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# The absence of benefit of perioperative chemotherapy in initially resectable peritoneal metastases of colorectal cancer origin treated with complete cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: A retrospective analysis

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ABSTRACT

*Introduction:* The aim of this study was to compare the outcome of patients with peritoneal metastasis (PM) of colorectal origin treated with complete cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) with or without perioperative systemic chemotherapy (PCT+/PCT-).
*Patients and methods:* Retrospective analysis of 125 patients treated with complete CRS (R0/R1) and HIPEC for PM from colorectal origin in two Belgian academic centers between 2008 and 2017. Disease-free survival (DFS) and overall survival (OS) were assessed with regard to PCT. Statistical analyses were adjusted for non-balanced survival risk factors.
*Results:* The PCT+ group (n = 67) received at least 5 cycles of PCT and the PCT-group (n = 56) did not receive PCT. The groups were well balanced for all prognostic factors except presentation of synchronous disease (more in PCT+). Survival analysis was adjusted to peritoneal cancer index and presentation of synchronous disease. After a median follow-up of 54±5-months, the 1, 3, 5-years OS in the PCT+ group were 98%, 59% and 35% compared to 97%, 77% and 56% in the PCT-group (HR = 1.46; 95% CI:0.87–2.47; p = 0.155). The 1,3 and 5 years DFS in the PCT+ group were 47%, 13% and 6% compared to 58%, 29% and 26% respectively in the PCT- (HR = 1.22; 95% CI:0.78–1.92; p = 0.376).
*Conclusion:* This study does not show any clear benefit of PCT in carefully selected patients undergoing R0/R1 CRS and HIPEC for colorectal PM. The ongoing CAIRO6 trial randomizing CRS/HIPEC versus CRS/HIPEC and PCT will probably clarify the role of PCT in patients with resectable PM.


## Introduction

Currently, the 5-year overall survival (OS) of patients with Colorectal (CRC) peritoneal metastasis (PM) treated with complete macroscopic R0/R1 resection and Hyperthermic intraperitoneal chemotherapy (HIPEC) is estimated to be 30%–35%, approaching the results obtained with curative-intent resection in patients with limited colorectal liver metastases [1,2]. However, the number of patients that are cured after complete cytoreductive surgery (CRS) and HIPEC for CRC PM remains limited and, in fact, more than 80%

*Abbreviations:* ACT, adjuvant chemotherapy; CRC, colorectal cancer; CRS, cytoreductive surgery; DFS, disease-free survival; FOLFOX, leucovorin, 5-fluorouracil, oxaliplatin; FOLFIRI, leucovorin, 5-fluorouracil, irinotecan; HIPEC, hyperthermic intraperitoneal chemotherapy; LM, liver metastases; NACT, neoadjuvant chemotherapy; OS, overall survival; PCI, peritoneal carcinomatosis index; PCT, perioperative systemic chemotherapy; PM, peritoneal metastases.

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of these patients develop recurrence and eventually die of disease progression [1].

Neoadjuvant chemotherapy (NACT) and/or 'pseudo' adjuvant chemotherapy (ACT) is regularly administered and often considered to be a standard of care in metastatic CRC [3]. However, its precise indications and benefits remain unclear [4–12]. Extrapolating the results in non-metastatic stage III CRC (e.g. the MOSAIC trial) [6], ACT has been proposed to theoretically reduce the risk of recurrence by eliminating circulating tumor cells and occult micro metastases in patients with colorectal peritoneal metastasis. Some studies have suggested that PCT may be effective in patients treated for PM of CRC origin but none of these were randomized, focused on neoadjuvant chemotherapy, or included patients with incomplete CRS (R2 resection) [14,15]. Only one case-matched study comparing patients that received PCT (PCT+) versus no PCT (PCT-) showed a benefit of NACT for 1-year disease-free survival (DFS) but without improvement in OS [4].

The aim of this study was to compare the outcome of patients with PM of CRC origin treated with complete CRS and HIPEC, who received or did not receive PCT.

