

REVIEW ARTICLE

Primary curative surgery and preemptive or adjuvant hyperthermic peritoneal chemotherapy in colorectal cancer patients at high risk to develop peritoneal carcinomatosis: A systematic review

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Summary

Purpose: To evaluate all available data on the effect of preemptive intervention in patients who have curative surgery for colorectal cancer (CRC) and are at high risk to develop peritoneal carcinomatosis (PC).

Methods: The authors conducted a systematic review of all published studies from January 2000 to July 2016. Twelve studies were eventually considered for analysis, and were divided in four categories, according to different approaches for adjuvant intra-peritoneal chemotherapy: a) hyperthermic intraperitoneal chemotherapy (HIPEC), during primary surgery for CRC; b) early postoperative intraperitoneal chemotherapy (EPIC), after primary surgery for CRC; c) early re-intervention (laparotomy or laparoscopy) and HIPEC; and d) as second look laparotomy and HIPEC + cytoreductive surgery (CRS), several months after primary surgery.

Results: Considering prophylactic HIPEC during primary surgery, the studies that were analysed showed a peritoneal

recurrence rate of 0-12.9%, a 3- and 5-year disease free survival (DFS) of 67-97.5% and 54.8-84% respectively, and a 3- and 5-year overall survival (OS) of 67-100% and 84%, respectively. These oncological results are probably better than what is expected in patients at high risk to develop PC and have only adjuvant systemic chemotherapy.

Because of the great heterogeneity in inclusion criteria (risk factors for PC) and methodology of intra-peritoneal chemotherapy (different timing, different techniques, different agents), a meta-analysis was not performed.

Conclusions: At present and because of the insufficient available evidence, preemptive intervention at the immediate postoperative adjuvant setting is recommended only in the setting of a registered clinical trial.

Key words: colorectal cancer, EPIC, HIPEC, intraperitoneal chemotherapy, peritoneal carcinomatosis

Introduction

According to several large registries, the overall incidence of PC in patients with CRC may be as high as 13%, whilst the incidence of synchronous to the primary lesion PC ranges from 3.8 to 5.1%, and the cumulative incidence of metachronous PC

is reported in rates of 3.5-19% [1-6]. The actual prevalence of PC in autopsy studies is remarkably higher reaching 40-80% [7]. Systemic chemotherapy, combined with palliative surgery and best supporting care is associated with a poor overall

median survival of 5.2 to 18.2 months; 5-fluorouracil-based systemic chemotherapy offers a median survival of 9-11 months, oxaliplatin-irinotecan containing regimes a median survival of 10.1-15 months and combination containing monoclonal antibodies a median survival of 15.2-18.2 months [1,4]. It is common in studies to pool patients with PC together with stage IV cancer patients with liver metastases. As a result, most conclusions on the effect of systemic chemotherapy are extrapolated from studies on mixed patient populations.

If systemic chemotherapy is combined with CRS and HIPEC, the median OS is reported to increase to 31.6 months (range: 16-51) and the 5-year OS to 20-30% [8-25]. The extent of PC, as assessed with the peritoneal cancer index (PCI) [26], is the key prognostic factor after CRS and HIPEC [26-29]. In a series of 523 patients with PC, who had CRS and HIPEC, a PCI <7 was associated with an OS of 49%, as opposed to 10% in patients with a PCI >20 [29]. Conceivably, PC should be diagnosed at early stages in order to achieve more favourable oncological outcomes after CRS and HIPEC.

Non-invasive diagnostic procedures, including current imaging techniques, yield poor results in identifying patients with PC at early stage. Several risk factors for developing PC after curative surgery for CRC have been proposed [30], although evidence-based data is lacking. In a recent systematic review [31] of the literature until the end of 2011, 16 studies of low methodological quality, including 598 patients with PC of CRC, were analysed. It was suggested that the most important risk factors for metachronous PC after curative surgery of CRC were concomitant PC, isolated ovarian synchronous metastasis and perforation of the primary tumour at primary surgery. Other factors bearing less risk were the histological subtype, namely lesions with mucinous and signet ring cell components, positive peritoneal cytology and T4a and T4b tumours.

The concept of identifying high risk factors for metachronous PC of CRC after curative primary surgery is to attempt a preemptive intervention,

in order to improve overall oncological outcomes. Sugarbaker et al. [32] proposed the first preventive intervention in 1985: in a randomized study, CRC patients at high risk to develop PC received either adjuvant i.v. 5-fluorouracil for one year, or early EPIC with 5-fluorouracil through Tenckhoff catheters, that started immediately after surgery and lasted for one year. No difference in oncological outcomes, including occurrence of PC, was observed. Safe conclusions could not be drawn mainly because of the poorly defined inclusion criteria, a heterogeneity in the adjuvant treatments used (some patients had pelvic irradiation), the choice of the single chemotherapeutic agent that was used and the non-uniform perfusion of the infusate. Increasing understanding of the natural history of the disease and the introduction of modern chemotherapy renewed the interest on preemptive measures for PC in the mid-2000s. The two suggested strategies are: second look surgery to detect and treat PC with HIPEC ± CRS [27], or HIPEC ± EPIC at primary surgery [33].

