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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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Summary

Background The addition of hyperthermic intraperitoneal chemotherapy (HIPEC) to cytoreductive surgery has been associated with encouraging survival results in some patients with colorectal peritoneal metastases who were eligible for complete macroscopic resection. We aimed to assess the specific benefit of adding HIPEC to cytoreductive surgery compared with receiving cytoreductive surgery alone.

Methods We did a randomised, open-label, phase 3 trial at 17 cancer centres in France. Eligible patients were aged 18–70 years and had histologically proven colorectal cancer with peritoneal metastases, WHO performance status of 0 or 1, a Peritoneal Cancer Index of 25 or less, and were eligible to receive systemic chemotherapy for 6 months (ie, they had adequate organ function and life expectancy of at least 12 weeks). Patients in whom complete macroscopic resection or surgical resection with less than 1 mm residual tumour tissue was completed were randomly assigned (1:1) to cytoreductive surgery with or without oxaliplatin-based HIPEC. Randomisation was done centrally using minimisation, and stratified by centre, completeness of cytoreduction, number of previous systemic chemotherapy lines, and timing of protocol-mandated systemic chemotherapy. Oxaliplatin HIPEC was administered by the closed (360 mg/m²) or open (460 mg/m²) abdomen techniques, and systemic chemotherapy (400 mg/m² fluorouracil and 20 mg/m² folinic acid) was delivered intravenously 20 min before HIPEC. All individuals received systemic chemotherapy (of investigators' choosing) with or without targeted therapy before or after surgery, or both. The primary endpoint was overall survival, which was analysed in the intention-to-treat population. Safety was assessed in all patients who received surgery. This trial is registed with ClinicalTrials.gov, NCT00769405, and is now completed.

Findings Between Feb 11, 2008, and Jan 6, 2014, 265 patients were included and randomly assigned, 133 to the cytoreductive surgery plus HIPEC group and 132 to the cytoreductive surgery alone group. After median follow-up of 63·8 months (IQR 53·0–77·1), median overall survival was 41·7 months (95% CI 36·2–53·8) in the cytoreductive surgery plus HIPEC group and 41·2 months (35·1–49·7) in the cytoreductive surgery group (hazard ratio 1·00 [95·37% CI 0·63–1·58]; stratified log-rank p=0·99). At 30 days, two (2%) treatment-related deaths had occurred in each group.. Grade 3 or worse adverse events at 30 days were similar in frequency between groups (56 [42%] of 133 patients in the cytoreductive surgery plus HIPEC group *vs* 42 [32%] of 132 patients in the cytoreductive surgery group; p=0·083); however, at 60 days, grade 3 or worse adverse events were more common in the cytoreductive surgery plus HIPEC group (34 [26%] of 131 *vs* 20 [15%] of 130; p=0·035).

Interpretation Considering the absence of an overall survival benefit after adding HIPEC to cytoreductive surgery and more frequent postoperative late complications with this combination, our data suggest that cytoreductive surgery alone should be the cornerstone of therapeutic strategies with curative intent for colorectal peritoneal metastases.

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Introduction

Peritoneal metastases, a clinical form of disease progression in colorectal cancer, are synchronous in approximately 7% of cases of colorectal cancer and the first and only localisation of metastases in more than 4% of cases. In population-based studies, the 5-year cumulative risk of metachronous peritoneal metastases in colorectal cancer is 6%.[1] Peritoneal metastases are associated with reduced overall survival, and, in 30–40% of cases, they are associated with significantly worse prognosis compared with non-peritoneal metastases (16·3 months [95% CI 13·5–18·8] for peritoneal

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Research in context

Evidence before this study

We searched PubMed with the medical subject heading terms "cytoreduction surgical procedures", "peritoneum, "neoplasm metastasis", "colorectal neoplasms", "colorectal cancer", and "hyperthermia, induced" to identify articles published in English between Jan 1, 2000, and Dec 31, 2019. We identified only one randomised clinical trial (cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy [HIPEC] versus systemic chemotherapy), which was done in 2003. Peritoneal metastases secondary to colorectal cancer are associated with poorer prognosis than extraperitoneal metastases from colorectal cancer. In patients eligible for complete surgical resection, the combination of cytoreductive surgery and HIPEC has been used for more than a decade. Retrospective studies show median overall survival of 35–40 months for patients amenable to macroscopically complete resection of peritoneal metastases. However, we did not identify any studies in which the specific effect of HIPEC on survival was assessed.

Added value of this study

To our knowledge, ours is the first study to address the specific role of HIPEC when used in combination with cytoreductive surgery to treat peritoneal metastases secondary to colorectal cancer. The addition of oxaliplatin-based HIPEC to cytoreductive surgery did not significantly affect overall survival or relapse-free survival compared with cytoreductive surgery alone, but was associated with a higher number of postoperative complications at 60 days. The curative management of peritoneal metastases secondary to colorectal cancer with cytoreductive surgery alone (in association with systemic chemotherapy) at specialised cancer centres was unexpectedly efficacious in terms of long-term recurrence-free survival.

Implications of all the available evidence

High-dose oxaliplatin-based HIPEC given over a short duration should no longer be used, and macroscopically complete cytoreductive surgery should be considered the mainstay of treatment of peritoneal metastases. Eligibility for surgical resection should be the main consideration in patients with colorectal cancer and peritoneal metastases. Such changes to clinical practice would spare patients with colorectal cancer from undergoing unnecessary intraperitoneal chemotherapy.

metastases *vs* 19·1 months [18·3–19·8] for liver-only metastases and 24·6 months [22·7–26·4] for lung-only metastases).[2,3]

In patients with isolated peritoneal metastases, administration of systemic chemotherapeutic regimens—the only treatment available for patients with unresectable disease—slightly increases median overall survival to 16·3 months (95% CI 13·5–18·8).[3] In patients with potentially resectable disease, surgical management of peritoneal metastases of colorectal origin has evolved profoundly in the past 15 years. Worldwide, hyperthermic intraperitoneal chemotherapy (HIPEC) has been added to cytoreductive surgery. HIPEC delivers high local concentrations of antineoplastic drugs, the cytotoxic effects of which are enhanced by hyperthermia. In several retrospective studies,[4–7] median overall survival with cytoreductive surgery plus HIPEC was encouraging in patients amenable to macroscopically complete resection (as long as 40 months in some patients). In a Dutch phase 3 controlled trial,[8] cytoreductive surgery plus HIPEC was superior to systemic chemotherapy in terms of overall survival in patients in whom surgery was done only to relieve symptoms caused by bowel obstruction. In specialised centres, cytoreductive surgery plus HIPEC can cure (ie, no evidence of disease at 5 years) around 16% of patients in whom resection is macroscopically complete.[9]

In clinical practice, surgical resection and HIPEC have always been used in combination. The specific benefits associated with adding HIPEC to cytoreductive surgery have not been assessed in prospective trials. In this trial, we aimed to evaluate the specific role of HIPEC when added to cytoreductive surgery in patients with peritoneal metastases of colorectal origin.

