Second-look surgery plus hyperthermic intraperitoneal chemotherapy versus surveillance in patients at high risk of developing colorectal peritoneal metastases (PROPHYLOCHIP–PRODIGE 15): a randomised, phase 3 study

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Summary

Background Diagnosis and treatment of colorectal peritoneal metastases at an early stage, before the onset of signs, could improve patient survival. We aimed to compare the survival benefit of systematic second-look surgery plus hyperthermic intraperitoneal chemotherapy (HIPEC), with surveillance, in patients at high risk of developing colorectal peritoneal metastases.

Methods We did an open-label, randomised, phase 3 study in 23 hospitals in France. Eligible patients were aged 18–70 years and had a primary colorectal cancer with synchronous and localised colorectal peritoneal metastases removed during tumour resection, resected ovarian metastases, or a perforated tumour. Patients were randomly assigned (1:1) to surveillance or second-look surgery plus oxaliplatin-HIPEC (oxaliplatin 460 mg/m², or oxaliplatin 300 mg/m² plus irinotecan 200 mg/m², plus intravenous fluorouracil 400 mg/m²), or mitomycin-HIPEC (mitomycin 35 mg/m²) alone in case of neuropathy, after 6 months of adjuvant systemic chemotherapy with no signs of disease recurrence. Randomisation was done via a web-based system, with stratification by treatment centre, nodal status, and risk factors for colorectal peritoneal metastases. Second-look surgery consisted of a complete exploration of the abdominal cavity via xyphopubic incision, and resection of all peritoneal implants if resectable. Surveillance after resection of colorectal cancer was done according to the French Guidelines. The primary outcome was 3-year disease-free survival, defined as the time from randomisation to peritoneal or distant disease recurrence, or death from any cause, whichever occurred first, analysed by intention to treat. Surgical complications were assessed in the second-look surgery group only. This study was registered at ClinicalTrials.gov, NCT01226394.

Findings Between June 11, 2010, and March 31, 2015, 150 patients were recruited and randomly assigned to a treatment group (75 per group). After a median follow-up of 50·8 months (IQR 47·0–54·8), 3-year disease-free survival was 53% (95% CI 41–64) in the surveillance group versus 44% (33–56) in the second-look surgery group (hazard ratio 0·97, 95% CI 0·61–1·56). No treatment-related deaths were reported. 29 (41%) of 71 patients in the second-look surgery group had grade 3–4 complications. The most common grade 3–4 complications were intra-abdominal adverse events (haemorrhage, digestive leakage) in 12 (23%) of 71 patients and haematological adverse events in 13 (18%) of 71 patients.

Interpretation Systematic second-look surgery plus oxaliplatin-HIPEC did not improve disease-free survival compared with standard surveillance. Currently, essential surveillance of patients at high risk of developing colorectal peritoneal metastases appears to be adequate and effective in terms of survival outcomes.

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Introduction

Over the past two decades, the prognosis of patients with peritoneal metastases from colorectal cancer has been improved by aggressive treatment, including complete surgical resection and hyperthermic intraperitoneal chemotherapy (HIPEC). This combined treatment has improved 5-year survival outcomes in these patients by up to 40–45%,[1–5] and has been curative (disease-free interval of at least 5 years) in 16% of patients in one retrospective study.[6] After complete resection and HIPEC, the prognosis depends primarily on two factors, the completeness of resection and the extent of the peritoneal disease as evaluated with the peritoneal cancer index.[7,8] Thus, the earlier the disease is treated, the better the prognosis. Unfortunately, colorectal peritoneal metastases are typically asymptomatic at early disease stages,

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed from Jan 1, 1980, to Jan 1, 2012, for studies with the terms "second-look surgery", "peritoneal carcinomatosis" or "peritoneal metastases", and "colorectal cancer" or "peritoneal malignancy". We found no randomised trials published during this time.

Only two prospective studies have been reported investigating systematic second-look surgery in patients at high risk of developing colorectal peritoneal metastases, and one retrospective study in patients after initial resection of peritoneal carcinomatosis from appendiceal malignancy. For patients at high risk of colorectal peritoneal metastases, the previous studies showed that peritoneal metastases are diagnosed during second-look surgery in 55% of patients, and that prolonged survival can be obtained with this strategy.

An updated search done on Jan 1, 2018, found no further relevant randomised trials.

Added value of this study

To our knowledge, this is the first reported phase 3 study to evaluate systematic second-look surgery plus hyperthermic intraperitoneal chemotherapy (HIPEC) in patients at high risk of colorectal peritoneal metastases.