The aim of the present systematic review was to evaluate all available data on the effect of preemptive intervention on general oncological outcomes, in patients who had curative surgery for CRC and were at high risk to develop PC.

Methods

Two authors (NG and KS) conducted a systematic review of English written literature in PubMed, Embase, Medline, the Cochrane database and Ovid published from January 2000 to July 2016. The search terms used alone or in combination in order to identify studies on the incidence of PC were: "colon cancer", "rectal cancer", "colorectal cancer", "metastatic disease", "peritoneal carcinomatosis", "peritoneal recurrence", "ovarian metastasis", "colon T4 tumour", "serosal invasion", "mucinous carcinoma", "signet ring cell carcinoma", "perforated colorectal cancer", "obstructive colorectal cancer", "peritoneal lavage", and "peritoneal cytology". "preemptive treatment", "proactive treatment", "prophylactic treatment", "adjuvant chemotherapy", "cytoreductive sur-

Table 1. Level of evidence

- | | |
|-----|--|
| I | Evidence from at least one large randomized controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted RCTs without heterogeneity |
| II | Small RCTs or large RCTs with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity |
| III | Prospective cohort studies |
| IV | Retrospective cohort studies or case-control studies |
| V | Studies without control group, case reports, experts' opinions |

RCTs: randomized clinical trials

gery”, “intraoperative chemotherapy”, “hyperthermic intra-peritoneal chemotherapy – HIPEC”, and “immediate postoperative intra-peritoneal chemotherapy – EPIC”.

The authors NG and EX assessed independently all references found by title, abstract and full text. Studies on CRS for previously confirmed PC of CRC origin and HIPEC or of cancer of various intra-peritoneal origins were excluded. Of multiple publications from centers reporting on the same cohort of patients, the most complete or the most recent ones were analysed, unless reporting different outcomes on the same cohort of patients.

Data analysis

From the studies selected for final review, the following data were extracted: i) risk factors for PC, ii) stage of primary disease, iii) chemotherapeutic agents used for intraperitoneal chemotherapy, iv) morbidity and mortality, v) length of hospital stay, vi) histopathology of the resected specimen, vii) adjuvant chemotherapy, and viii) oncological outcomes. In case of second-look assessment for PC, in addition to the above data, the need for CRS and its impact on outcome were assessed. The methodological quality of the selected studies was assessed according to the grading system of levels of evidence (LOE) based on the version adopted by the ESMO Consensus Guidelines for colorectal cancer [34] (Table 1). Because of the great heterogeneity in inclusion criteria (risk factors for PC) and methodology of intraperitoneal chemotherapy (different timing, different techniques, dif-

ferent agents) in the included studies, no meta-analysis was performed.

Results

Three hundred forty four studies were identified at the initial search. Of these studies most were excluded because they were reporting on CRS and HIPEC in patients with preoperatively confirmed PC from either CRC and/or other intraperitoneal malignancies. There remained 15 studies reporting on perioperative or adjuvant intraperitoneal chemotherapy in patients who had primary curative surgery for CRC and were considered at high risk of developing PC. All authors assessed the full text of these studies and excluded another three: one reporting on appendiceal carcinoma (different pathogenetic basis) [35] and two presenting the protocol of ongoing trials on adjuvant treatment [36,37] (Table 2).

Twelve studies were eventually considered for analysis and were divided in four categories, according to three different approaches for adjuvant intraperitoneal chemotherapy in CRC patients at high risk of developing PC: a) HIPEC, during primary surgery for CRC; b) EPIC, after primary surgery for CRC; c) early re-intervention (laparotomy

Table 2. Inclusion flowchart of studies reporting on adjuvant-preemptive-proactive intraperitoneal chemotherapy in CRC patients

	<i>References (n)</i>
MeSH Search - Full Text Selection	344
Excluded (Initial selection)	329
CRS plus HIPEC for CRC-PC	99
CRS plus HIPEC for PC (various origin)	98
Diagnosis, research, nomograms of PC	39
Risk factors for PC	4
Economics of CRS – HIPEC	3
Case reports on PC	2
Comments – Letters to editors	5
Reviews – Metaanalyses	71
Guidelines – Consensuses – Surveys	5
Irrelevant reports	3
Adjuvant intraperitoneal CT in CRC patients	15
Excluded	3
Adjuvant intraperitoneal CT for appendiceal cancer	1
Ongoing trials on adjuvant intraperitoneal CT	2
Included	12
Perioperative intraperitoneal CT	7
At second look intraperitoneal CT + CRS	5

CRS: Cytoreductive surgery, HIPEC: Hyperthermic intraperitoneal chemotherapy, CRC: Colorectal cancer, PC: Peritoneal carcinomatosis, CT: chemotherapy

or laparoscopy) and HIPEC; and d) as second look laparotomy and HIPEC + CRS, several months after primary surgery.