See Online for appendix

Methods

Study design and participants

PRODIGE 7 was a randomised, open-label, phase 3 trial done at 17 cancer centres in France (appendix p 2). Eligible patients were aged 18–70 years; had histologically confirmed colorectal cancer, peritoneal metastases, a Peritoneal Cancer Index (PCI) of 25 or less, a WHO performance status of 0 or 1, adequate haematological function (defined as a neutrophil count of at least $1·5\times10^9$ per L and a platelet count of at least 100×10^9 per L), and adequate liver function (defined as a total bilirubin concentration of 1·5 times the upper limit of normal [ULN] or less; aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase concentrations of three times the ULN or less; and plasma creatinine concentrations of 1·25 times the ULN or less); and were eligible to receive systemic chemotherapy for 6 months (ie, they had adequate organ function and life expectancy of at least 12 weeks).

Any previous treatments were allowed, and no washout period was mandatory—although many investigators chose to impose a 4-week washout before surgery (6 weeks in patients who had been given bevacizumab). Any comorbidities were allowed if the patient was still deemed operable. The main exclusion criteria were extraperitoneal metastases, non-colorectal carcinomatosis, previous HIPEC treatment, and grade 3 or worse peripheral neuropathy (per the National Cancer

Institute's Common Terminology Criteria for Adverse Events [CTCAE], version 3.0). A full list of inclusion and exclusion criteria is in the appendix (p 2). This study was done in accordance with the Helsinki Declaration and Good Clinical Practice requirements. Independent local ethics committees at each study site approved the trial protocol. All patients provided written informed consent.

Randomisation and masking

Eligible patients were recruited by the trial investigators and randomly assigned (1:1) peroperatively to receive either HIPEC or no further treatment after complete cytoreductive surgery. Only patients in whom cytoreductive surgery resulted in complete macroscopic resection or less than 1 mm of residual tumour tissue were included in the trial. The study statistician (LR) used the TenAlea software (version 2.2; National Cancer Institute, Amsterdam, Netherlands) to generate the randomisation sequence, which incorporated a minimisation process via the Pocock and Simon method for any random factor on the basis of baseline prognostic variables. This minimisation (with a probability of 0·8) allowed an allocation in favour of the treatment that would counteract any potential imbalance. To minimise biases associated with the individual surgical units, patients were stratified by trial centre on the basis of the completeness of cytoreduction (complete macroscopic resection *vs* minimal residual disease), number of previous lines of systemic chemotherapy lines (first-line only *vs* second-line or more, not including systemic preoperative chemotherapy in the context of the trial protocol), and timing of systemic chemotherapy (preoperative *vs* postoperative). This trial was open-label, and thus neither investigators nor patients were masked to group assignment.

Procedures

All patients received identical cytoreductive surgery. If disease was too extensive (ie, PCI>25), complete macroscopic resection was ruled out and patients were not included in the trial; if disease was deemed resectable, every attempt was made to fully resect as much of the macroscopically resectable disease as possible. HIPEC was administered with either the closed or open abdomen techniques[6,10] according to each centre's standard approach. In both approaches, systemic chemotherapy (400 mg/m² fluorouracil and 20 mg/m² folinic acid) was delivered intravenously 20 min before intraperitoneal infusion of oxaliplatin (460 mg/m² if the open technique was used and 360 mg/m² if the closed technique was used) in 2 L/m² of dextrose at 43°C over 30 min. No drug substitutions or dose modifications were allowed for HIPEC. The HIPEC procedure could be paused if important complications occurred, but the oxaliplatin dose could not be decreased. For systemic chemotherapy, dose reductions as a result of important complications were at investigators' discretion.

All patients also received systemic chemotherapy with or without targeted therapy before or after surgery, or both. The chemotherapy and targeted therapy regimens used were at investigators' discretion. Patients were followed up 1 month after surgery, then every 3 months for the first 3 years and every 6 months up to 5 years. Comorbidies were assessed, and blood counts, ionograms, liver and kidney function tests, pregnancy tests, and measurements of tumour markers (specifically carcinoembryonic antigen and cancer antigen 19-9) and albumin concentrations were done, at baseline. Tumour markers were also assessed at 3-year and 5-year follow-up. Disease was assessed via clinical examination, measurement of tumour markers, and thoracicoabdominal–pelvic CT at all follow-up appointments. PET and peritoneal MRI were also used at investigators' discretion. For all time-to-event analyses, patients without events at the time of analysis were censored at the date of their last informative follow-up.