## Patients and methods

### *Study design, patient population, and primary tumor characteristics*

This was a retrospective study conducted in two Belgian Centers (Institut Jules Bordet, Université Libre de Bruxelles and Cliniques Universitaires Saint-Luc, UCLouvain) including consecutive patients who received complete CRS and HIPEC for CRC PM between January 2008 and December 2017. Patients with primary appendix tumors were excluded. Included patients had a peritoneal carcinomatosis index (PCI) score $\leq$25 and had benefited from a complete macroscopic resection (R0/R1). A maximum of 3 resectable liver metastases (LM) treated with complete hepatic resection at the time of surgery or before was accepted. Ethical approval was obtained at each institution (CE3106).

A database was used to collect patient information including demographic data, primary tumor information including the use of chemotherapy for the primary tumor, for metastases and the type of chemotherapeutic agent used. To clarify the setting of administrated chemotherapy during the disease evolution, we defined chemotherapeutic lines in Table 1.

### *CRS and HIPEC*

PM was diagnosed based on preoperative imaging. Patients having extra-abdominal metastasis were automatically excluded from CRS. The majority of patients with suspicion of PC on imaging underwent exploratory laparoscopy and PCI scoring. Patients having a PCI >25 were excluded. At the CRS day, operation started by mini-laparotomy and resectability assessment. When R0/R1 resection could not be anticipated, surgery was aborted. Information was also collected regarding PM, risk factors, and CRS. Synchronous PM were defined as those diagnosed within 6 months after the primary diagnosis. For the CRS impact comparison between the two groups, the number of digestive and hepatic resections and the presence of a stoma were considered. For the HIPEC technique, temperature, duration, type, and doses of cytostatic agents were recorded.

### *Perioperative chemotherapy*

The administration of chemotherapy was dependent to centers policy. Patients who received at least 5 cycles of chemotherapy, either within 3 months prior and/or after CRS and HIPEC, were included in the PCT+ group. Patients, who did not receive any chemotherapy, except the use of neoadjuvant and/or adjuvant chemotherapy for the primary tumor before diagnosis of PM, were included in the PCT-group. Patients who received fewer than 5 cycle protocols 3 months before or after CRS and HIPEC were excluded.

The type of chemotherapy and number of cycles received were recorded. (Table 1).

### *Complications*

The occurrence of postoperative complications was classified according to the Clavien-Dindo score [16].

### *Follow up*

Follow-up was conducted at 3-month intervals during the first year after surgery, at 4-month intervals during the second year, and every 6 months thereafter. At each follow-up visit, a series of blood test were performed, including a serum CEA assay with Chest-abdomino-pelvic CT. PET/CT scan was done only if recurrence was suspected.

### *Statistical analysis*

The data were analyzed with SAS 9.4 statistical software. At first, Clinical and histological parameters were compared between groups. For continuous variables we used the Mann–Whitney *U* test and the Chi-Square test or Fisher's exact test for categorical variables. Last follow-up and life-status data were used for the survival analysis (OS). Disease-free survival (DFS) was considered to be the interval between the date of surgery and the detection of recurrent disease or death, whichever occurred first. To avoid bias, early postoperative deaths (within 30 days) were excluded from the statistical analysis. Survival curves were generated using the Kaplan-Meier method, and the two groups were compared using the Log-Rank test. A Cox model was used to derive crude and adjusted hazard ratio (HR) with 95% confidence interval (CI) between the two groups. Statistical analyses were adjusted for non-balanced survival risk factors. A $p$ value of <0.05 was considered statistically significant.

## Results

### *Patient characteristics*

One hundred fifty two patients were scheduled for CRS and HIPEC after exploratory laparoscopy. Out of 152 patients, 125 patients met the inclusion criteria. Fourteen patients were excluded for PCI> 25, 9 patients for more than 3 LM. Four patients had only 2 cycles of chemotherapy, thus could not be included in any of the 2 groups.

Sixty-five patients (52%) presented with synchronous PM, 24 of which (19%) underwent CRS and HIPEC as their primary surgery. Thirty-four patients (27%) presented with 3 or fewer resectable LMs treated prior to or during the CRS and HIPEC procedure (Table 2).