Implications of all the available evidence

This randomised phase 3 study (PROPHYLOCHIP) does not support a disease-free survival or overall survival benefit from systematic second-look surgery plus oxaliplatin-HIPEC in patients at high risk of colorectal peritoneal metastases. However, an important point raised by this study is that this at-risk population should be recognised, and that all medical staff should be aware of this risk and systematically look for signs of colorectal peritoneal metastases during routine surveillance.

and all non-invasive imaging strategies tested to date have had disappointing detection rates in nodules smaller than 5 mm in diameter.[9] To overcome this difficulty in detection, a strategy based on a complete surgical exploration of the abdomen in patients at high risk for colorectal peritoneal metastases has been described and evaluated in prospective non-randomised studies.[10–14] Results of these studies suggested that systematic second-look surgery was efficient for diagnosing colorectal peritoneal metastases that were not visible on imaging (in more than half of the patients), and that any such patients with a low peritoneal cancer index should be treated at an early stage, thereby improving survival.

The aim of this study was to analyse the effect on disease-free survival of surveillance according to standard guidelines, versus systematic second-look surgery plus HIPEC, in patients at high risk of developing colorectal peritoneal metastases.

Methods

Study design and participants

We did an open-label, randomised, phase 3 trial at 23 hospitals in France (appendix p 1). Eligible patients were those who met the criteria for high risk of developing colorectal peritoneal metastases, meaning patients with a histologically proven primary colorectal cancer and one of the following: synchronous and localised colorectal peritoneal metastases removed during tumour resection, resected ovarian metastases, or a perforated tumour. To be included in the trial, patients also had to have received standard adjuvant chemotherapy (initially FOLFOX4 [leucovorin, fluorouracil, and oxaliplatin] or XELOX [oxaliplatin and capecitabine], but could be modified if standard therapy changed during the course of the study) for 6 months after resection of the colorectal tumour, with no evidence of detectable tumour recurrence on a CT scan or on serosal tumour markers at the end of the 6-month period. Other inclusion criteria included age of 18–70 years; life expectancy of more than 12 weeks; a WHO performance status score of 0–1; and adequate haematological function (≥$1{\cdot}5\times10^9$ neutrophils per L, ≥$100{\cdot}0\times10^9$ platelets per L), liver function (serum bilirubin ≤1·50 times the upper limit of normal; alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase ≤3·00 times the upper limit of normal), and renal function (creatinine ≤1·25 times the upper limit of normal). The main exclusion criteria were cancer other than colorectal origin, in particular appendicular carcinomas; patients with detectable recurrence; grade 3 or higher peripheral neuropathy; history of cancer (except basal cell carcinoma of the skin or in-situ carcinoma of the cervix) having recurred in the 5 years preceding entry into the trial; metastases (other than ovarian) at the time of diagnosis; inclusion in another first-line therapeutic trial for the disease studied; pregnancy; likely pregnant or breastfeeding; being deprived of liberty or under guardianship; and inability to adhere to medical monitoring of the trial for geographical, social, or psychological reasons. The protocol was approved by the French national health authorities and all relevant local ethics committees. The study was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent before enrolment.

Randomisation and masking

After completing 6 months of adjuvant systemic chemotherapy, with the absence of disease recurrence on CT scan, patients were randomly assigned (1:1) to undergo systematic second-look surgery plus HIPEC or

standard surveillance only. Randomisation was done by minimisation (non-random) using a web-based system, TENALEA. Stratification factors were treatment centre, nodal status (N0, N1, or N2), and the factor denoting a high risk of peritoneal recurrence (perforated tumour, presence of peritoneal metastasis, or presence of ovarian metastasis). To avoid deterministic minimisation and ensure allocation concealment, the treatment which minimises the imbalance was assigned with a probability of 0·8 (ie, <1·0). Randomisation was done centrally at the biostatistics unit of the Gustave Roussy Institute (Villejuif, France). Participants, investigators, and treating clinicians were unblinded to the group allocation.

Procedures

In the second-look surgery plus HIPEC group, at laparotomy, a complete exploration of the abdominal cavity was performed through a xyphopubic incision. The extent of peritoneal seeding was calculated with the peritoneal cancer index. Macroscopically detectable peritoneal disease had to be completely resected before administering HIPEC. Oxaliplatin was administered alone intraperitoneally in an open abdominal cavity (Coliseum technique), or using the closed abdomen technique, at a dose of 460 mg/m² in 2 L/m² of iso-osmotic 5% dextrose,[15] or 300–360 mg/m² when given with irinotecan (200 mg/m²).[15,16] The intraperitoneal temperature was homogeneous at 43°C (range 42–44°C) for 30 min. Patients received an intravenous perfusion of fluorouracil (400 mg/m²) with leucovorin (20 mg/m²) immediately before starting HIPEC. After second-look surgery, patients were evaluated for morbidity and toxicity every day until discharge from hospital (physical examination every day, blood tests every day of the first week and then every two days until discharge; CT scan was performed and hospital stay was prolonged in case of postoperative complication or if complication was suspected). Surgical complications (digestive leakage, deep abscess, intra-abdominal haemorrhage, urinary leakage, reoperation) and extra-abdominal complications, including haematological toxicity, were recorded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. For patients in the surveillance group who went on to have surgery and HIPEC, adverse events after HIPEC were not monitored.