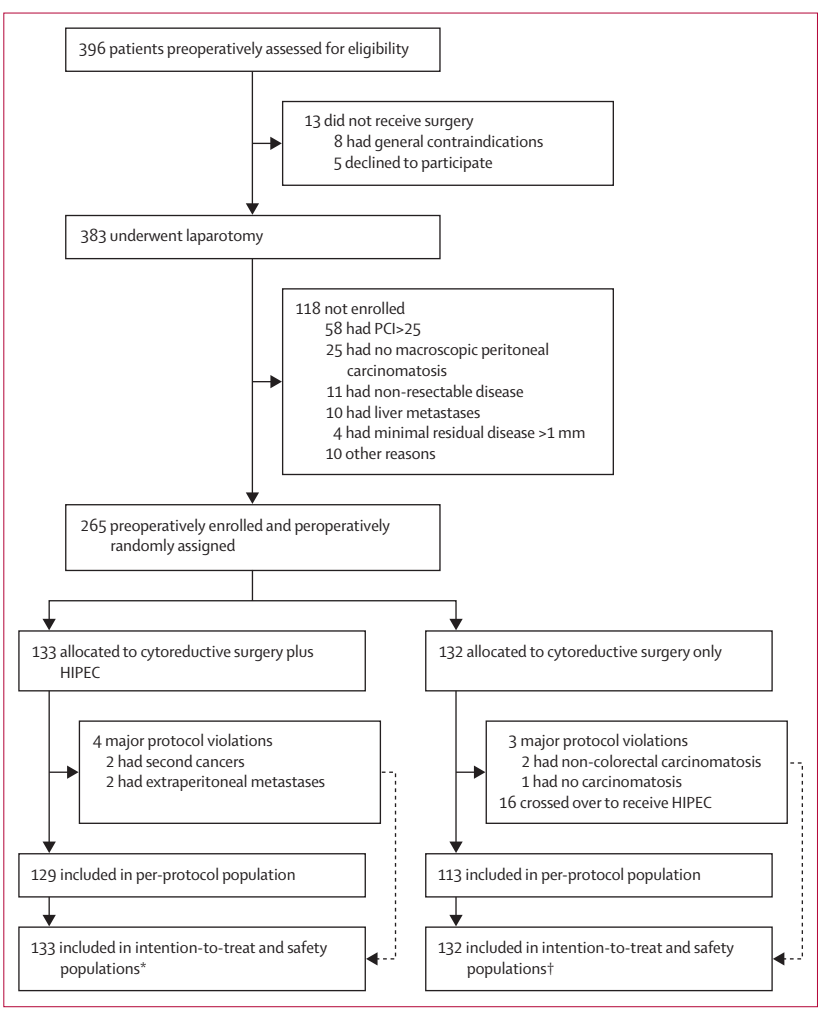


Figure 1: **Trial profile**
HIPEC=hyperthermic intraperitoneal chemotherapy. PCI=Peritoneal Carcinomatosis Index. *Includes seven patients who did not receive systemic chemotherapy. †Includes five patients who did not receive systemic chemotherapy (we did not specifically class the absence of systemic chemotherapy as a protocol violation because systemic chemotherapy was the standard of care).

	Cytoreductive surgery plus HIPEC group (n=133)	Cytoreductive surgery group (n=132)
Age, years	60 (53–64)	61 (52–66)
Sex		
Male	65 (49%)	67 (51%)
Female	68 (51%)	65 (49%)
WHO performance status*		
0	105 (80%)	100 (77%)
1	26 (20%)	30 (23%)
2	1 (1%)	0
Primary tumour localisation		
Right colon	51 (38%)	51 (39%)
Transverse colon	10 (8%)	8 (6%)
Left colon	61 (46%)	64 (48%)
Rectum	13 (10%)	14 (11%)
Colon (no specific information)	1 (1%)	4 (3%)
Synchronous peritoneal metastases†	51 (39%)	54 (41%)
Previous surgery		
For primary tumour	107 (80%)	100 (76%)
For peritoneal metastases	29 (22%)	37 (28%)
Previous chemotherapy		
For primary tumour	65 (49%)	63 (48%)
For peritoneal metastases	19 (14%)	20 (15%)
Oxaliplatin (for primary tumour or peritoneal metastases)	59 (44%)	58 (44%)
Systemic chemotherapy‡		
No chemotherapy	7 (5%)	5 (4%)
Preoperative	30 (23%)	22 (17%)
Postoperative	16 (12%)	18 (14%)
Both	80 (60%)	87 (66%)
Preoperative chemotherapy cycles§	6 (4–7)	6 (4–8)
Carcinoembryonic antigen, IU/mL	4 (2–6)	3 (2–8)

Data are median (IQR) or n (%). Because of rounding, some percentages might not total 100%. HIPEC=hyperthermic intraperitoneal chemotherapy. IU=international units. *Data were available for 132 patients in the cytoreductive surgery plus HIPEC group and 130 patients in the cytoreductive surgery group. †Data were available for 132 patients in the cytoreductive surgery plus HIPEC group. ‡Systemic chemotherapy proposed in the protocol (patients received systemic chemotherapy for 6 months preoperatively or postoperatively, or both). §The median is given for patients who received preoperative chemotherapy, including patients who were treated with an interval strategy (n=219).

Table 1: **Baseline characteristics in intention-to-treat population**

Immediate postoperative morbidity was reported twice: once for complications between surgery (ie, day 1) and day 30 (30-day complication rate), and once for complications between days 31 and 60 (60-day complication rate). Adverse events were graded according to the CTCAE (version 3.0).

Outcomes

The primary endpoint was overall survival, which was defined as the time from randomisation to death from any cause. Relapse-free survival (defined as the interval between randomisation and the first peritoneal or distant relapse or death from any cause), peritoneal-free survival (the interval between randomisation and the first peritoneal relapse). safety, and postoperative morbidity were secondary endpoints. Survival prognostic factors, although detailed in the protocol, are not reported here because of the negative results of the trial.

Statistical analysis

The study was powered to achieve a median increase in overall survival from 30 months to 48 months in the cytoreductive surgery plus HIPEC group, with a hazard ratio (HR) of 0·625. To achieve such an increase, we estimated that we would need to recruit 264 patients (ie, 132 per group) according to East (version 5). To obtain 80% power and to detect the difference between groups with a two-sided log-rank test with a nominal α of 5%, 154 events (deaths) were required. The trial design was adaptive, with two planned intermediate analyses to test efficacy and futility according to O'Brien-Fleming boundaries: at the 51st death, the analysis would be significant for efficacy if p was 0·0002 or less and futile if p was greater than 0·965. Meanwhile after the 102nd death, the analysis would be significant for efficacy if p was less than or equal to 0·012 and futile if p was greater than 0·331. A planned interim analysis for the primary endpoint was done in April 25, 2014, after 70 deaths had occurred in a sample of patients that was similar to the overall population in terms of clinical characteristics. At the first interim analysis, recruitment was already completed and the independent data monitoring committee recommended waiting for complete database maturity before drawing conclusions. The final analysis was planned after the 154th event, at which point p values of less than 0·0463 with adjusted CIs were deemed significant.

All analyses were done on the intention-to-treat population, which included all randomly assigned patients. In post-hoc analyses, overall survival, relapse-free survival, and peritoneal-free survival were also analysed in the per-protocol population, which included all randomly assigned patients who received cytoreductive surgery with or without HIPEC without any violations of major inclusion or exclusion criteria (crossover patients who received HIPEC for recurrent peritoneal metastases were excluded from the per-protocol analysis). Because systemic chemotherapy was the standard of care, we did not specifically class the absence of systemic chemotherapy as a protocol violation. We also did a sensitivity analysis in which not receiving systemic chemotherapy was classed as a protocol violation. The safety population included all patients who were operated on and was analysed by treatment actually received. Qualitative variables were compared with the χ^2 or Fisher's exact test, and quantitative variables with the Kruskal-Wallis test. Survival estimates were calculated via the Kaplan-Meier method and compared with the stratified log-rank test. We used a stratified Cox proportional-hazards model to estimate HRs with 95% CIs and 95·37% CIs for the primary endpoint. The SEs of the estimated HRs were adjusted to account for possible within-centre correlation.