HIPEC during primary surgery for colorectal cancer

Design of the studies

Seven studies [33,38-43] reported on the outcomes of HIPEC performed during primary surgery for CRC. Of these, two studies [38,41] were excluded from pooled analysis because they included cases recruited at the same center and within the same

period of time, and already reported elsewhere [39,40]. The remaining 5 studies (Table 3) involved 117 patients (male: 54.7%; median age 60.7 years [range: 55-67]). In 88 cases primary tumour was located in the colon and in the remaining 29 in the rectum. High risk factors for PC mandating HIPEC varied between studies, and included peritoneal lavage positive for cancer cells, T3, T4, T4a, T4b, mucinous tumours, tumours with signet ring cells, peritoneal metastatic deposit at the vicinity of the primary tumour, or metastatic deposit in the ovaries (Table 3). In the study by Tentes et al. [42] all patients had negative peritoneal lavage, whilst in

Table 3. Data from studies reporting on intraoperative HIPEC

Study	Design (LOE)	Risk factors for PC	Chemotherapeutic agents	Morbidity	SSI	Anastomotic leak	LOS
Noura et al 2011	prospective comparative ^a (LOE: III)	(+) peritoneal lavage	mitomycin				
Sammartino et al 2014	prospective comparative ^a (LOE: III)	T3, T4, mucinous, signet ring cell	oxaliplatin	5/25			
Shumizu et al 2014	prospective case control (LOE: IV)	(+) peritoneal lavage, T4b peritoneal deposit at vicinity	oxaliplatin + mitomycin +5 fluorouracil	3/5	1/5		11(1.5)
Tentes et al 2011	comparative ^b case control (IV)	T3, T4	mitomycin or oxaliplatin	16/40	4/40	4/40	30.7(8.9)
Virzi et al 2013	prospective case control (LOE: IV)	(+) peritoneal lavage, T4a, T4b peritoneal tumour deposits at vicinity tumour deposits at ovaries	oxaliplatin + mitomycin		0/12	0/12	15(3.3)
Sum (%)				24/70 (34.3)	5/57 (8.8)	4/52 (7.7)	15 (11-30.7)

^aprospective HIPEC series compared to matched controls from archives, ^bprospective HIPEC series compared to prospective EPIC series, SSI: Surgical site infection, LOS: length of hospital stay, LOE: level of evidence, PC: peritoneal carcinomatosis

Table 4. Histopathological outcomes from studies reporting on intraoperative HIPEC

Study	T stage	N stage	Differentiation
Noura et al 2011	T3: 17/31; T4: 14/31	N(-): 7/31; N(+): 24/31	gm: 13/31; p: 18/31
Sammartino et al 2014	T3: 19/25; T4: 6/25	N(-): 16/25; N(+): 9/25	gm: 17/25; p: 8/25
Shumizu et al 2014	T3: 2/5; T4: 3/5		gm: 5/5; p: 0/5
Tentes et al 2011	T3: 25/40; T4: 15/40	N(-): 20/40; N(+): 20/40	gm: 36/40; p: 4/40
Virzi et al 2013	T3: 2/12; T4: 10/12	N(-): 5/12; N(+): 7/12	gm: 11/12; p: 1/12
Sum/median	T3: 65/113; T4: 48/113	N(-): 48/108; N(+): 60/108	gm: 82/113; p: 31/113

gm: good/moderate, p: poor

the Shumizu et al. study [40] peritoneal lavage was positive in 4 out of the 9 patients, and one patient had a deposit in the Douglas pouch.

In all but one cases a R0 resection of the primary tumour was achieved. In the study by Sammartino et al. [39] surgery for primary tumour was complemented with appendectomy, oophorectomy and resection of the round hepatic ligament and the lesser omentum, whilst Virzi et al. [43] reported that surgery for primary tumour was complemented with resection of the pelvic peritoneum, oophorectomy and resection of the greater omentum. The chemotherapeutic agents used during HIPEC also varied between studies. Oxaliplatin and/or mitomycin were the most commonly agents used in various dosages (Table 3).

Outcomes of the studies

There was one postoperative death reported by one study [42]. Three studies [39,40,42] reported an average morbidity rate of 34.4%. Surgical site infection was reported at an average rate of 8.8% in three studies [40,42,43], and anastomotic leak at an average rate of 7.7% in two studies [42,43]. The median length of hospital stay was 15 days, as reported in three studies [40,42,43] (Table 3).

At histopathological examination, 72.6% of the tumours were well or moderately well differentiated; 57.5% of them were T3 and the remaining 42.5% T4, as reported by all 5 studies. Involved lymph nodes were found in 55.5% of the patients, as reported in 4 studies [33,39,42,43]. In only one study [39], presence of mucinous or signet ring cell tumours was reported in 92% and 8% respectively. In all 5 reporting studies 65.8% of the patients had adjuvant chemotherapy (Table 4).

Median follow up was 48 months (range: 17-83.1). One study [40] reported one local recurrence, whilst another two [42,43] reported no local recurrence. The median rate of peritoneal recurrence was 5.1% (range: 0-12.9), and the distant metastasis rate was 11.6% (range: 2.5-33.3), as reported by all 5 studies. Two studies [40,42] reported a 3-year OS of 66.7% and 100% respectively, and another two [39,43] reported a 5-year OS of 84% and 83.3% respectively. Three-year DFS was 66.7% and 97.5% in two studies, respectively [40,42]. Five-year disease-specific survival was 54.8% in one study [33]. Five-year DFS was 84 and 75%, respectively, in two studies [39,43] (Table 5).