For patients in the surveillance group, and for patients after second-look surgery, the follow-up consisted of a physical examination, CT scan, and blood tumour marker determination every 3 months for the first 3 years after entering the trial and every 6 months for the following 2 years.

Outcomes

The primary outcome was 3-year disease-free survival. Disease-free survival was defined as the time from randomisation to peritoneal recurrence, distant recurrence, or death from any cause, whichever occurred first. Secondary outcomes included overall survival (defined as time from randomisation to death from any cause) at 3 years and 5 years, peritoneal recurrence-free survival (time from randomisation to peritoneal recurrence or death, whichever occurred first), and postoperative morbidity.

For more on **TENALEA** see https://acc.tenalea.net/cctu/dm/about-tenalea-en.html

Statistical analysis

This trial was powered at 80% to detect a difference of 25% in 3-year disease-free survival (increase from 40% to 65%) with a two-sided test at an α level of 0·05. 150 patients were required (75 in each group). All analyses were done by intention to treat (ie, all patients who were enrolled and randomly allocated to treatment were included in the analysis and were analysed in the groups to which they were randomised). Difference in disease-free survival, overall survival, and peritoneal recurrence-free survival between the two groups were tested with the log-rank test adjusted for the stratification variables. The assumption of proportional hazards was assessed by the Kolmogorov supremum test on the cumulative sums of Martingale residuals. Patient characteristics were compared with a χ^2 test. Survival rates and their 95% CIs were estimated by the Kaplan-Meier method. Follow-up maturity was estimated by the reverse Kaplan-Meier

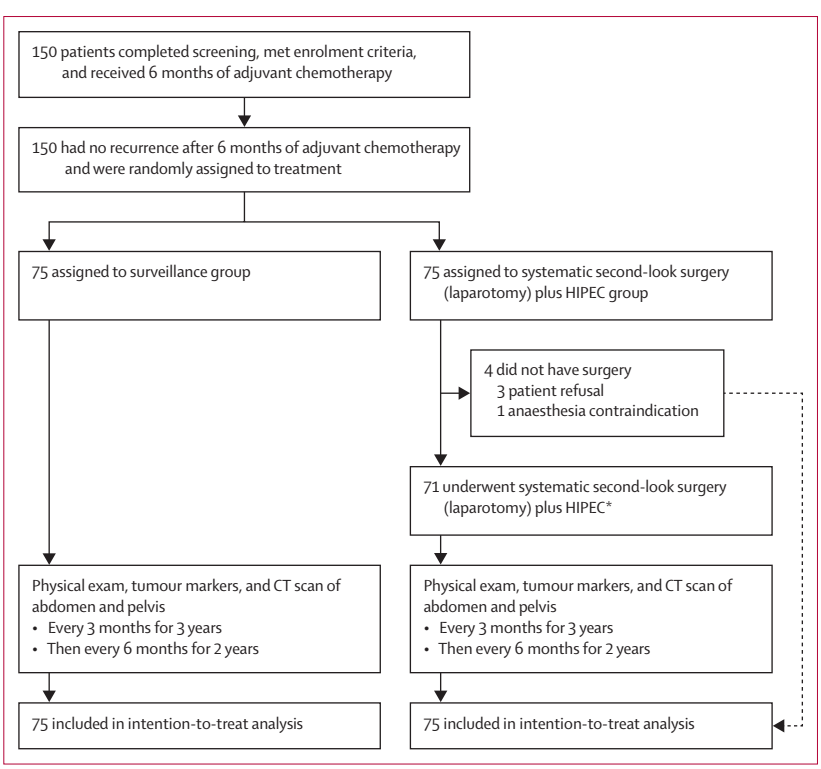


Figure 1: **Trial profile**

HIPEC=hyperthermic intraperitoneal chemotherapy. *Using oxaliplatin alone at a dose of 460 mg/m² in 38 patients; using oxaliplatin at a dose of 300 mg/m² associated with irinotecan at a dose of 200 mg/m² in 21 patients; and using mitomycin 35 mg/m² alone in eight patients; all patients who received oxaliplatin-HIPEC also received fluorouracil 400 mg/m².