. Adjustment for potential within-centre correlation was done on SEs, and results are expressed as modified CIs. The proportional-hazards assumption was verified with the Schoenfeld residual method. We did a sensitivity analysis for the primary endpoint in which we used the inverse probability of censoring weighting method to account for crossover patients. Forest plots for overall and relapse-free survival were constructed for different subgroups (prespecified). We did post-hoc exploratory analyses to assess the association between PCI and time-to-event endpoints in the intention-to-treat and per-protocol populations. No imputation was done for missing data.

All statistical analyses were done in Stata (version 13.0). This trial is registered with ClinicalTrials.gov, NCT00769405.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. FQ, LR, and HdF had full access to all the data in the study and FQ had final responsibility for the decision to submit for publication.

Results

Between Feb 11, 2008, and Jan 6, 2014, 265 patients were randomly assigned to treatment, 133 to the cytoreductive surgery plus HIPEC group and 132 to the cytoreductive surgery alone group (figure 1). A further 131 patients were assessed before surgery but excluded before randomisation (mostly because PCI>25 or because their peritoneal metastases were non-resectable as a result of major visceral involvement). At baseline, demographic characteristics, tumour characteristics, and previous treatments (both surgical and chemotherapeutic) were similar in both groups (table 1). The primary tumour was previously resected in 207 (78%) patients, 128 of whom were treated with systemic adjuvant chemotherapy.

110 patients in cytoreductive surgery plus HIPEC group and 109 in the cytoreductive surgery alone group were treated with preoperative chemotherapy. Patients in both groups received a median of six cycles of preoperative chemotherapy (table 1). 48 (44%) of 133 patients in the HIPEC group and 46 (42%) of patients in the surgery only group received preoperative oxaliplatin-based treatment (appendix p 3). When systemic regimens before trial inclusion, adjuvant treatment for primary tumour resection, and treatments for previous peritoneal metastases were taken into account, 98 (74%) patients in HIPEC plus cytoreductive surgery group and 96 (63%) in the surgery only group received systemic oxaliplatin-based chemotherapy.

25 (19%) patients in the cytoreductive surgery plus HIPEC group and 24 (18%) in the surgery only group received chemotherapy (preoperatively or postoperatively, or both) with anti-EGFR agents, and 71 (53%) and 72 (55%), respectively, received anti-VEGF treatment.

	Cytoreductive surgery plus HIPEC group (n=133)	Cytoreductive surgery group (n=132)	p value
Completeness of cytoreduction			
Complete macroscopic cytoreduction	119 (89%)	121 (92%)	0·54
<1 mm residual disease	14 (11%)	11 (8%)	..
Peritoneal Carcinomatosis Index			
Median	10 (5–16)	9 (5–15)	0·50
<11	77 (58%)	75 (57%)	0·094
11–15	28 (21%)	18 (14%)	..
>15	27 (20%)	40 (30%)	..
Time from diagnosis of peritoneal metastases to surgery, days	149 (112–230)	164 (117–260)	0·39
Regions affected by peritoneal metastases*	5 (3–9)	6 (3–9)	0·071
Resected organs	2 (1–3)	2 (1–3)	0·95
Anastomoses during surgery†	1 (1–2)	1 (1–2)	0·89
Duration of surgery, min‡	365 (280–460)	300 (240–360)	0·00010
Duration of hospital stay, days§	18 (14–27)	13 (11–20)	0·00010
Duration of intensive-care-unit stay, days¶	3 (1–8)	3 (1–7)	0·58
Interval between surgery and food intake, days‖	8 (5–10)	6 (4–8)	0·00040
Surgical reinterventions**	1 (1–2)	1 (1–2)	0·27

Data are n (%) or median (IQR). HIPEC=hyperthermic intraperitoneal chemotherapy. *Data were available for 128 patients in the cytoreductive surgery group. †103 patients in the cytoreductive surgery plus HIPEC group and 94 patients in the cytoreductive surgery group had anastomoses. ‡Data were available for 131 patients in the patients in the cytoreductive surgery plus HIPEC group and 128 patients in the cytoreductive surgery group. §Data were available for 131 patients in the patients in the cytoreductive surgery group. ¶88 patients in the cytoreductive surgery plus HIPEC group and 41 patients in the cytoreductive surgery group had stays in intensive care units. ‖Data were available for 112 patients in the cytoreductive surgery plus HIPEC group and 110 patients in the cytoreductive surgery group. **30 patients in the cytoreductive surgery plus HIPEC group and 16 patients in the cytoreductive surgery group needed surgical reintervention.

Table 2: **Treatment characteristics in intention-to-treat population**

30 (27%) of the 110 patients in the cytoreductive surgery plus HIPEC group who received preoperative chemotherapy, and 31 (28%) of the 109 in the cytoreductive surgery group, discontinued treatment early, because of toxic effects (13 [45%] of 29 patients for whom data were available *vs* 11 [39%] of 28 patients for whom data were available), investigators' decision (five [17%] *vs* three [11%]), disease progression (one [3%] *vs* 0), patient's decision (one [3%] *vs* 0), or other reasons (nine [31%] *vs* 14 [50%]). 68 (34%) of the 201 patients who received postoperative chemotherapy discontinued treatment early: 37 (39%) of 96 in the cytoreductive surgery plus HIPEC group and 31 (30%) of 105 in the cytoreductive surgery group. Data detailing reasons for discontinuation were available for 36 patients and 29 patients, respectively. Discontinuations were because of toxic effects (22 [61%] of 36 *vs* 15 [52%] of 29), investigators' decision (four [11%] *vs* three [10%]), disease progression (three [8%] *vs* three [10%]), patients' decision (one [3%] *vs* two [7%]), or other reasons (six [17%] *vs* six [21%]).

