6 cycles, n = 127/219). Among all patients who received preoperative chemotherapy, 94/219 (42.9%) received oxaliplatin-based treatment, including patients (n = 50/127, 39.4%) with \geq 6 cycles (Supplementary Table S2). Taking into account systemic regimens prior to trial inclusion, adjuvant treatment to surgery for primary tumor or for previous PM treatment, a proportion of 73.2% of patients (n = 194/265) received oxaliplatin-based systemic chemotherapy (cumulative oxaliplatin-based treatment, Supplementary Table S2). A number of 49/265 patients (18.5%) received chemotherapy with anti-EGFR (either pre- or post-operatively or

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

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

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

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

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

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

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

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

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

DISCUSSION

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

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

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

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

The 30-day mortality rate was of 1.5% and the grade ≥ 3 morbidity rate of 37%, 42.1% in the HIPEC arm and 31.8% in the non-HIPEC arm. These numbers are comparable to those published by other specialized institutions.^{6,7,13} Recently, Foster et al.¹³ used data from the American College of Surgeons National Surgical Quality Improvement Project database to compare perioperative and 30-day postoperative morbidity and mortality rates for CRS and HIPEC with other high-risk surgical oncology procedures.¹⁴ They showed that CRS and HIPEC had lower or comparable morbidity rates than pancreatoduodenectomy or oesophagectomy.¹⁴ In our study, adding HIPEC with oxaliplatin to CRS did not significantly increase the overall rate of early postoperative complications at 30 days and resulted in a mortality rate similar to that of CRS alone. Grade ≥ 3 digestive fistulae occurred in 10.5% of patients vs. 6.8% for patients treated with CRS alone, rates which were not significantly different between the two arms and remained close to those reported by single- and multicenter studies.^{6,7,8} We did not report a statistical significant different for extra-abdominal complications, but hematologic toxicity was higher in the HIPEC group. We used the protocol of bi-directional chemotherapy¹⁵ and allowed HIPEC to be performed with either open or closed techniques, as no clear difference has been demonstrated between these two procedures.^{10,16,17} However, oxaliplatin-HIPEC significantly increased the 60-day grade ≥ 3 complications rate. This suggests that HIPEC may extend the time during which patients are at risk of developing postoperative complications, resulting in a 5-day longer hospital stay and a longer time to resume postoperative systemic chemotherapy in the

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

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

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

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

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

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

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

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

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

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

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

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

CONTRIBUTORS

The authors thank for their participation in the study : Dr Pascale Mariani (Institut Curie, Paris, France), Prof Cécile Brigand (CHU Strasbourg, Strasbourg, France), Dr Jean-Marc Bereder (CHU l'Archer, Nice, France) and Prof Simon Msica (Hôpital Louis Mourier, Colombes, France), Prof Guillaume Portier (Centre Hospitalier Purpan, Toulouse, France), and Prof Patrick Rat (CHU Dijon, Dijon, France).

DECLARATION OF INTEREST

The authors declared no conflicts of interest

ACKNOWLEDGMENTS

The authors thank the patients who participated in the study and their families for their trust. They also thank R&D UNICANCER for sponsorship and all regulatory aspects of the study, the members of the PRODIGE intergroup (Unicancer Gastrointestinal Fédération Francophone de Cancérologie Digestive), Trevor Stanbury (R&D Unicancer) for study management, Sylvain Boudon (Montpellier Cancer Institute, ICM, Montpellier, France) for data management, Andrew Kramar and Sophie Gourgou (Montpellier Cancer Institute, ICM, Montpellier, France) for study design and methodology, and all clinical research assistants at all the participating centers. The authors thank the members of the independent study data monitoring committee, Prof Jean-Pierre Delord (IUCT-Oncopôle, Toulouse, France) and Dr Gwenaél Ferron (IUCT-Oncopôle, Toulouse, France) for their advice, and Prof Thierry André (Hôpital Saint Antoine, Paris, France) and Dr Florin Grigorescu (florin.grigorescu@inserm.fr) for their valuable review of the manuscript.