	Surveillance (n=75)	Second-look surgery plus HIPEC (n=75)
Median age, years (IQR)	57 (48–63)	58 (47–64)
Sex		
Male	40 (53%)	44 (59%)
Female	35 (47%)	31 (41%)
High-risk PMCRC factors		
One risk factor		
Isolated perforated tumour	26 (35%)	27 (36%)
Isolated peritoneal metastases	29 (39%)	29 (39%)
Isolated ovarian metastases	10 (13%)	5 (7%)
Two risk factors		
Concurrent perforated tumour and peritoneal metastases	6 (8%)	7 (9%)
Concurrent ovarian metastases and peritoneal metastases	3 (4%)	6 (8%)
Concurrent ovarian metastases and perforated tumour	1 (1%)	1 (1%)
Primary colorectal tumour*		
Lymph node metastasis	51 (68%)	58 (77%)
Right colon	26 (35%)	26 (35%)
Left colon	46 (61%)	45 (60%)
Rectum	4 (5%)	5 (7%)
Adjuvant systemic chemotherapy		
FOLFOX or XELOX	65 (87%)	67 (89%)
Other regimen	10 (13%)	8 (11%)
Number of cycles, median (IQR)	8 (7–9)	7 (6–9)

Data are n (%), unless otherwise stated. HIPEC=hyperthermic intraperitoneal chemotherapy. PMCRC=peritoneal metastases of colorectal cancer. FOLFOX=leucovorin, fluorouracil, and oxaliplatin. XELOX=oxaliplatin and capecitabine. *Two patients each had two synchronous colorectal cancers.

Table 1: **Baseline characteristics**

method. 5-year disease-free survival was analysed as an exploratory outcome. For all tests, the level of significance was 5%. Analyses were performed with SAS (version 9.4).

The study was registered with ClinicalTrials.gov, NCT01226394.

Role of the funding source

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

Results

Between June 11, 2010, and March 31, 2015, 150 patients were randomly assigned to the control group (standard surveillance, n=75) or the experimental group (second-look surgery plus HIPEC, n=75; figure 1) and were included in the intention-to-treat population. 71 (95%) of the 75 patients allocated to the experimental group had a surgical exploration of the abdomen, with a median delay of 38 days (IQR 25–60) after randomisation. In the remaining four patients, surgery was not performed because of patient refusal (three patients) or an anaesthesia contraindication (one patient). In four (6%) of the 71 patients who had second-look surgery, the exploration of the cavity revealed a large peritoneal involvement that was not accessible to complete resection. HIPEC was given to 67 (94%) of the 71 patients, using an open technique in 53 patients. Patient demographics and baseline disease characteristics are summarised in table 1.

After a median follow-up of 50·8 months (IQR 47·0–54·8), 71 patients experienced recurrence, including 36 (48%) of 75 patients in the surveillance group and 35 (47%) of 75 patients in the second-look surgery group. Recurrences were located in the peritoneum in 50 patients (26 in the surveillance group *vs* 24 in the second-look group), the liver in 30 patients (17 *vs* 13), the lungs in 25 patients (seven *vs* 18), and in nodes in 23 patients (11 *vs* 12). 3-year disease-free survival was 53% (95% CI 41–64) in the surveillance group versus 44% (33–56) in the second-look surgery group (hazard ratio 0·97, 95% CI 0·61–1·56; p=0·82; figure 2). 5-year disease-free survival was 49% (37–60) in the surveillance group versus 42% (32–54) in the second-look surgery group (p=0·82). 3-year peritoneal recurrence-free survival also did not differ between the groups, at 61% (50–72) in the surveillance group versus 59% (48–70) in the second-look surgery group.

During follow-up, 19 patients (25%) in the surveillance group and 21 patients (28%) in the second-look surgery group died. Overall survival did not differ between the two groups (figure 3). 3-year overall survival was 80% (95% CI 69–88) in the surveillance group versus 79% (68–87) in the second-look group. 5-year overall survival was 72% (60–82) in the surveillance group versus 68% (55–79) in the second-look group.

Recurrences were accessible to surgery in 43 patients, 25 (33%) of 75 patients in the surveillance group and 18 (24%) of 75 in the second-look surgery group. 17 patients from the surveillance group underwent cytoreductive surgery with HIPEC for peritoneal recurrence. In the second-look group, resection of peritoneal recurrence without HIPEC was performed in eight patients (associated with resection of extra-peritoneal recurrence in four of them), and resection of isolated extra-peritoneal recurrence was done in another eight patients. A new HIPEC procedure was performed in two patients in the second-look group (at the decision of the investigator, as there was no instruction about the treatment of recurrence after second-look surgery and HIPEC). Systemic chemotherapy was administered in 56 patients (28 in each group), and eight patients (four in each group) had radiotherapy.