One hundred and fourteen patients (91%) underwent HIPEC with oxaliplatin 460 mg/m$^2$ at 42 °C for 30 min, 9 patients (7%) received a reduced dose of 360 mg/m$^2$ due to a change in protocol at one of the hospitals in 2017, and 2 patients (2%) received mitomycin 35 mg/m$^2$ for 90 min at 42 °C due to known allergies to oxaliplatin. For HIPEC, 72 patients (58%) underwent surgery following the coliseum technique and 53 patients (42%) underwent a closed technique.

**Table 1**
Definitions of administered chemotherapy.

| | |
|---|---|
| **Adjuvant chemotherapy** | Administered to treat the 'non metastatic' primary tumor |
| **Perioperative chemotherapy** | Neo-adjuvant and/or pseudo-adjuvant chemotherapy. |
| Neo-adjuvant chemotherapy | Administered within 3 months prior to CRS/HIPEC. |
| Pseudo-adjuvant chemotherapy | Administered within 3 months after curative intent CRS and HIPEC (before any relapse) |
| **Palliative chemotherapy** | Administered after non operable recurrence post CRS/HIPEC |

*Chemotherapy*

*Adjuvant chemotherapy for primary tumor*

Sixty patients, representing 48% of the total population, received adjuvant chemotherapy for a non-metastatic primary tumor. Among them, 39 (65%) patients were treated exclusively with the standard FOLFOX (leucovorin [LV], 5-fluorouracil [5-FU], oxaliplatin) protocol over 6 months. Fourteen patients (23%) developed PM while on FOLFOX and they were switched to another molecule (FOLFIRI [LV, 5-FU, irinotecan], bevacizumab, aflibercept, or LV plus 5-FU) following metastatic disease guidelines. Seven patients (12%) received another combination of chemotherapy (LV plus 5-FU, capecitabine).

*Perioperative chemotherapy and no chemotherapy*

Sixty-seven patients (55%) did not receive chemotherapy and 56 (45%) received at least 5 PCT cycles. The groups were balanced for all prognostic factors except for synchronous disease ($p = 0.001$) and consequently, for adjuvant chemotherapy ($p = 0.011$) (Table 2). We observed the same rates of mKras and microsatellite instability tumoral status in both groups.

The total number of chemotherapy lines received was not different between groups, despite the limited retrieved information (Table 3). A total of 12 patients benefited from a second CRS and HIPEC procedure for recurrence, 11 patients in the PCT-group and one in the PCT+ group.

*Palliative chemotherapy in the metastatic setting*

Among the PCT group patients, 48 patients (85.7%) received a unique line of chemotherapy and 8 patients received 2 lines of PCT (Table 3). Most of these PCT regimens were an association of either Folfox or Folfiri with our without a target drug (Cetuximab or

**Table 2**
Comparison of patient characteristics between the 2 groups (no perioperative chemotherapy versus perioperative chemotherapy).