Peritoneal metastases were completely resected in 119 (89%) of 133 patients in the cytoreductive surgery plus HIPEC group and in 121 (92%) of 132 patients in the surgery only group (table 2). The median time between

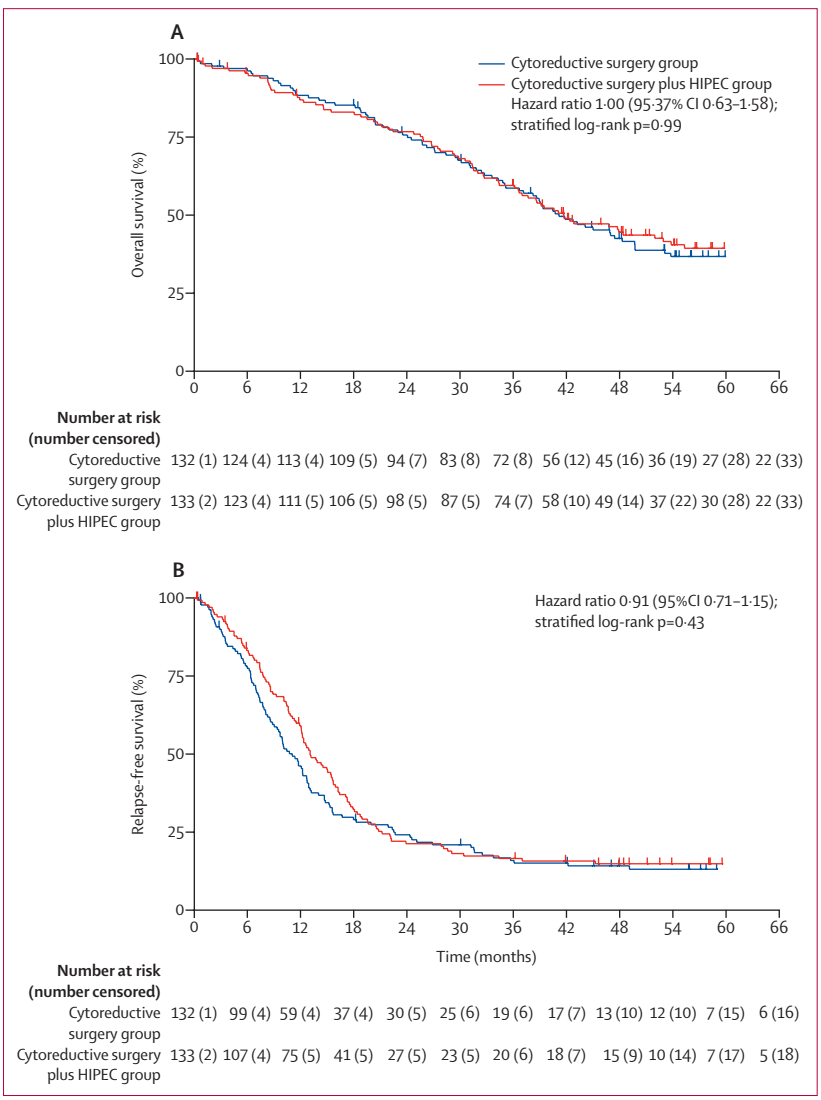


***Figure 2*: Kaplan-Meier estimates of overall survival (A) and relapse-free survival (B) in intention-to-treat population**

Overall survival data are presented with 95·37% CIs rather than 95% CIs because of interim analyses planned. HIPEC=hyperthermic intraperitoneal chemotherapy.

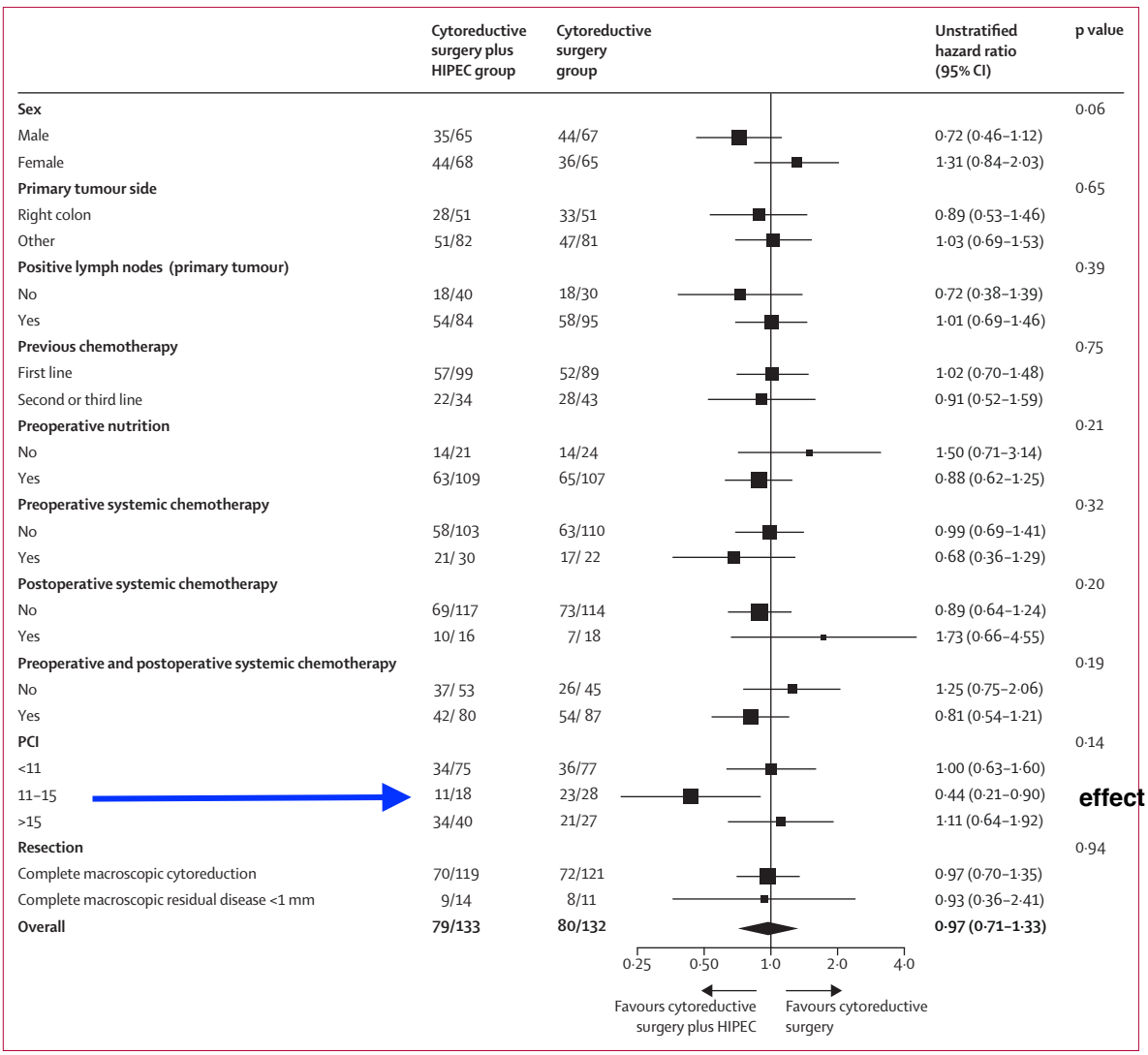
diagnosis of peritoneal metastases and cytoreductive surgery was 149 days (IQR 112–230) in the cytoreductive surgery plus HIPEC group and 164 days (117–260) in the surgery only group.