Second-look surgery outcomes are summarised in table 2. The median peritoneal cancer index at second-look surgery was 4·0 (IQR 2·0–9·5). HIPEC using oxaliplatin at a dose of 300 mg/m² with irinotecan at a

dose of 200 mg/m² was given to 21 patients, HIPEC using oxaliplatin alone at a dose of 460 mg/m² was given to 38 patients, and eight patients received mitomycin 35 mg/m² monotherapy HIPEC because of neurotoxicity from previous treatment with oxaliplatin. All patients who received oxaliplatin HIPEC also received fluorouracil 400 mg/m². No dose reduction was required and no toxicity during surgery required stopping HIPEC. Surgery included 16 colonic resections, 13 small bowel resections, nine rectal resections, eight oophorectomies, four hysterectomies, two wedge liver resections, one splenectomy, and one atypical gastrectomy. Reconstructions included 21 colorectal, seven ileocolic, six ileo-ileal, and five ureteral anastomoses.

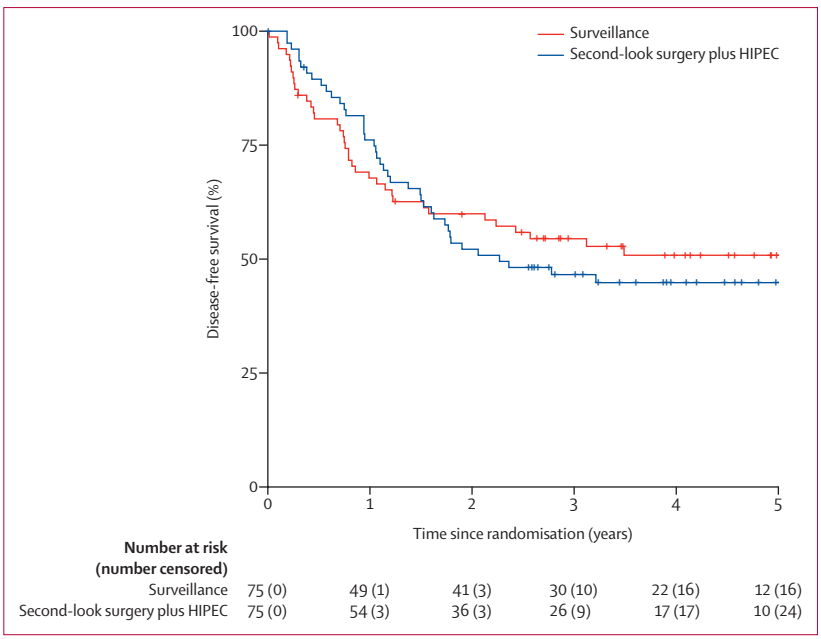
Major postoperative complications (grade 3–4) occurred in 29 (41%) of the 71 patients (table 3) in the second-look surgery group, and no patients died postoperatively. The most frequent of all-cause grade 3–4 events were intra-abdominal complications (12 [17%] of 71 patients) and haematological toxicity (13 [18%] of 71 patients). For eight patients, treatment of intra-abdominal complications required a reoperation. The most frequent grade 2 adverse event was anaemia (20 [28%] of 71 patients).

Definitive histological analysis identified peritoneal metastases in 26 (37%) of 71 patients who had second-look surgery, meaning that the macroscopic diagnosis of peritoneal metastases was not confirmed by the pathologists in 11 (30%) of 37 patients with this diagnosis.

