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Adjuvant Hyperthermic Intraperitoneal Chemotherapy in Patients With Locally Advanced Colon Cancer (COLOPEC): 5-Year Results of a Randomized Multicenter Trial

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ABSTRACT

Clinical trials frequently include multiple end points that mature at different times. The initial report, typically based on the primary end point, may be published when key planned co-primary or secondary analyses are not yet available. Clinical Trial Updates provide an opportunity to disseminate additional results from studies, published in JCO or elsewhere, for which the primary end point has already been reported.

Whether adjuvant hyperthermic intraperitoneal chemotherapy (HIPEC) might prevent peritoneal metastases after curative surgery for high-risk colon cancer is an ongoing debate. This study aimed to determine 5-year oncologic outcomes of the randomized multicenter COLOPEC trial, which included patients with clinical or pathologic T4N0-2M0 or perforated colon cancer and randomly assigned (1:1) to either adjuvant systemic chemotherapy and HIPEC (n = 100) or adjuvant systemic chemotherapy alone (n = 102). HIPEC was performed using a one-time administration of oxaliplatin (460 mg/m², 30 minutes, 42°C, concurrent fluorouracil/leucovorin intravenously), either simultaneously (9%) or within 5-8 weeks (91%) after primary tumor resection. Outcomes were analyzed according to the intention-to-treat principle. Long-term data were available of all 202 patients included in the COLOPEC trial, with a median follow-up of 59 months (IQR, 54.5-64.5). No significant difference was found in 5-year overall survival rate between patients assigned to adjuvant HIPEC followed by systemic chemotherapy or only adjuvant systemic chemotherapy (69.6% *v* 70.9%, log-rank; $P = .692$). Five-year peritoneal metastases rates were 63.9% and 63.2% ($P = .907$) and 5-year disease-free survival was 55.7% and 52.3% (log-rank; $P = .875$), respectively. No differences in quality-of-life outcomes were found. Our findings implicate that adjuvant HIPEC should still be performed in trial setting only.

ACCOMPANYING CONTENT

Appendix

Data Supplement

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INTRODUCTION

Patients who underwent curative surgery for colon cancer with local invasion into the peritoneum are at high risk of developing metachronous peritoneal metastases (PM), with reported risks around 20%-30%.[1,2] Prognosis of patients with PM remains poor, whereas only patients with limited extent of peritoneal disease and sufficient clinical condition are amenable for intentional curative treatment consisting of at least cytoreductive surgery.[3,4] Since systemic chemotherapy seems to barely affect peritoneal dissemination, adjuvant intraperitoneal chemotherapy was introduced as treatment strategy to prevent the development of metachronous PM after promising results by several cohort studies.[5] However, the randomized multicenter COLOPEC trial could not confirm these findings on the basis of similar peritoneal metastasis-free survival (PMFS) at 18 months among patients who received adjuvant hyperthermic intraperitoneal chemotherapy (HIPEC) with oxaliplatin followed by adjuvant systemic therapy versus adjuvant systemic therapy alone.[6]

The debate whether HIPEC improves oncologic outcomes after curative surgery for high-risk colon cancer is still ongoing. Worldwide, adjuvant HIPEC using different protocols for different indications is still used in trial setting, and in some institutes even as part of daily clinical practice.[7-9] So far, to our knowledge, no long-term survival data from randomized trials on adjuvant HIPEC in colon