Comparison of HIPEC to standard adjuvant systemic chemotherapy

There were two studies [33,39] that compared the oncological outcomes of intraoperative HIPEC and standard adjuvant chemotherapy for patients at high-risk to develop PC from CRC. In the study by Noura et al. [33], 52 patients with positive cytology of the peritoneal fluid at the surgery for the primary tumour were enrolled in the study. Thirty-one patients were given intraoperative HIPEC and the remaining 21 were offered adjuvant chemotherapy. The basis of selection to either treatment was not stated, and there was given a variety of perioperative chemotherapeutic regimes for metastatic disease. Tumour location, stage and differentiation distribution were similar between the two groups. Approximately 35% of patients in either group had rectal cancer. Mitomycin-C was used for HIPEC. Peritoneal recurrence was found to be significantly less common ($p=0.0362$) in the HIPEC (12.5%) than in the non-HIPEC (50%) group.

Table 5. Oncological outcomes from studies reporting on intraoperative HIPEC

Study	Adjuvant chemotherapy n	Follow-up months n (%)	Local recurrence	Peritoneal recurrence n (%)	Distant metastasis n (%)	Overall survival n (%)	Disease free survival n (%)
Noura et al 2011	23/31	83.1(43.3)	-	4/31 (12.9)	-		17/31 (54.8) (5-y)
Sammartino et al 2014	13/25	48	-	1/25 (4)	5/25 (20)	21/25 (84) (5-y)	21/25 (84) (5-y)
Shumizu et al 2014	8/9	28.1(3.2)	1/9	0/9 (0)	3/9 (33.3)	6/9 (67) (3-y)	6/9 (67) (3-y)
Tentes et al 2011	21/40	17	0/40	0/40 (0)	1/40 (2.5)	40/40 (100) (3-y)	39/40 (97.5) (3-y)
Virzi et al 2015	12/12	49 (12.5)	0/12	1/12 (8.3)	2/12 (16.7)	10/12 (83.3) (5-y)	9/12 (75) (5-y)
Sum/median	77/117 (65.8)	48 (17-83.1)		6/117 (5.1)	10/86 (11.6)		

Peritoneal recurrence-free 5-year survival rate was also significantly higher ($p=0.0003$) in the HIPEC (88%) than in the non-HIPEC (40.1%) group. Peritoneal recurrence-free and cancer specific survival were significantly associated with disease stages II and III in either treatment group (HIPEC: 85.6% vs adjuvant systemic chemo: 45.5%; $p=0.0047$ and HIPEC: 67.5% vs adjuvant systemic chemo: 16.7%; $p=0.0037$, respectively) (Table 6).

At univariate analyses in the study by Noura et al. [33], it was shown that i) histological grade and presence of limited PC at the vicinity of the tumour was significantly associated with the peritoneal recurrence-free survival rate ($p=0.0257$ and $p=0.0003$, respectively); ii) histological grade, PC at primary surgery, T stage, lymphatic invasion, venous invasion and distant metastasis were significantly associated with cancer-specific survival; and iii) regional lymph node status and adjuvant chemotherapy were not associated with either peritoneal recurrence-free or cancer specific survival.

At multivariate Cox regression analysis in the same study [33], i) PC at the vicinity of the tumour at primary surgery was the only independent risk factor for peritoneal recurrence-free survival ($p=0.0274$); ii) distant metastasis was the only independent risk factor for cancer specific survival ($p<0.0001$), while iii) regional lymph node status was not a significant risk factor for peritoneal recurrence.

In the study by Sammartino et al. [39], 75 patients at high risk to develop PC were either given HIPEC during surgery for primary tumour (25 patients) or standard adjuvant chemotherapy after curative surgery (50 patients). T3 or T4 or mucinous or signet ring cell tumours were considered as high-risk features for PC. Selection of patients for either treatment was based on different strategic approaches between medical teams involved. There were no significant differences in demographics,

tumour location and histopathological characteristics between the two groups. At surgery, HIPEC was complemented with appendectomy, oophorectomy and resection of the round hepatic ligament and lesser omentum. At a median follow-up of approximately 3 years, distant metastasis rate was similar between groups (HIPEC: 20%, non-HIPEC: 18%). However, a significantly lower rate of peritoneal recurrence ($p<0.05$) was seen in the HIPEC group (1/25 patients; 4%) as compared to the non-HIPEC group (11/50 patients; 22%). Also, actuarial DFS rate and actuarial OS were significantly higher ($p<0.04$ and $p<0.05$, respectively) in the HIPEC group (Table 6).

Early postoperative intra-peritoneal chemotherapy (EPIC)

In the study by Tentès et al. [42], 57 patients with CRC and at high risk to develop PC had EPIC for the first 5 postoperative days, following resection of the primary lesion. High risk factors were T3 or T4 tumours. Peritoneal lavage was negative for tumour cells in all patients. 5-fluorouracil was instilled intraperitoneally through a Tenckhoff catheter. Immediate postoperative mortality was 15.8% and morbidity 38.6%. Surgical site infection was reported in one, and anastomotic leak in 4 patients (7%). Of the patients, 45.6% had adjuvant chemotherapy. After a median follow-up of 28 months, peritoneal recurrence rate was 8.3% and distant metastasis 25%. The 3-year OS was 69%.