Discussion

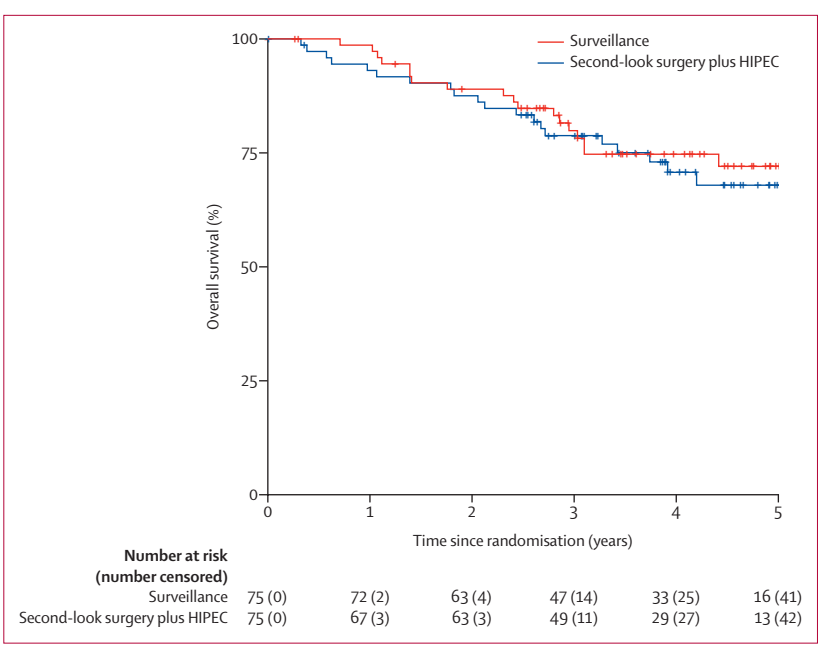
The results of this open-label, randomised, phase 3 study that enrolled patients at high risk of developing colorectal peritoneal metastases after a clinical, biological, and radiological assessment, did not show a significant difference in disease-free survival or overall survival between standard surveillance and systematic second-look surgery plus HIPEC. We aimed to compare these two strategies, but the study was not designed to evaluate the potential benefit of prophylactic HIPEC, since HIPEC was also given in the presence of colorectal peritoneal metastases in patients who did not have peritoneal metastases during the second-look surgery. In this regard, the objective of this trial differed from that of the recently reported COLOPEC trial,[17] in which patients at risk (with a perforated tumour or stage T4 colorectal cancer but without colorectal peritoneal metastases) were randomised to surveillance or systematic HIPEC performed simultaneously or within 5–8 weeks after the primary tumour resection. The COLOPEC trial showed that adjuvant HIPEC with oxaliplatin did not result in improved 18-month progression-free survival compared with surveillance alone.[17]

In 2018, the results of the randomised, phase 3 PRODIGE 7 study were reported,[18] which compared overall survival of patients who had complete cytoreductive surgery for colorectal peritoneal metastases, with or without HIPEC. This study did not show a survival benefit in patients who underwent HIPEC with the same protocol used in our randomised trial (high-dose oxaliplatin at 43°C for 30 min). The PRODIGE 7 study confirmed the major role of complete cytoreductive surgery (without HIPEC) in colorectal peritoneal metastases, which resulted in median overall survival of more than 41 months, and the prognostic impact of the extent of the peritoneal extension, evaluated in terms of the peritoneal cancer index. Thus, the question of the



Number at risk (number censored)						
Surveillance	75 (0)	49 (1)	41 (3)	30 (10)	22 (16)	12 (16)
Second-look surgery plus HIPEC	75 (0)	54 (3)	36 (3)	26 (9)	17 (17)	10 (24)

Figure 2: **Kaplan-Meier estimates of disease-free survival for patients in the intention-to-treat population**
HIPEC=hyperthermic intraperitoneal chemotherapy.



Number at risk (number censored)						
Surveillance	75 (0)	72 (2)	63 (4)	47 (14)	33 (25)	16 (41)
Second-look surgery plus HIPEC	75 (0)	67 (3)	63 (3)	49 (11)	29 (27)	13 (42)

Figure 3: **Kaplan-Meier estimates of overall survival for patients in the intention-to-treat population**
HIPEC=hyperthermic intraperitoneal chemotherapy.

	No macroscopic peritoneal metastases (n=34)	Macroscopic peritoneal metastases (n=37)	Total (n=71)
Median age, years (range)	60 (51–64)	55 (46–64)	56 (47–64)
Sex			
Male	21 (62%)	19 (51%)	40 (56%)
Female	13 (38%)	18 (49%)	31 (44%)
High-risk PMCRC factors			
Perforated tumour	19 (56%)	12 (32%)	31 (44%)
Peritoneal metastases	16 (47%)	23 (62%)	39 (55%)
Ovarian metastases	4 (12%)	8 (22%)	12 (17%)
Primary colorectal tumour*			
Lymph node metastasis	21 (62%)	31 (84%)	52 (73%)
Right colon	13 (38%)	12 (32%)	25 (35%)
Left colon	20 (59%)	23 (62%)	43 (61%)
Rectum	2 (6%)	3 (8%)	5 (7%)
Adjuvant systemic chemotherapy			
FOLFOX or XELOX	32 (94%)	31 (84%)	63 (89%)
Other regimen	2 (6%)	6 (16%)	8 (11%)
Number of cycles, median (range)	8 (6–9)	8 (3–11)	8 (3–11)
HIPEC			
Total	34 (100%)	33 (89%)	67 (94%)
Open	26 (76%)	27 (82%)	53 (79%)
Closed	8 (24%)	6 (18%)	14 (21%)
Peritoneal cancer index			
0–9	NA	24 (65%)	..
10–14	NA	3 (8%)	..
15–20	NA	3 (8%)	..
>20	NA	2 (5%)	..
Missing	NA	5 (14%)	..
Median operative time, min (IQR)	320 (250–420)	324 (250–450)	324 (250–434)
Median blood loss, mL (IQR)	250 (100–300)	200 (100–400)	200 (100–340)
Blood transfusion, n (%)	1 (3%)	3 (8%)	4 (6%)
Median hospitalisation duration, days (IQR)	13 (9–15)	14 (12–21)	14 (10–16)