| | N total = 125* | PCT - | PCT + | P |
|---|---|---|---|---|
| | N = 125 (%) | N = 69 (55%) | N = 56 (45%) | |
| **Sex (female)** | 75 (60%) | 44 (63.8%) | 31 (55.4%) | 0.364 |
| **Age (years)** | 58 [18–116] | 59 [31–77] | 57.5 [18–75] | 0.369 |
| Age >50 | 86 (68.8%) | 49 (71%) | 37 (66.1%) | 0.567 |
| **T stage (missing = 11)** | | | | 0.359 |
| 2 | 1 (0.9%) | 0 (0%) | 1 (1.8%) | |
| 3 | 38 (33.9%) | 29 (43.3%) | 19 (34.5%) | |
| 4 | 73 (65.2%) | 38 (56.7%) | 35 (63.6%) | |
| **N stage** | | | | |
| N0 | 29 (23.2%) | 17 (25%) | 12 (21,4%) | 0.867 |
| **Localisation** | | | | 0.697 |
| Right colon | 45 (36%) | 27 (39.1%) | 18 (32.1%) | |
| Rectum | 7 (5.6%) | 4 (5.8%) | 3 (5.4%) | |
| Other localisation | 73 (58.4%) | 38 (55.1%) | 35 (62.5%) | |
| **Adjuvant chemotherapy (missing = 1)** | | | | 0.011 |
| Yes | 60 (48.4%) | 40 (59.7%) | 20 (35.7%) | |
| No | 64 (51.6%) | 27 (40.3%) | 37 (66.1%) | |
| **Synchronous PM disease** | 65 (52%) | 26 (37.7%) | 39 (69.6%) | 0.001 |
| **Liver metastasis**** | 34 (27%) | 17 (24.6%) | 17 (30.4%) | 0,546 |
| **Grade (missing = 12)** | | | | 0.196 |
| Well | 24 (21.2%) | 18 (26.9%) | 6 (13%) | |
| Moderate | 65 (57.6%) | 35 (52.2%) | 30 (65.2%) | |
| Poor | 24 (21.2%) | 14 (20.9%) | 10 (21.7%) | |
| **Microsatellite instability (missing = 49)** | 8/76 (10.5%) | 6/45 (13.3%) | 2/31 (6.4%) | 0.259 |
| **Mutated KRAS (missing = 41)** | 39/84 (46.4%) | 17/39 (43.6%) | 22/45 (48.9%) | 0.666 |
| **PCI score** | 6 [1–25] | 6 [1–23] | 8 [1–25] | 0.068 |
| 1-6 | 64 (51.2%) | 38 (55.1%) | 26 (46.4%) | 0.294 |
| 7-12 | 33 (26.4%) | 20 (29%) | 13 (23.2%) | |
| 13-19 | 13 (10.4%) | 5 (7.2%) | 8 (14.3%) | |
| >19 | 15 (12%) | 6 (8.7%) | 9 (16.1%) | |
| **Clavien-Dindo complications** | | | | 0.001 |
| No complications | 14 (11.2%) | 4 (5.8%) | 10 (17.9%) | |
| I | 13 (10.4%) | 2 (2.9%) | 11 (19.6%) | |
| II | 71 (56.8%) | 50 (72.3%) | 21 (38%) | |
| III | 12 (9.6%) | 3 (4.3%) | 9 (16%) | |
| IV | 13 (10.4%) | 8 (11.6%) | 5 (8%) | |
| V | 2 (1.6%) | 1 (1%)* | 1 (1%)* | |
| **Recurrence sites** | 89 (71.2%) | 43 (64.2%) | 46 (82.1%) | 0.177 |
| Hepatic | 14 (11.2%) | 6 (13.9%) | 8 (17.4%) | |
| Peritoneal | 43 (34.4%) | 18 (41.9%) | 25 (54.3%) | |
| Hepatic and peritoneal | 20 (16%) | 14 (32.6%) | 6 (13.1%) | |
| Non-hepatic non-peritoneal | 12 (9.6%) | 5 (11.6%) | 7 (15.2%) | |

**Table 3**
Perioperative chemotherapy and palliative chemotherapy.

| n = 123 | No PCT (n = 67) | PCT (n = 56) | *p* |
|---|---|---|---|
| **Perioperative chemotherapy** | 0 | 56 (100%) | |
| 1 chemotherapy lines | | 48 (85.7%) | |
| 2 chemotherapy lines | | 8 (14.3%) | |
| **Palliative chemotherapy** | 32 | 16 | |
| **Number of lines** | | | 0.058 |
| 1 chemotherapy line | 18 (56.3%) | 5 (31.3%) | |
| 2 chemotherapy lines | 7 (21.8%) | 4 (25%) | |
| 3 chemotherapy lines | 3 (9.4%) | 0 | |
| Unknown | 4 (12.5%) | 7 (43.7%) | |

Bavacizumab).

After CRS and HIPEC procedure, 43 and 46 patients presented a disease recurrence respectively in the PCT- and the PCT+ group. Data on chemotherapy regimens was missing for 27 patients but a total of respectively 31 and 37 patients in the PCT- and PCT+ groups received at least one palliative chemotherapy line (Table 3). Among these patients, chemotherapy regimens were highly variable but the most frequent regimen was folfiri with or without a targeted drug given to 23 patients (25.8%) followed by folfox with or without a targeted drug given to 10 patients (11.2%). A total of 4 patients (4.5%) received Regorafenib at a stage of their recurrent disease.