HIPEC vs EPIC

Tentès et al. [42] also compared the outcomes of their series after EPIC to those after HIPEC (see above). The selection of patients was based on time period: CRC patients at risk to develop PC after curative surgery, recruited between 1999 and 2004, had EPIC, and those recruited between 2005

Table 6. Oncological outcomes from studies reporting on intraoperative HIPEC

Study	Pts	Peritoneal recurrence %	Distant metastasis %	Peritoneal cancer-free 5-year survival %	5-year DFS %	5-year OS %
Noura et al 2011						
Adjuvant systemic chemo	21	50		40.1		
Perioperative HIPEC	31	12.5		88		
		$p=0.0362$		$p=0.0003$		
Sammartino et al 2014						
Adjuvant systemic chemo	25	22	18		57	59
Perioperative HIPEC	50	4	20		84	86
		$p<0.05$	n.s.		$p<0.05$	$p<0.04$

DFS: disease-free survival, OS: overall survival, n.s.: not significant

and 2010 had HIPEC. There were no significant differences in patients' demographic and tumor characteristics between groups, with the exception of the performance status which was worse in the HIPEC group. The chemotherapeutic agents that were used differed between groups. HIPEC involved perfusion with either mitomycin or oxaliplatin. In EPIC only 5-fluorouracil was instilled. Although morbidity did not differ significantly between treatments, mortality was significantly higher in the EPIC group (p=0.009). Overall recurrence rate (locoregional/peritoneal and distant) was higher in the EPIC group (p=0.01). Also, 3-year OS rate was significantly higher in the HIPEC group (EPIC: 69% vs HIPEC: 100%; p=0.011). At univariate analyses, intraperitoneal chemotherapy and grade of differentiation were significant factors for recurrence (p=0.01 and p=0.024, respectively). Intraperitoneal chemotherapy and regional lymph node status were significant predictors for OS (p=0.11 and p=0.262, respectively). At multivariate analyses, again intraperitoneal chemotherapy and the grade of differentiation were independent risk factors for recurrence (p=0.001 and p=0.017, respectively). The regional lymph node status was the only independent risk factor for OS (p=0.022).

Early re-intervention for proactive HIPEC

Early diagnostic laparoscopy with HIPEC

Two studies [45,46] reported on the outcomes of 97 CRC patients (male: 48 patients) who had R0 resection of the primary tumour and were at high risk to develop PC. The patients were explored

laparoscopically according to different criteria: Sloothaak et al. [46] explored proactively patients who had evidence of limited peritoneal dissemination at primary surgery and underwent a R0 resection, whereas in the study by Lygidakis et al. [45] only patients with stage III tumour and positive lymph nodes with neurovascular invasion were included for second look surgery. Histopathological characteristics are shown in Table 7.

Design of the studies

The time interval from primary surgery to re-intervention for laparoscopic HIPEC differed between studies: it was 3 weeks in the Lygidakis et al. study [45] and 6 (+1.5) weeks in the Sloothaak et al. study [46]. Patients in the Lygidakis et al. study [45] had an additional laparoscopic second look 2.5 weeks later. Also, the chemotherapeutic agents used in HIPEC varied between studies, but mitomycin was common in all regimes. All patients in both studies had adjuvant chemotherapy after the second look.

Outcomes of the studies

Both studies reported low postoperative morbidity rate: Lygidakis et al [45]: 0/87pts (0%); Sloothaak et al. [46]: 2/10pts (20%). The reported length of follow-up was 18 and 13 months, respectively. Sloothaak et al. [46] reported no peritoneal recurrence, whereas Lygidakis et al. [45] reported no peritoneal recurrence in all 87 patients at one year and two peritoneal recurrences in 40 patients (5%) who completed the 2-year follow up.

Table 7. Data from studies reporting on second look HIPEC+CRS and laparoscopic re-intervention for HIPEC

Study	Design (LOE)	Selection criteria	T stage p. s	N stage p. s	HIPEC agents
Lygidakis et al 2010	prospective (LOE: III)	stage III (N+) (p.s.) neurovascular invasion (p.s.)	N0: 0/87 N1 or N2: 87/87		mitomycin + oxaliplatin + irinotecan + 5-FU + leucovorin
Sloothaak et al 2014	prospective (LOE: III)	T4 of primary tumour (p.s.) peritoneal tumour deposit at vicinity (p.s.) tumour deposits at ovaries (p.s.) tumour deposits at omentum (p.s.) perforation at tumour site (p.s.) (-) distant metastasis	T3 and T4: 0/10	N0: 4/10 N1 or N2: 6/10	mitomycin
Elias et al 2011	prospective database retrospective comparative analysis (LOE: III)	peritoneal tumour deposit at vicinity (p.s.) tumour deposits at ovaries (p.s.) perforation at tumour site (p.s.) (-) distant metastasis	T1: 3/41 T2: 1/41 T3: 15/41 T4: 22/41	N0: 9/41 N1: 15/41 N2: 11/41 Nx/unknown: 6/41	mitomycin + irinotecan + iv. 5-FU + leucovorin

p.s.: primary surgery, LOE: level of evidence

Second look laparotomy and HIPEC + CRS after primary surgery

Two studies [27,44] reported on the outcomes of second look surgery and HIPEC with or without CRS in CRC patients who had R0 resection for the primary tumour and were at high risk to develop PC. Both studies reported on patient cohorts deriving from the same database and treated at the same center. Criteria for patients to be subjected to second-look surgery for HIPEC and, if needed to CRS, included patients who had evidence of limited peritoneal dissemination at primary surgery, and/or ovarian metastasis, and/or perforation of primary tumour and underwent a R0 resection. Histopathological characteristics are shown in Table 7.