16 (12%) of the 132 patients who were randomly assigned to the surgery only group crossed over and received HIPEC for isolated relapses of peritoneal metastases (figure 1); these patients were excluded from the per-protocol analysis.

After median follow-up of 63·8 months (IQR 53·0–77·1), 159 (60%) of 265 patients had died—79 (59%) of 133 in the cytoreductive surgery plus HIPEC group and 80 (61%) of 132 in the cytoreductive surgery group. 110 (83%) patients in the cytoreductive surgery plus HIPEC group and 111 (84%) in the cytoreductive surgery group died or had disease progression. Median overall survival did not differ significantly between the cytoreductive surgery plus HIPEC group and the cytoreductive surgery group (41·7 months [95% CI 36·2–53·8] *vs* 41·2 months [35·1–49·7]; HR 1·00 [95·37% CI 0·63–1·58]; stratified log-rank p=0·99; figure 2A). 1-year and 5-year overall survival rates were 86·9% (95% CI 79·7–91·6) and 39·4% (30·6–48·1) in the cytoreductive surgery plus HIPEC group, respectively, and 88·3% (81·4–92·8) and 36·7% (28·1–45·4) in the cytoreductive surgery group, respectively. Median relapse-free survival did not differ between treatment groups (13·1 months [CI 12·1–15·7] *vs* 11·1 months [9·0–12·7]; HR 0·91 [95% CI 0·71–1·15]; p=0·43; figure 2B). Relapse-free survival rates at 1 year were 59·0% (95% CI 50·0–66·9) in the cytoreductive surgery plus HIPEC group and 46·1% (37·3–54·5) for the cytoreductive surgery group, whereas the 5-year relapse-free survival rates were 14·8% (9·3–21·6) and 13·1% (7·8–19·8) for these groups, respectively. Peritoneal-free survival did not significantly differ between groups (appendix pp 4, 7). The frequency of multiple metastatic occurrence was similar in both groups (39 [29%] in the cytoreductive surgery plus HIPEC group *vs* 41 [31%] in the cytoreductive surgery group). Patients with recurrent peritoneal metastases were treated with systemic chemotherapy (appendix p 5). In patients who received interval or exclusively postoperative systemic chemotherapy, the median time between discharge after surgery and the start of a new chemotherapy cycle was significantly longer in the cytoreductive surgery plus HIPEC group than in the cytoreductive surgery group (67 days [IQR 50–85] *vs* 56 days [45–68]; p=0·0036).

Survival results in the per-protocol population and with the inverse probability of censoring weighting method were similar to those in the intention-to-treat population (appendix pp 4, 8). Sensitivity analyses in which failure to receive systemic chemotherapy was classed as a protocol violation produced similar results (appendix p 4). Post-hoc exploratory analyses showed that overall survival was associated with PCI score (appendix p 9). Forest plots showed no differences in overall survival between the two treatment groups in different patient subgroups (figure 3). Subgroups analyses of relapse-free survival, including a breakdown of results by PCI score, are shown in the appendix (appendix pp 10–11).

Four patients died within 30 days of cytoreductive surgery with or without HIPEC, two (2%) in each group (table 3). The causes of death were cardiac failure and massive pneumonia in the cytoreductive surgery plus HIPEC group, and intraperitoneal haemorrhage and septic shock in the cytoreductive surgery group. By 60 days, a further three deaths had been reported, two (2%) in the cytoreductive surgery plus HIPEC group (pulmonary embolism and bilateral pneumonia) and one (1%) in the cytoreductive surgery group (acute respiratory distress). All deaths reported were classed as treatment-related.



effect on that specific sub grou

Figure 3: **Forest plot of overall survival by subgroup**

Data are n/N, where n equals the number of events (ie, deaths) and N equals the number of patients. HIPEC=hyperthermic intraperitoneal chemotherapy. PCI=Peritoneal Carcinomatosis Index. Error bars represent 95% CI. The sizes of the squares are proportional to the precision of the estimates. Data are given for the whole trial population (n=265) except for the subgroups broken down by lymph node positivity (n=249 [124 in the cytoreductive surgery plus HIPEC group and 125 in the cytoreductive surgery group]) and by preoperative nutrition (n=261 [130 in the cytoreductive surgery plus HIPEC group and 131 in the cytoreductive surgery group]).

At 30 days, 56 (42%) patients in the cytoreductive surgery plus HIPEC group and 42 (32%) in the cytoreductive surgery group had severe (ie, grade 3 or worse) complications (table 3). The frequency of complications at 30 days was similar between two groups (table 3). The most common intra-abdominal complications were digestive fistulae (14 [11%] patients in the cytoreductive surgery plus HIPEC group *vs* nine [7%] in the surgery only group) and abscesses (seven [5%] *vs* four [3%]; appendix p 6). 34 (26%) of 131 patients in the cytoreductive surgery plus HIPEC group had severe complications at day 60 (including 27 who had also had severe complications at day 30). The corresponding proportion in the cytoreductive surgery group was 20 (15%) of 130 patients (including 14 who had also had severe complications at day 30). Complications were significantly more common in the cytoreductive surgery plus HIPEC group than in the cytoreductive surgery group (p=0·035; table 3) between days 31 and 60.