### *CRS, morbidity, and perioperative mortality*

Ninety-eight patients (78%) had minor postoperative complications (CDS I-II) and 25 patients (20%) presented with mild-to-severe complications requiring re-intervention (CDS III-IV) (Table 2). Two patients died within 30 days of their hospital stay and were not included in the comparative analysis (due to impossibility to classify into any group). There rate of major complication (CD ≥IIIa) was similar between the 2 groups ($p = 0.263$).

### *Disease-free survival and overall survival*

The survival analysis in the PCT + and PCT groups were adjusted to PCI and to synchronous disease. The median Follow up was 54 ± 5 months. When PCT was assessed (PCT+ versus PCT-), median OS was 43 [31–58] months versus 72 [53–88] months. Median DFS in the PCT+ group was 11.4 [9.3–15.6] months compared to 17.3 [9.3–25] months in the PCT-group. The 1, 3, 5-years and median OS in the PCT+ group were 98%, 59% and 35% compared to 97%, 77% and 56% in the PCT-group (Logrank-P = 0.039; Adjusted HR = 1.46; 95% CI:0.87–2.47; p = 0.155). The 1,3 and 5 years DFS in the PCT+ group were 47%, 13% and 6% compared to 58%, 29% and 26% respectively in the PCT-group (Logrank-P = 0.035; Adjusted HR = 1.22; 95% CI:0.78–1.92; p = 0.376) (Figs. 1 and 2).

During the follow-up period, 89 (72%) patients developed a recurrence and only 5 (4%) patients became disease-free after being treated for their recurrence with a second CRS with or without HIPEC, at the time of latest follow-up.

Fourteen patients (16%) developed hepatic recurrences and 8 of these later developed other non-peritoneal recurrences. Forty-three patients (48%) developed peritoneal metastases, 18 of them being associated with or followed by non-hepatic metastases. Twenty patients (22%) developed hepatic and peritoneal metastases (6 associated with other localizations). Finally, 12 patients (14%) developed non-peritoneal and non-hepatic metastases, mostly lung and/or lymph node recurrences (Table 3).

## Discussion

Perioperative chemotherapy is frequently considered to be the standard of care in patients undergoing CRS and HIPEC for resectable CRC PM, but the scientific evidence to support such a recommendation is weak and mainly relies on the results from studies of adjuvant chemotherapy in patients with locally advanced CRC and the potential benefit of perioperative chemotherapy in patients undergoing surgery for CRC LM [2,3,11,17]. Recent studies have even reported worse prognoses for patients who underwent surgery for LM after ACT for their primary tumor (stage III CRC at diagnosis), suggesting the induction of chemo-resistance in pre-treated patients or the selection of more aggressive disease phenotypes [18,19]. In fact, very few studies have focused on the role of PCT (neoadjuvant and/or ACT) in patients treated for resectable CRC PM [4–13]. Most studies reporting ACT as a prognostic factor have come from large retrospective cohort studies that were not focused primarily on PCT and postoperative chemotherapy was given when a good response to preoperative chemotherapy was already observed (whenever administered) or in patients with poor prognostic factors [14,15]. These studies also have methodological weaknesses as they gathered no details regarding the type of chemotherapy or number of lines, and included postoperative deaths in the survival analysis, making it difficult to assess the benefit of a given PCT protocol. Maillet et al. reported a possible transient effect of ACT on DFS (1-month difference at 1-year follow-up) but no effect on OS [4].

Our study evaluates the effect of PCT on survival in a specific series of carefully selected patients (median PCI = 6) that received R0/R1 surgery. In 2015, Maillet et al. reported a possible transient effect of ACT on DFS (1-month difference at 1-year follow-up) but no effect on OS [4]. The effect of NACT was not analyzed in this study. However, this was the first reported study showing no clear evidence for the role of pseudo-ACT in patients with resectable colorectal PM treated with CRS and HIPEC. Kuijpers et al. reported the benefit of PCT in patients at high risk of recurrence (i.e. positive LN with synchronous PM) with 3-year survival rates of 45% (PCT+) and 16% (PCT-) [8]. This is quite different from our results which showed 3-year OS of 59% (PCT+) and 77% (PCT-). However, they included patients with incomplete resection (R2a), meaning that those patients were not treated with curative intent, and the standard attitude was to administer ACT. The latter was administered in 30% of patients with major complications and in 90% in patients without major complication (reported p = 0.001). This would bias any survival analysis in this setting and any benefit of survival is mainly related to the effect of post-operative complications. Two recent studies have focused on the role of NACT [11,12]. In the first study, Leimkühler et al. reported on a small prospective study of the safety and feasibility of administering NACT [11]. They did not find any prognostic benefit but no definitive conclusions can be drawn because of the limited number of patients included in the study (14 patients). In the second study, Beal et al. reported no effect of NACT on OS in multivariable analysis [12]. Moreover, no benefit in terms of DFS was observed.