Design of the studies

Eligible patients had adjuvant chemotherapy for 6 months after primary surgery, and underwent second look surgery for HIPEC and CRS, if necessary, after a minimum of 6-month resting period. Hence the mean time interval between primary surgery and second look was 11.1 +7.1 months. Twenty-three out of 41 patients (56.1%) had PC. The mean PCI for the extent of peritoneal seeding was 9±6, 7±5 and 5±2 for the initial PC, ovarian and perforated groups and were subjected to CRS and HIPEC.

Outcomes of the studies

Macroscopic PC was discovered in 23 of 41 (56%;group PC+) of these asymptomatic patients during the second-look procedure. The incidence of macroscopically visible PC was 62% in the ovarian group, 60% in the initial PC group and 37% in the perforated group. There was one postoperative death. Postoperative morbidity rate was 9.8% (4/41 patients). The reported median length of follow-up was 27 months [27]. Details on recurrence patterns are shown in Table 8. The overall recurrence rate for all patients was 46.3%, for those after CRS and HIPEC 73.9% and for those after HIPEC only 11.1%. No distant recurrence was seen in the patients after HIPEC. Two thirds of recurrences in the group with CRS and HIPEC were distant. The 5-year OS and

DFS in the whole series of patients were 89% and 44%, respectively.

Anastomotic invasion and PC

At the most recent study from the Gustave Roussy Centre by Cloutier et al [47], the interest was focused on the outcomes of 40 patients after second look surgery with HIPEC plus CRS, as regards to anastomotic invasion. Second look surgery was performed 13+0.5 months after primary surgery. The patients were divided according to the likelihood of invasion of the anastomosis into those with possible invasion (PI=12 patients) and those with unlikely invasion (UI=28 patients). PI was based on the presence of anastomotic stenosis or tumour deposit on the anastomosis or tumour deposit away of the anastomosis. The PC Index was 8.2+7.8 in the PI group and 2.8+3.8 in UI group (p=0.006).

Oxaliplatin with or without irinotecan were used in HIPEC. In addition, i.v. 5-fluorouracil and leucovorin were given one hour prior to HIPEC according to a protocol of bi-directional chemotherapy. CRS was attempted in all patients. The anastomosis was removed in all patients in the PI group and in 4 in the UI for technical reasons (3 patients) or other pathology (Lynch syndrome: 1 patient). There were no postoperative deaths and severe morbidity was minimal in both groups. There were no significant differences in ICU stay and hospital stay between the groups.

Histologically, 5 out of the 12 anastomoses resected in the PI group and none out of the 4 anastomoses in the UI showed true anastomotic invasion. Histologically, anastomosis invasion was likely only in the case of deposits at the anastomosis and simultaneous presence of deposits away of the anastomosis (5 out of 9 cases). When evaluating the entire cohort, deposits on the anastomosis represented a significant predictor of histologically anastomosis invasion (p<0.0001). At follow-up (57+47.8 months), 2 patients (16.7%) of the PI group developed anastomotic and distant peritoneal recurrence. The 2 patients (7.1%) in the UI group, who had an involved anastomosis, developed both intraperitoneal recurrence and hepatic metastasis, both at 7 months post-CRS and HIPEC.

Table 8. Oncological outcomes after second look HIPEC+CRS in Gustave Roussy Centre Series

Recurrence	All cases n (%)	CRS + HIPEC cases n (%)	HIPEC cases n (%)
Anastomotic	1/41 (2.4)	0/23 (0)	1/18 (5.6)
Peritoneal	7/41 (17.1)	6/23 (26.1)	1/18 (5.6)
Distant	11/41 (26.8)	11/23 (47.8)	0/18 (0)
Total	19/41 (46.3)	17/23 (73.9)	2/18 (11.1)

Discussion

Considering prophylactic HIPEC during primary surgery for CRC in patients at high risk of developing PC, the 5 studies that were analysed showed a peritoneal recurrence rate of 0-12.9%, a 3-year and 5-year DFS of 67-97.5% and 54.8-84% respectively, and a 3-year and 5-year OS of 67-100% and 84%, respectively. These figures on oncological results are much higher than those seen in patients at high risk to develop PC and have only adjuvant systemic chemotherapy, according to historical data. Furthermore, in two studies [33,39] where perioperative HIPEC was compared to adjuvant systemic chemotherapy in patients at high risk for PC, preemptive HIPEC was associated with a significantly reduced rate of PC and higher survival rates. It should be noted that overall post-operative morbidity and mortality are low, and the reported impact of HIPEC on the anastomotic healing non-significant.