Data are n (%), unless otherwise stated. PMCRC=peritoneal metastases of colorectal cancer. FOLFOX=leucovorin, fluorouracil, and oxaliplatin. XELOX=oxaliplatin and capecitabine. HIPEC=hyperthermic intraperitoneal chemotherapy. NA=not applicable. *Two patients each had two synchronous colorectal cancers.

Table 2: **Systematic second-look surgery outcomes with patient demographics and baseline disease characteristics**

	Grade 1–2	Grade 3	Grade 4
Digestive leakage	..	2 (3%)	1 (1%)
Intra-abdominal haemorrhage	2 (3%)	4 (6%)	2 (3%)
Intra-abdominal abscess	2 (3%)	1 (1%)	..
Urinary leakage	..	2 (3%)	..
Reoperation	..	8 (11%)	..
Paralytic ileus	2 (3%)	..	..
Denutrition	2 (3%)	2 (3%)	..
Pneumonia	..	4 (6%)	..
Respiratory insufficiency	..	2 (3%)	..
Haematological toxicity*	20 (28%)	13 (18%)	..

HIPEC=hyperthermic intraperitoneal chemotherapy. Data are n (%). *Including anaemia. Adverse events in patients in the surveillance group who had HIPEC were not monitored.

Table 3: **All-cause adverse events occurring after systematic second-look surgery and HIPEC in 71 patients**

usefulness of early cytoreductive surgery is still relevant; however, second-look surgery alone was not assessed in our study, so comparisons with other studies must be made with caution.

The results from the second-look surgery group in this study are similar to those published previously,[10–14] in that we found a low peritoneal cancer index in cases of peritoneal recurrence in patients in this group. In this regard, the second-look approach appears to be able to diagnose subclinical peritoneal recurrence at an early stage. The extent of peritoneal disease was considered inaccessible to complete resection in four of the 75 patients, in whom the radiological assessment was normal before surgery. This result appears to confirm the low sensitivity of radiological examinations for diagnosing colorectal peritoneal metastases. Currently, the radiological examination with the best sensitivity and specificity for diagnosing colorectal peritoneal metastases is a CT scan with intravenous contrast injection,[19,20] which is why CT scan was chosen as the reference examination in this study. The sensitivity of PET scans remains disappointing for small lesions of less than 1 cm diameter, and it is currently only recommended to complete the investigations with a PET scan in case of an anomaly on the CT scan, or elevated serum markers without a visible abnormality on the CT scan. Regarding MRI, the sensitivity of diffusion MRI does not seem to be greater than that of CT,[21] except with mucinous lesions, which appear hyperintense in T2 sequences, and are probably more visible on diffusion MRI than on a CT scan. This finding should be taken into account when monitoring patients having surgery for mucinous colonic adenocarcinoma, which has a greater peritoneal tropism than other types of colonic adenocarcinoma. Moreover, the timing of the second-look surgery should be discussed. It might have been too early in the COLOPEC study and too late in our study, as evidenced by the number of peroperative diagnoses of unresectable colorectal peritoneal metastases during second-look surgery. In future protocols, so-called interval second-look surgery—after four to six cycles of adjuvant systemic chemotherapy—could be evaluated.

In the second-look surgery group, colorectal peritoneal metastases was reported by the surgeon in approximately half of the 71 patients, which is similar to the findings of previous studies,[10–14] in which patients considered to be at high risk met the same definitions as in this study. Again, in this sense, the yield of the second-look surgery to diagnose colorectal peritoneal metastases not visible on imaging examinations is efficient. However, the diagnosis of peritoneal recurrence was not histologically confirmed in 11 patients. These non-malignant lesions might correspond to either postoperative inflammatory nodules or to lesions sterilised by the chemotherapy that all patients received before the second-look surgery. This