DATA SHARING STATEMENT

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

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

AUTHORS' CONTRIBUTIONS

Conception and design: FQ, DE, LR, OG

Study coordination and funding: FQ, BJ

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

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

Drafting of the manuscript: FQ, LR, HF

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

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

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607

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

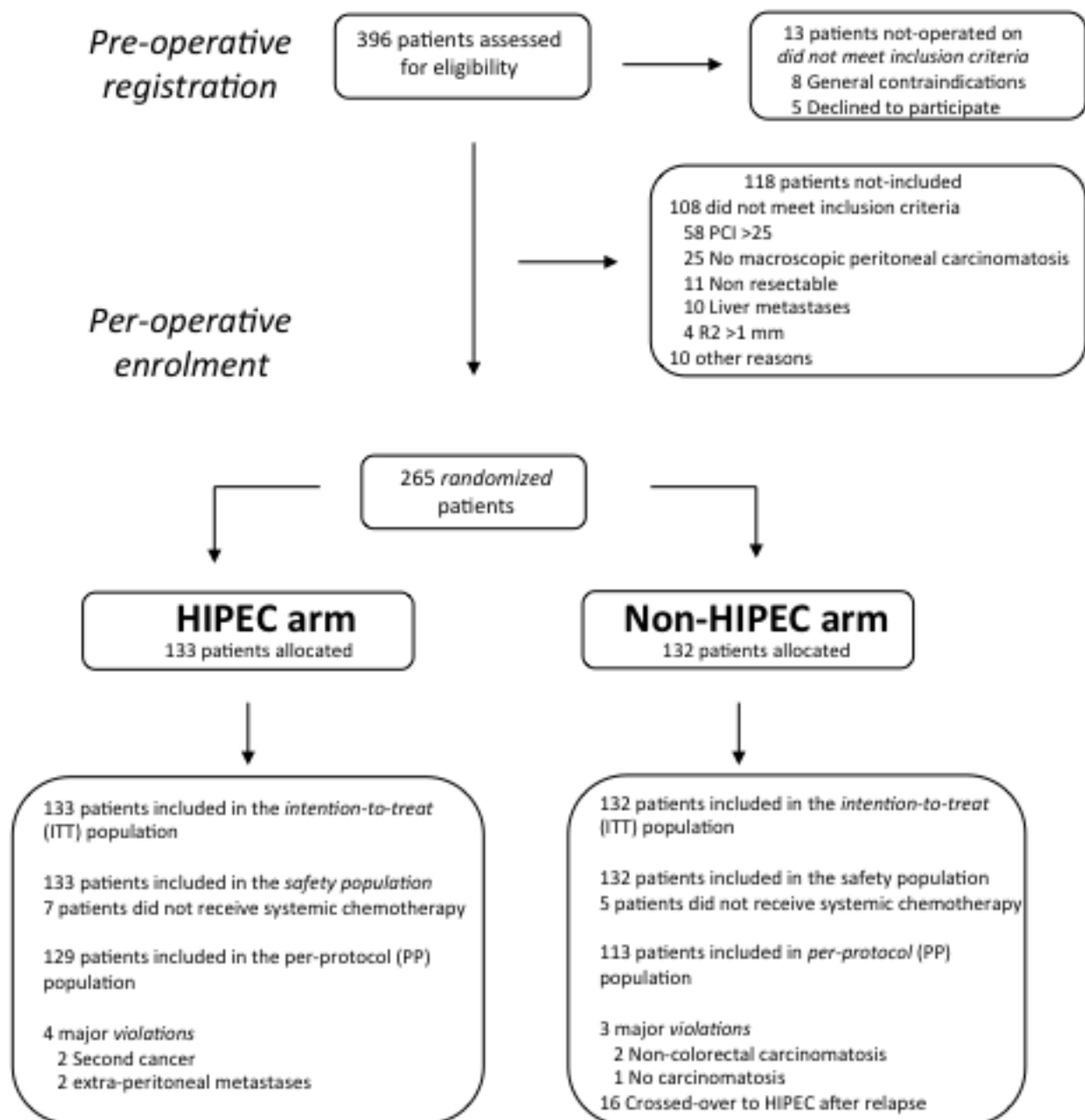
HIPEC denotes hyperthermic intraperitoneal chemotherapy, PCI Peritoneal Carcinomatosis Index, ITT intention-to-treat population, and PP per-protocol population.