The studies could not be meta-analyzed because of several heterogeneous factors. At first, high-risk factors for PC that justified preemptive HIPEC included either a positive peritoneal lavage only or T3 and 4 tumors only or a combination of the above plus unfavorable histological characteristics (mucinous, signet ring cells) and limited synchronous peritoneal deposits at the vicinity of the primary and synchronous ovarian metastasis. Considering that the incidence of synchronous PC is 4.3-5.1% and the cumulative incidence of metachronous PC is 4.2% [3,5], a small percentage of CRC patients is to gain benefit from a preemptive HIPEC. Also, considering that the 1- and 3-year PC rate is only 4.5% and 9.3% in T3 tumors but 15.6% and 36.7% for T4 tumors respectively, it can be assumed that patients with T4 tumors are more likely to develop PC and possibly will benefit from prophylactic perioperative intraperitoneal chemotherapy [48-50]. Furthermore, considering that 50% of the T4a tumors developed PC, as opposed to 20% of the T4b tumors, it can be speculated that patients with T4a tumors are to gain substantial benefit from perioperative HIPEC [48]. Although 44% of the metachronous PC from CRC show features of mucinous tumors [50], the initial risk for PC is unknown. Hence, CRC patients with this particular and only high-risk feature cannot safely be considered as candidates for perioperative prophylactic HIPEC. A limitation in considering patients with high-risk for PC histological characteristics is that these features may not be available from initial biopsies and also cannot be definitely identified at surgery of the primary tumor.

Another, easily identifiable finding at primary surgery that can be considered as high-risk factor for PC is positive peritoneal lavage at primary surgery [51-53]. This was the only high-risk factor in the Noura et al. study [33] and the most common one in the studies by Shumizu et al. [40] and Virzi et al. [43]. The incidence of detection of disseminated tumor cells in the peritoneal fluid at primary surgery was 3-28% by plain cytology [54,55] and as high as 12-47% by immunocytochemistry or reverse transcriptase-polymerase chain reaction [56-58]. However, as aforementioned, the rate of metachronous PC is only 4.2% [3], and if prophylactic HIPEC is offered to all patients with positive peritoneal cytology, the intervention will not be of any additional benefit in the majority of them. For example, 50% of patients with positive cytology and conventional systemic adjuvant chemotherapy in the Noura et al. study [33] did not develop PC. The authors speculated that disseminated peritoneal tumor cells may not always be viable, and thus may not give rise to actual tumor nodules and metachronous PC in a substantial percentage of patients. Nevertheless, as data supporting positive peritoneal cytology and even T4 tumors to be high-risk factors for PC are rather insufficient at present, several authors do not recommend prophylactic intervention in CRC patients with such features [44,59-61]. The Dutch COLOPEC randomized multicentre trial [37] aims at providing some more solid evidence on the issue of perioperative prophylactic HIPEC in CRC patients at high risk to develop PC. The risk factors for inclusion in the trial are T4 and perforated tumours at primary surgery, and patients will have either systemic chemotherapy or perioperative intraperitoneal chemotherapy.

Implementation of EPIC during the first 5 postoperative days in CRC patients at high risk to developing PC (T3 and T4 tumours) showed favourable results in terms of peritoneal recurrence (8.3% at 28 months of median follow-up) and 3-year OS (69%), but at the expense of a rather high morbidity rate (38.6%) and very high mortality (15.8%) [42]. When the authors compared their adjuvant EPIC outcomes to those after perioperative HIPEC, they found that the latter approach was associated with minimal mortality and significantly better peritoneal recurrence and OS rates. The authors attributed the increased morbidity and mortality in the EPIC group of patients to the rapid infusion and to the long-lasting bathing of peritoneal tissues, including anastomosis, into the chemotherapeutic solution. Poorer oncological results after EPIC than HIPEC could be the result of either peritoneal tumour cell encapsulation into fibrin, and/or the prevention of chemotherapeutic fluid to come into

contact with the whole peritoneal surface, again because of fibrin adhesions. However, due to the poor design of the study, namely different centres with possibly different practical approach involved, different criteria of patients' selection, and arbitrarily various regimes in the HIPEC group and only 5-fluorouracil in the EPIC one, safe and solid conclusions cannot be drawn.

Favorable results in terms of peritoneal recurrence (1/97 patients) after adjuvant HIPEC by laparoscopy few weeks following primary R0 surgery are reported in two studies [45,46]. The results are questionable as the length of follow-up in both studies was short. Also, in the study with the larger series of patients [45], stage III disease was considered as the only risk factor for PC. However, reports on lymph node positivity as a risk factor for PC are conflicting [3,44,48,49]. Conceivably, some patients with T2 or T3 tumors may have been offered HIPEC unnecessarily, and this justifies the low rate of peritoneal recurrence. Nevertheless, postoperative HIPEC offers several advantages over perioperative HIPEC: i) adequate time for healing of the anastomosis is allowed; ii) a more precise selection of patients is allowed, based on the full histological report; iii) a complete information and consent of the patient can be acquired; and iv) there is time for referral of the patient to a specialized centre. On the contrary, the approach carries the disadvantage of a second surgical intervention, which may be laborious in terms of lysis of all adhesions in order to obtain access to the whole peritoneal cavity. Also, there is the theoretical disadvantage of peritoneal cancer cell encapsulation in fibrin that could prevent the cytotoxic action of chemotherapy.