Overall, this lack of evidence for a role for PCT, in particular in patients with upfront resectable CRC PM, was acknowledged in a recent review of the literature where the authors highlighted the “significant limitations of available evidence” in this setting [6]. Still, and despite these strong limitations, PCT was considered to be the standard of care in the ongoing PRODIGE 7 prospective trial and remains recommended in a recent treatment consensus in France [20,21].

The main observation from this study was the absence of benefit of PCT in patients with initially resectable CRC PM undergoing CRS and HIPEC. Our data suggest that in carefully selected patients

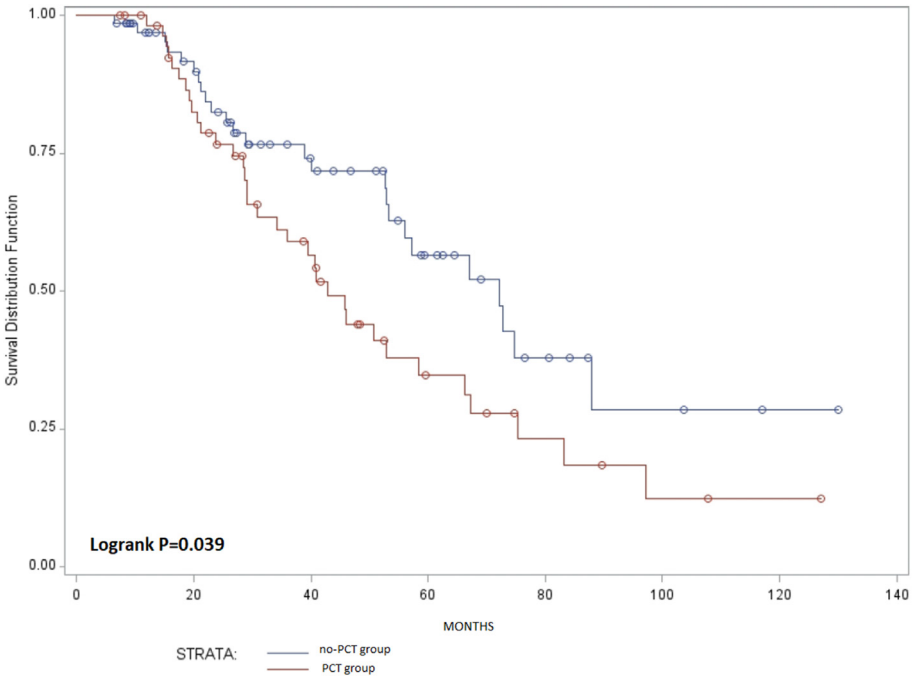


**Fig. 1.** Kaplan Meier curves of overall survival. Blue curve: PCT-group; Red curve: PCT+ group.

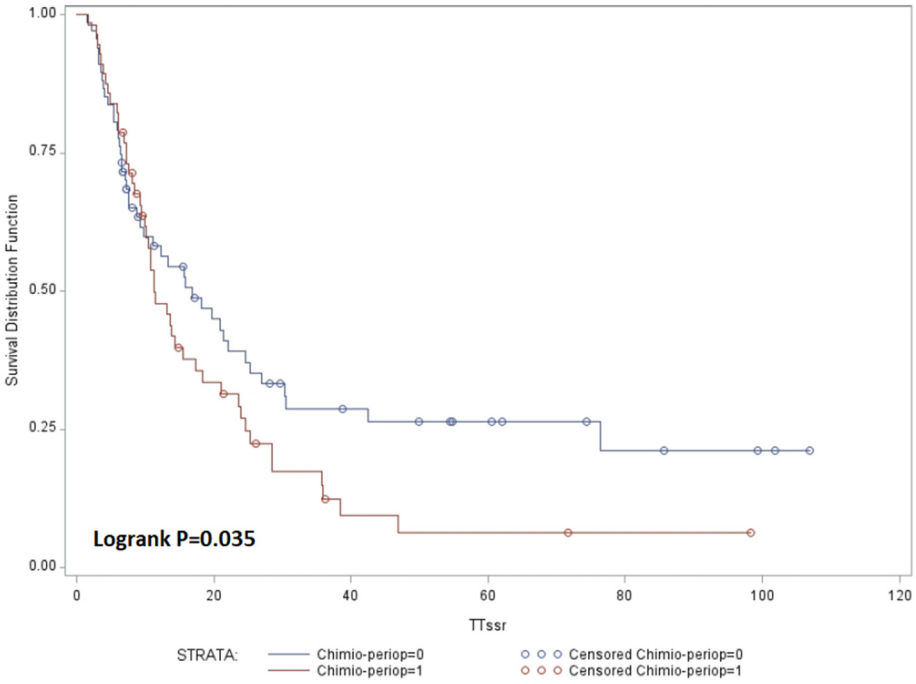


**Fig. 2.** Kaplan Meier curves of disease-free survival: Blue curve: PCT-group; Red curve: PCT+ group.

receiving complete CRS and HIPEC where R0/R1 could be anticipated and with limited LM and no extra-abdominal metastasis, there is no proven effect of PCT. Survival of patients in the PCT-group may appear to be surprisingly high in comparison to survival data reported in other studies reporting 3-year OS rates from 16% to 58% [4,8,14,15]. This is mainly explained by patient selection during the study period in both centers and highlights the fact that the categorization of patients with colorectal PM is of utmost importance.

Our results do not support the systematic use of PCT in patients with upfront resectable CRC PM. The interpretation of these findings should be tempered by several factors, mainly related to the retrospective nature of the study. First, despite the fact that both groups were comparable for major prognostic factors, the

PCT+ group had a higher rate of synchronous PM, a known negative predictive factor [22,23] and higher median PCI (median PCI: 8 vs 6). Nevertheless, Hazard ratios were adjusted according to these 2 variables. Second, the total number of chemotherapy lines received in the course of the disease and its heterogeneity could be a potential bias. These data are missing in the majority of reported studies [7–12]. We were able to limit this bias, but details on the number of received chemotherapy cycles were still