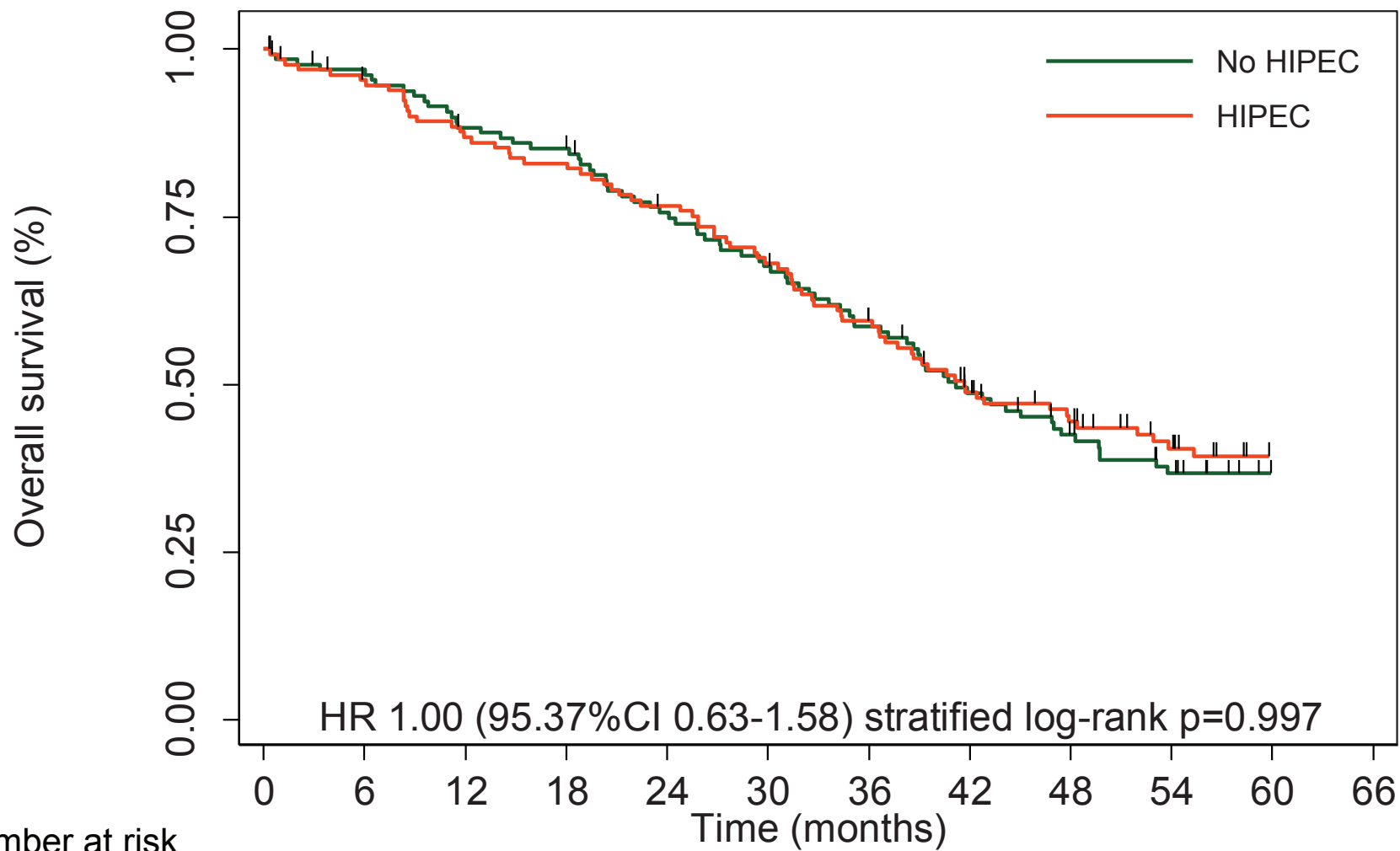
Figure 2. Kaplan-Meier estimates of (A) OS and (B) RFS in the Intention-to-Treat Population, According to treatment Group