disparity between the macroscopic diagnosis made by the surgeon and the histological diagnosis has recently been emphasised in a study by Berger and colleagues.[22] In their study, the diagnosis of colorectal peritoneal metastases was suspected preoperatively, and the authors reported that final examinations of specimens resected during cytoreductive surgery plus HIPEC revealed non-pathological specimens in up to 69% of cases. Moreover, all histological samples were negative in 18 (17%) of 108 patients. Consequently, the pathological peritoneal cancer index differed from the intraoperative peritoneal cancer index in 46% of cases. In our study population, who had no anomalies on the preoperative assessment, the rate of false positives for malignant lesions was even higher than in the aforementioned study.[22] A complete pathological response to preoperative systemic chemotherapy, which has previously been reported in nearly 10% of patients treated for colorectal peritoneal metastases,[23] could also explain this rate of non-malignant lesions on final pathological examinations. However, in the study by Berger and colleagues, the rate of non-malignant specimens was comparable between the group of patients who received preoperative chemotherapy and those who did not. Finally, the lower than expected rate of peritoneal recurrence could also be explained by the high proportion of patients with a perforated tumour (which increases the risk of peritoneal metastases, but less so than history of peritoneal metastases or of ovarian metastases). Inclusion criteria were based on a wide review of the literature, and integrated the most at-risk patients (those with synchronous peritoneal metastases, ovarian metastases, and perforated tumours).[24,25] However, it is important to note that the rate of peritoneal recurrence in patients with perforated tumours is much lower than for patients in the other two at-risk groups. In a recent study with broader inclusion criteria, the rate of colorectal peritoneal metastases at second-look surgery was 30·3%.[12] Conversely, when inclusion criteria were restricted to synchronous colorectal peritoneal metastases resected with the primary tumour, or ovarian metastases, the rate of colorectal peritoneal metastases during second-look surgery reached 71·0%.[11] Therefore, the lower than expected rate of detection of peritoneal metastases of the second-look surgery in our study might be explained by the high proportion of patients at medium risk of recurrent peritoneal disease.

The results seen early in the postoperative course also reflect the literature;[10] it should be highlighted that second-look surgery can be a complex procedure, as evidenced by the operating time of more than 5 h and the high rate of postoperative complications, which could also have negatively influenced the survival results.[26] During this surgery, the surgeon explores the entire abdominal cavity, re-opens all previous dissection planes, and resects any lesions that appear malignant, which requires new digestive resections and anastomoses.

A potential limitation of our study is the choice of the intraperitoneal chemotherapy; the results of the PRODIGE 7 study have recently challenged our HIPEC protocol for patients with colorectal peritoneal metastases, because patients could be considered resistant to oxaliplatin as the majority of them have already received adjuvant systemic chemotherapy that included oxaliplatin. Our choice for using intraperitoneal oxaliplatin was driven by the encouraging survival results observed in previous studies.[3,5,6] Another limitation is based on the fact that the patients were managed in centres specialising in peritoneal disease. This might have resulted in better diagnosis and treatment of colorectal peritoneal metastases at an early stage in the surveillance group leading to improved survival outcomes.

In conclusion, we found that the strategy consisting of a systematic second-look surgery plus HIPEC with high-dose oxaliplatin for 30 min, in patients at high risk of developing colorectal peritoneal metastases, does not result in increased survival compared with standard surveillance. The main point highlighted by this study for the clinical setting lies in identifying the patients at risk of colorectal peritoneal metastases in order to properly monitor them and to diagnose peritoneal recurrence at an early enough stage to propose a complete surgical resection. New and alternative strategies—which could include early second-look surgery, other protocols of HIPEC, or reinforced surveillance including new imaging—should now be evaluated.

Contributors

DE and DG designed the study protocols, oversaw the implementation of the study, oversaw data collection, analysed the data, and drafted and revised the paper. MT analysed and interpreted the data and revised the draft paper. OG, FQ, J-MG, J-MB, GL, ET, LG, AP, J-JT, RK, MC, FM, CA, CB, PM, PR, SD-F, PM, ZL, VL, NP, and cs implemented the study and supported data collection, interpreted the data, and revised the draft paper.

Declaration of interests

DG reports personal fees from Amgen, Merck Serono, Novartis, Roche, and Sanofi, outside the submitted work. All other authors declare no competing interests.

Data sharing

External researchers can make written requests to the corresponding author (DG) for sharing of data before publication or presentation. Requests will be assessed on a case-by-case basis in consultation with lead and co-investigators. A brief analysis plan and data request will be required and reviewed by the investigators for approval of data sharing. When requests are approved, data will be sent electronically in password protected files. All data sharing will abide by rules and policies defined by the sponsor; relevant institutional review boards; and local, state, and federal laws and regulations. Data sharing mechanisms will ensure that the rights and privacy of individuals participating in research will be guaranteed.

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