Discussion

The PRODIGE 7 trial showed no evidence of an overall survival benefit with cytoreductive surgery plus HIPEC compared with cytoreductive surgery alone. After a decade of encouraging survival results for this combined treatment strategy, to our knowledge our trial is the first to investigate the specific role of HIPEC (previous trials have not included a cytoreductive surgery only group).

cumulative day 1-60
the difference is significative

	Cytoreductive surgery plus HIPEC group (n=133)	Cytoreductive surgery group (n=132)	p value
Mortality			
Overall	4 (3%)	3 (2%)	..
Day 1–30	2 (2%)	2 (2%)	..
Day 31–60	2 (2%)	1 (1%)	..
Grade ≥3 adverse events (Day 1–30)			
Any complication	56 (42%)	42 (32%)	0·083
Intra-abdominal complications	36 (27%)	24 (18%)	0·084
Extra-abdominal complications	36 (27%)	29 (22%)	0·33
Haematological complications			
Neutropenia	22 (17%)	10 (8%)	0·025
Thrombopenia	12 (9%)	2 (2%)	0·011
Grade ≥3 adverse events (Day 31–60)*			
Any complication	34 (26%)	20 (15%)	0·035
Intra-abdominal complications	8 (6%)	4 (3%)	0·38
Extra-abdominal complications	28 (21%)	18 (14%)	0·11

Data are n (%). HIPEC=hyperthermic intraperitoneal chemotherapy. *Because of the two deaths in each group, percentages were calculated based on the available data for the remaining 131 patients in the cytoreductive surgery plus HIPEC group and 130 patients in the cytoreductive surgery group.

Table 3: **Mortality and morbidity in intention-to-treat population**

Our data suggest that the HIPEC regimen we studied confers no additional benefit to cytoreductive surgery, and thus have crucial implications for clinical practice.

In the cytoreductive surgery group, median overall survival was 41 months—substantially longer than expected. This finding suggests that the completeness of cytoreductive resection is the most important factor determining survival after surgical treatment of peritoneal metastases of colorectal origin, a well established result for peritoneal metastases of any origin.[7,8,11,12] Median overall survival in the cytoreductive surgery group in our trial was almost twice that in the cytoreductive surgery plus HIPEC group in a 2003 phase 3 Dutch trial.[8] However, complete macroscopic resection was achieved in only 18 (37%) of the 49 patients in the cytoreductive surgery plus HIPEC group in that trial.[8] Surgeons at expert centres can now achieve complete resection in a far higher proportion of patients than previously. Because radical resection was a prerequisite for inclusion in our trial, complete macroscopic resection was achieved in 91% of participants. This high rate probably also reflects that most included patients were treated at centres with substantial clinical experience (187 [71%] of included patients were recruited by investigators at three centres that each had experience of more than 500 procedures at the beginning of the study).

No significant difference was reported in median relapse-free survival between the two treatment groups. The frequency and patterns of recurrence did not differ between treatment groups—a strong argument against the efficacy of oxaliplatin-based HIPEC as a local treatment. The proportion of patients who were considered to be cured (ie, without disease progression at 5 years) was close to 15% in both groups, similar to that in previously published data.[9] The relapse-free survival curve seemed to level off after 24 months. It is plausible that the proportion of patients alive and without disease recurrence might continue to remain static in both groups beyond the 5 years of follow-up in this study.

In a post-hoc subgroup analysis, median overall and relapse-free survival were longer in patients with a PCI of 11–15 in the cytoreductive surgery plus HIPEC group than in those in the cytoreductive surgery group. This result might serve as a basis for future research into the role of HIPEC in patients with a PCI of 11–15 and in whom complete or near-complete surgical resection can be achieved.

The 30-day mortality rate was 2% in each group, and 37% of participants overall had grade 3 or worse adverse events (42% in the cytoreductive surgery plus HIPEC group and 32% in the non-HIPEC group). These proportions are similar to those reported by other specialised institutions for these procedures.[6,7,13] Foster and colleagues[14] used data from the American College of Surgeons National Surgical Quality Improvement Project database to compare the perioperative and 30-day postoperative morbidity and mortality associated with cytoreductive surgery plus HIPEC with those associated with other high-risk surgical oncology procedures.[14] They showed that cytoreductive surgery plus HIPEC was associated with a similar or lower frequency of morbidity than pancreatoduodenectomy or oesophagectomy.[14] In our study, the addition of oxaliplatin-based HIPEC to cytoreductive surgery did not significantly increase the overall rate of early postoperative complications or mortality at 30 days compared with cytoreductive surgery alone. The frequency of grade 3 or worse digestive fistulae did not differ between groups, and the overall incidence of this adverse event was similar to that reported in other single-centre and multicentre studies.[6–8] Although the frequency of extra-abdominal complications did not seem to differ between the two groups, haematological toxic effects were more common in the cytoreductive surgery plus HIPEC group than in the cytoreductive surgery group.

We used a bidirectional chemotherapy[15] protocol, and allowed HIPEC to be given via either the open or closed technique, because no clear difference has been shown between these two procedures.[10,16,17] However, use of oxaliplatin-based HIPEC increased the frequency of grade 3 or worse complications at 60 days. This finding suggests that HIPEC might extend the time during which patients are at risk of developing postoperative complications. Median hospital stays and time to resumption of postoperative systemic chemotherapy were both significantly longer in the cytoreductive surgery plus HIPEC group than in the cytoreductive surgery group. Very few intra-abdominal complications were reported at 60 days in either group. The severe complications that were reported differed from those

recorded in the early postoperative period, and tended to be more medical in nature than surgical (eg, pulmonary and infectious complications, undernutrition, anaemia).

Our results bring the efficacy of HIPEC into question. Unlike systemic results, in a previous study,[6] HIPEC intensification with irinotecan did not improve survival. In two randomised phase 3 studies,[18,19] the addition of prophylactic HIPEC (the same regimen that we studied) to systemic chemotherapy did not significantly reduce the occurrence of peritoneal metastases compared with systemic chemotherapy. The efficacy of oxaliplatin-based HIPEC in prophylactic settings is thus also under question. Prolonged peritoneal oxaliplatin exposure could improve the efficacy of HIPEC. In our study, oxaliplatin-based HIPEC was administered for only 30 min. In other protocols, HIPEC was administered for up to 120 min.[20] In patients with ovarian cancer, the addition of cisplatin-based HIPEC infused over 90 min to standard treatment was associated with a significant overall survival benefit.[21] Since our trial was initiated, other experimental studies[22,23] have shown that response to local oxaliplatin is related to duration of exposure. Future studies of both the dose and duration of oxaliplatin-based HIPEC might produce different results from those that we report here.