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

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

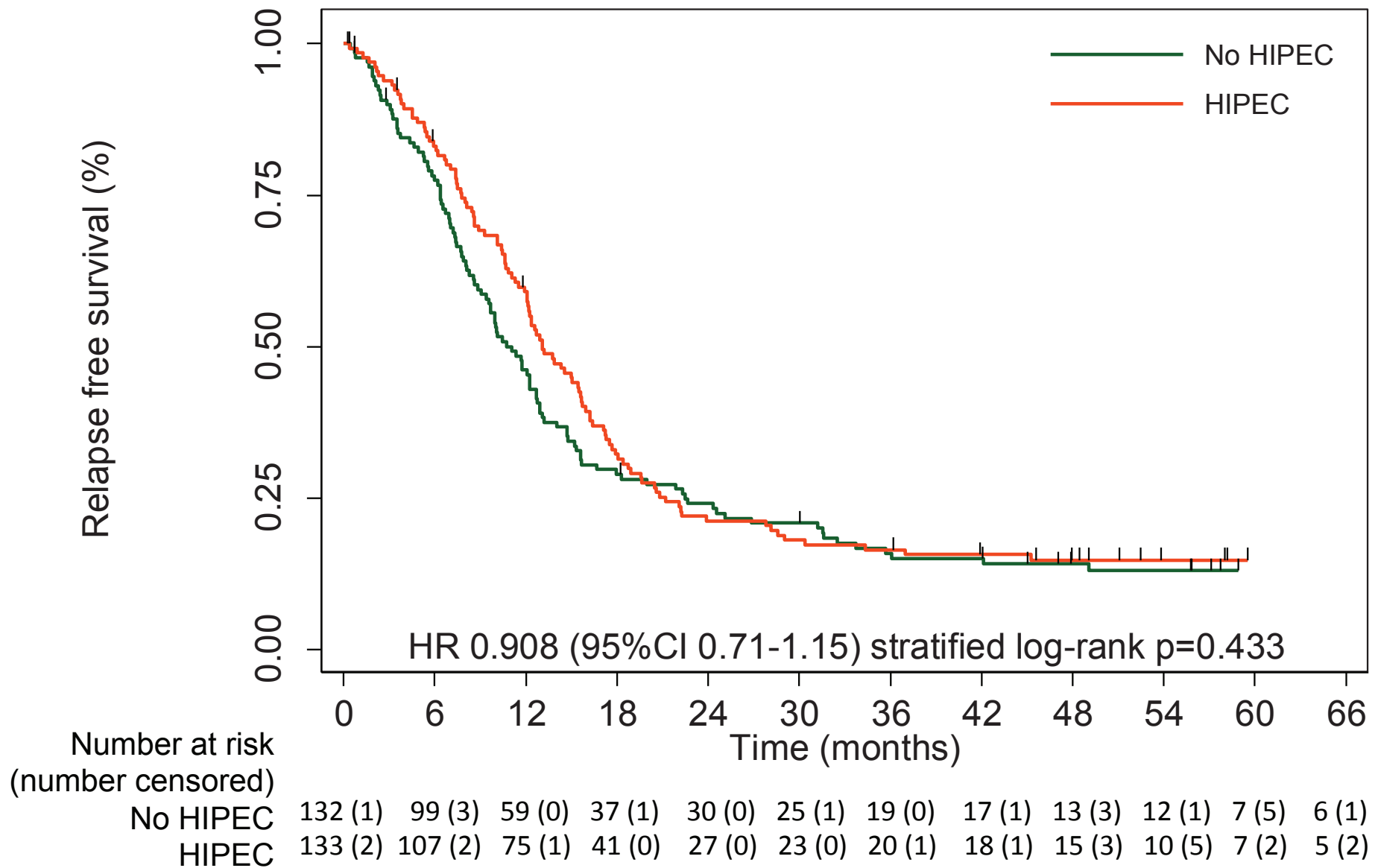
CI denotes confidence interval, CT chemotherapy, HIPEC hyperthermic intraperitoneal chemotherapy, HR hazard ratio, LN lymph node, PCI Peritoneal Carcinomatosis Index. The position of each square represents the point estimate of the treatment effect, and error bars represent 95% CI. The sizes of the squares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