In the Gustave Roussy Centre series [44], patients were considered at high risk for PC if they presented with limited peritoneal tumor deposits that were completely resected or ovarian metastasis or tumor perforation. After curative surgery, after a 6-month course of standard systemic chemotherapy and another 6-month resting period, a second look surgery was undertaken that involved CRS, in cases with apparent PC and HIPEC in all cases. Peritoneal recurrence was only 5.6% in the HIPEC only group and 26.1% in the CRS and HIPEC. The 5-year OS and DFS in all patients was 89% and 44% respectively. The low rate of DFS was attributed to the large proportion of other distant metastasis in patients with CRS and HIPEC.

As opposed to adjuvant perioperative or immediate postoperative HIPEC, second look surgery with HIPEC with or without CRS is associated with significant morbidity. The authors of the aforementioned study [44] considered that, at the setting of a second look approach, early detection of PC is

expected, requiring limited CRS, amenable to curative R0 resection. In fact, they reported a 10% morbidity rate and only one death in their series. The peritoneal recurrence rate after second look and CRS with HIPEC was substantially high. The authors speculated that response to adjuvant systemic chemotherapy allows selection of less aggressive tumor subtype from the aggressive ones, that exhibit a worse natural course and tend to re-occur. Immunosuppression as a result of cytoreduction may be an additional factor for increased recurrent PC rate after second look intervention. However, it could be argued that second look intervention at an earlier stage, i.e. after the end of systemic adjuvant chemotherapy, could detect even more limited PC and in fewer patients at risk, thus necessitating less aggressive surgery and better overall oncological outcomes. Again from the Gustave Roussy Centre, resection of a possibly invaded anastomosis by a deposit, in the context of CRS for PC at second look surgery, is strongly recommended [47].

Based on the conception of the Gustave Roussy Centre and aiming at providing evidence of higher level, a randomized trial has been launched in Bethesda USA [36], where patients at high risk to develop PC after curative primary CRC surgery are included. Inclusion criteria are those adopted by the Paris center, namely minimal peritoneal deposits, ovarian metastasis and perforated tumor at primary operation, and also T4 tumors and complicated tumors (obstruction, bleeding). Following standard systemic chemotherapy and at 11-14 months after primary surgery, patients are to be randomized to either second look surgery for HIPEC and CRS (if required) or observation, and the primary endpoint is overall survival.

Major issues must be addressed concerning prophylactic HIPEC in CRC patients at high-risk for PC, considering also the fact that only 4.2% of them will finally develop peritoneal recurrence [3]. At first, there is no concrete evidence concerning risk factors: although T3, T4 and particularly T4a tumors are significant risk factors for PC, only 15.6%, 36.7% and 50% of them, respectively, will develop PC. Conceivably, if all T4 patients receive adjuvant HIPEC, there will be no benefit for the majority of them, because 2/3 are not destined to metachronous peritoneal recurrence [5,48-50]. There is also evidence that metachronous PC will develop in 64-91% of cases with completely resected minimal PC [62,63], in 27-56% of cases with ovarian metastasis [64,65], and in 14-58% of cases with perforated tumor [61,65,66]. Hence, the only highly significant risk factor for PC is the presence of minimal PC at primary surgery for CRC, whilst if all patients with ovarian metastasis or perforated

tumor during primary surgery are subjected to prophylactic HIPEC, this prophylaxis will not be of any benefit in at least half of them. Considering that a substantial percentage of patients with PC at primary surgery will present with recurrent PC, an even less than the 4.2% of the overall incidence of metachronous PC [3] will be because of all the other risk factors. Also, there is additional concern as regards the significance of tumor perforation. Namely, it is clear whether perforation related to surgical manoeuvre is of the same significance as tumor-related perforation. Other proposed risk factors for PC, such as mucinous cell and signet ring cell tumors, must be thoroughly assessed, considering that oncological outcomes in these tumor subtypes are usually very poor, irrespective of the adjuvant treatment aggressiveness.

An additional issue, which must be addressed, is timing of prophylactic intervention. The question differs depending on the two different concepts: i) preemptive HIPEC during primary surgery or a few weeks postoperatively, and ii) second look surgery with HIPEC and CRS if required at 11-14 or 6-7 months postoperatively. Preemptive HIPEC few weeks postoperatively may be more attractive than the intraoperative one, because it allows healing of anastomosis, offers time for the patient to be fully informed and referred to the specialized center, and

prevents unnecessary intervention with the full histological report of the excised specimen available for multidisciplinary team discussion. Also in theory, earlier second look surgery soon after the termination of systemic adjuvant chemotherapy allows detection of limited PC, thus rendering CRS less aggressive, with lower morbidity and less immunosuppression. Whether this translates to a reduced rate of recurrent PC remains unknown. It is expected that the already launched and future trials that address the most important issues and provide adequate subgroup analysis may offer additional evidence on the usefulness of preemptive intervention in CRC patients at high risk to developing metachronous PC.

Conclusion

At present and because of the insufficient available evidence, preemptive intervention at the immediate postoperative adjuvant setting is recommended only in the setting of a registered clinical trial in this group of CRC patients.

Conflict of interests

The authors declare no conflict of interests.

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