missing. Third, in most reported studies, postoperative complications negatively impacted the no chemotherapy group as patients who presented with complications did not receive adjuvant chemotherapy, ACT being part of the standard treatment. This is not observed in our study, showing that the decision to not administer ACT is independent of postoperative complications and is related to multidisciplinary meeting (MDM) decisions. This is corroborated by the fact that we did not observe differences in terms of postoperative complications between the two groups, therefore limiting this potential bias. Fourth, not all patients had initial exploratory laparoscopy, this would constitute a bias since some of the patients might have falsely low PCI in the PCT+ group. Finally, in addition to morphological characterization, it is highly expected that the differences observed in outcomes in patients undergoing CRS and HIPEC with or without PCT may be also related to intrinsic tumor aggressiveness, a factor which is dependent on the genetic background of the tumor. As in most studies, this information was largely missing. Yet, when these data were available, we did not observe difference in the rates of K-RAS mutated tumors, a known poor prognostic factor, between PCT- and PCT+ groups.

## Conclusions

These results do not support the clinical benefit of PCT in patients treated with CRS and HIPEC for PM of colorectal cancer origin. Furthermore, they indicate that CRS and HIPEC is only curative in selected cases. These results highlight the need for better patient stratification that distinguishes between patients with initially resectable disease and those with initially extensive disease (PCI>16) and/or unresectable disease to allow for personalized therapeutic management. The ongoing CAIRO6 trial randomizing CRS/HIPEC versus CRS/HIPEC and PCT will probably clarify the role of PCT in patients with resectable PM in the future [24]

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No funding.

## Data statement

Data is unavailable due to confidentiality (local ethical comity). However, information's about the research data can be requested to the authors.

## Declaration of competing interest

Authors have no conflict of interest to disclose.

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