When we were designing this trial, oxaliplatin seemed to be an appropriate choice on the basis of good survival results obtained with cytoreductive surgery and oxaliplatin-based HIPEC in patients amenable to complete resection.[3,7] Furthermore, oxaliplatin's efficacy as a systemic treatment for metastatic colorectal cancer (and as an adjuvant treatment for non-metastatic colorectal cancer) had been widely shown.[24,25] Many HIPEC regimens have been used worldwide[26] for peritoneal metastases secondary to colorectal cancer, but most are based on two drugs—oxaliplatin and mitomycin C. Although no meaningful comparisons with the findings of retrospective studies could be made, oxaliplatin-based HIPEC showed equivalent (in a Dutch series by Hompes and colleagues[27]) or superior (in a single-centre Australian study by Leung and colleagues[28]) overall survival to mitomycin C-based HIPEC in previous studies, and was associated with improved overall survival compared with mitomycin C-based HIPEC plus cisplatin in an Italian comparative study.[29] Consistent with our findings, subgroup analyses in two of these studies[28,29] also showed a survival advantage associated with HIPEC in patients with PCIs of 10–15. In another large retrospective study,[30] no significant differences were found in overall survival between patients who received oxaliplatin-based HIPEC and those who received mitomycin C-based HIPEC. However, the mitomycin C regimen was associated with increased survival specifically in patients with low tumour burdens. The oxaliplatin regimen used in these studies[27–30] was the same as the one we used in our trial. Thus mitomycin C would have been unlikely to have been more efficacious than oxaliplatin. However, our data cannot be extrapolated to other HIPEC regimens, and further studies with different HIPEC protocols are needed before a survival benefit with HIPEC can be definitively ruled out.

The HIPEC regimen that we administered results in peritoneal oxaliplatin concentrations 25 times higher than those in plasma, and intratumoural oxaliplatin penetrations 17 times higher than that in non-bathed tissues (ie, muscle not in contact with the HIPEC).[15] The method of intravenous fluorouracil administration specified in our protocol is worth considering: a short intraoperative injection might not allow for the production of synergistic effects between oxaliplatin and fluorouracil. Indeed, intravenous oxaliplatin monotherapy has little effect in patients with metastatic colorectal cancer.[31] In our study, a short one-off infusion of fluorouracil at the time of surgery might not have been the the best way to achieve synergy between the two drugs. Since 2002, the particular HIPEC regimen that we administered has been adopted by many teams worldwide with similar results to ours.[5,27]

Our patient population might seem highly selective. The main criterion for inclusion in the trial was the possibility of complete resection of peritoneal lesions, irrespective of previous treatments and previous lines of chemotherapy. Thus our survival results reflect outcomes in anyone referred to the surgical teams whenever resection was deemed feasible after the diagnosis of peritoneal carcinomatosis. Although we focused only on patients amenable to complete resection, we attempted to impose as few other restrictions as possible by not selecting patients on the basis of previous systemic chemotherapy received or the extent of peritoneal disease (by including all eligible patients with a PCI<25). Operating only on patients in whom radical resection was possible at expert centres with a small number of expert surgeons might have resulted in particularly high survival in the cytoreductive surgery group. Thus HIPEC might have had very little room to show any additional survival benefit. However, our findings reflect what we think should be the preferred treatment for this patient population. Surgery for peritoneal metastases is highly specialised, and should be done by experts at specialised centres.

All patients in the study received substantial systemic chemotherapy, either in adjuvant settings for primary tumour resection, as previous treatment for peritoneal metastases, or as part of our trial systemic chemotherapy regimen. 194 (73%) of these 265 chemotherapy regimens were oxaliplatin-based. Finally, all patients were required to receive systemic chemotherapy and, if possible, preoperative and postoperative chemotherapy via an interval strategy per the trial protocol. Thus, most patients received systemic chemotherapy preoperatively (either completely or in an interval strategy), which might explain the low median PCI reported. Patients who underwent cytoreductive surgery might have been good responders to neoadjuvant chemotherapy and thus might have presented with less extensive residual peritoneal metastases. Furthermore, advances in both

systemic chemotherapies and targeted therapies might have increased overall survival in patients with metastatic colorectal cancer—improvements that could explain our better-than-expected results in both groups. The extensive use of systemic oxaliplatin before HIPEC in our study might also have resulted in increased somatic gene mutations causing oxaliplatin resistance, which could have affected survival in the HIPEC group. In Andreou and colleagues' study[32] in patients with liver metastases secondary to colorectal cancer, increased *RAS* mutations in patients treated with adjuvant oxaliplatin chemotherapy resulted in lower disease-free survival than in those who received adjuvant fluorouracil or no chemotherapy. In the well known MOSAIC trial,[24] median time from relapse to death was shorter in the FOLFOX (leucovorin, fluorouracil, and oxaliplatin) group than in the fluorouracil group. Although randomisation in our trial was stratified by the number of previous cycles of chemotherapy and the timing of chemotherapy, it is possible that our trial selected for so-called long-survivor patients, which would affect the ability of the trial to detect the potential efficacy of HIPEC.

Our trial had several other limitations. The hypothesis we used to generate the sample size might be criticised for two main reasons. First, at the time of the trial design, no survival data were available in the literature for patients treated with cytoreductive surgery alone. The 18-month increase in overall survival that we postulated in the cytoreductive surgery plus HIPEC group was probably an overestimate. Second, we chose overall survival as a primary endpoint. Patients who were assigned to the cytoreductive surgery group but subsequently received HIPEC when peritoneal metastases recurred might have biased our results. However, only 16 patients crossed-over to receive HIPEC, and per-protocol analyses showed no outcome differences between the two groups. Another limitation was that we were unable to collect data for *RAS* or *BRAF* mutations, because the technology to do such analyses was not available in the early stages of the study. Additionally, uncertainty about data or the location of transverse colon tumours meant that we could classify tumours only as being in the right colon or any other location.

In conclusion, our study did not show an additional overall survival benefit in patients treated with cytoreductive surgery plus oxaliplatin-based HIPEC compared with those who received cytoreductive surgery alone to treat peritoneal metastases from colorectal cancer.

Contributors

This study was conceived and designed by FQ, DE, LR, and OG, and coordinated by FQ and BJ. FQ, DE, DG, LG, MP, OF, CA, GL, DP, FM, VL, PM, JP, and OG collected data, which were analysed and interpreted by FQ, LR, HdF, and OG. FQ, LR, and HdF drafted the Article, and then critically revised it in conjunction with DG, MP, and OG. All authors approved the final version.

Declaration of interests

We declare no competing interests.

Data sharing

Unicancer will share anonymised individual data on a case-by-case basis. The data shared will be limited to that required for independent mandated verification of published results. The reviewer will need authorisation from Unicancer for personal access, and the data will be transferred only after signing of a data-access agreement. The study data will be available after publication to researchers for meta-analyses or other research proposals subject to approval and agreement from the study sponsor (Unicancer Research and Development), Related documents (study protocol and informed consent form) will also be made available. Requests should be sent to l-monard@unicancer.fr.

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