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)



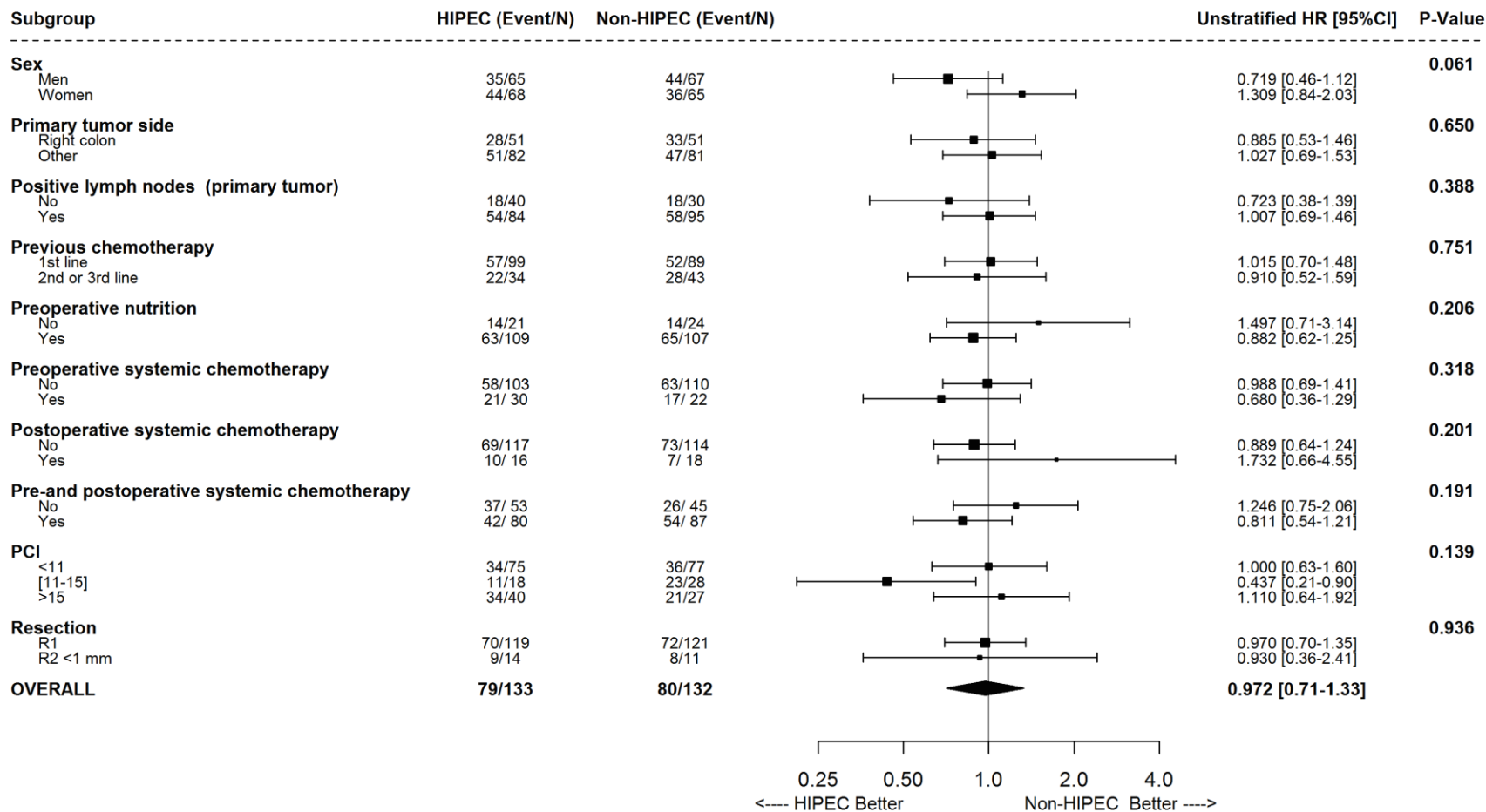


Table 1: Patient characteristics of the intention-to-treat (ITT) population

	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.