TABLE 1. Characteristics of Patients Included in the COLOPEC Trial

Characteristic	Experimental Group (n = 100)	Control Group (n = 102)
Age, years, median (IQR)	61 (56-68)	61 (54-68)
Female gender, No. (%)	47 (47)	50 (49)
ASA-score, No. (%)		
1	33 (33)	49 (48)
2	63 (63)	49 (48)
3	4 (4)	4 (4)
Elective setting, No. (%)	76 (76)	84 (83)
Perforation, No. (%)	23 (23)	18 (18)
Procedure, No. (%)		
Right hemicolectomy	38 (38)	39 (39)
Left hemicolectomy	14 (14)	12 (12)
Sigmoid resection	33 (33)	32 (32)
Anterior resection	13 (13)	16 (16)
Subtotal colectomy	2 (2)	2 (2)
Approach, No. (%)		
Laparoscopic	56 (56)	55 (55)
Converted	12 (12)	8 (8)
Open	32 (32)	38 (38)
Multivisceral resection, No. (%)		
No	66 (66)	65 (64)
Limited	13 (13)	11 (11)
Extended	21 (21)	25 (25)
cT1	1 (1)	0 (0)
cT2	7 (7)	5 (5)
cT3	29 (29)	28 (28)
cT4	41 (41)	53 (52)
cTx	22 (22)	16 (16)
pT4a	71 (71)	72 (71)
pT4b	16 (16)	16 (16)
pT2 or pT3 (perforation)	10 (10)	9 (9)
pT2 or pT3 (cT4)	3 (3)	4 (4)
pN0	24 (24)	29 (29)
pN1	36 (36)	34 (34)
pN2	40 (40)	38 (38)
Histopathology, No. (%)		
Well/moderately differentiated adenocarcinoma	75 (75)	72 (71)
Poorly differentiated or undifferentiated adenocarcinoma	13 (13)	12 (12)
Mucinous adenocarcinoma	8 (8)	9 (9)
Signet ring cell carcinoma	2 (2)	8 (8)
Medullary carcinoma	2 (2)	0 (0)
Residual tumor, No. (%)		
R0	99 (99)	99 (98)
R1	1 (1)	2 (2)
R2	0 (0)	1 (1)
Maximum tumor diameter, mm, median (IQR)	42 (30-60)	42 (30-60)
Postoperative complications after primary tumor resection (Clavien-Dindo score ≥3), No. (%)	10 (10)	3 (3)

Abbreviations: ASA, American Society of Anesthesiologists; cT, clinical T category; pN, pathologic nodal status; pT, pathologic T category; R, residual.

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cancer have been published. Therefore, this study aimed to determine long-term recurrence and survival outcomes and quality of life (QoL) after the last included patient of the COLOPEC trial had reached 5-year follow-up.

METHODS

The study design and inclusion and exclusion criteria of the COLOPEC-trial have been published previously, as well as the primary outcome parameter, PMFS at 18 months.[6,10] In short, between April 2015 and 2017, patients with resectable primary clinical or pathologic T4N0-2M0 or perforated colon cancer were included and randomly assigned (1:1) to either adjuvant HIPEC using intraperitoneal oxaliplatin (460 mg/m², 30 minutes, concurrent fluorouracil/leucovorin intravenously) with standard adjuvant systemic chemotherapy or standard adjuvant systemic chemotherapy alone. Administration of HIPEC was done simultaneously with the initial procedure (9%) or 5-8 weeks postoperatively (91%). In this long-term study, outcomes were 5-year overall survival (OS), disease-free survival (DFS), and PMFS, assessed by Kaplan-Meier analysis. In case of crossing lines, Cox regression with time-dependent covariates will be used to estimate two hazard ratios (HRs) with the time crossing point as cutoff value. Generic QoL was assessed using the 5-dimensional EuroQol (EQ-5D-5L) questionnaire, and the EORTC (QLQ-C30/CR29) questionnaires for GI QoL, sent out at 3, 6, 12, 18, 24, 36, 48, and 60 months postoperatively. All analyses were done according to the intention-to-treat principle.

RESULTS

Of all patients, 102 were assigned to adjuvant HIPEC followed by adjuvant systemic chemotherapy and 102 to adjuvant systemic chemotherapy alone. Two patients in the HIPEC group withdrew informed consent after random assignment (100 evaluable patients), and 87% of patients were eventually treated with adjuvant HIPEC in the experimental arm. Table 1 presents the characteristics of all 202 patients included for analysis. Follow-up continued for a median period of 59 months (IQR, 54-56), with the last patient's last visit in February 2022.

The 5-year OS rates did not differ between patients assigned to adjuvant HIPEC followed by adjuvant systemic chemotherapy or to adjuvant systemic chemotherapy alone (69.6% *v* 70.9%, log-rank; $P = .692$), as shown in Figure 1A. Subgroup analyses did not show any significant differences in 5-year OS depending on patient, tumor, or procedural characteristics (Data Supplement [Suppl File S1], online only). Five-year DFS rate neither differed between the experimental arm and the control arm (55.7% *v* 52.3%, Fig 1B). During complete follow-up, 49 patients (24.0%) developed PM, detected within 18 months in 42 (85.7%) patients. The 5-year PMFS was 63.9% in patients intentionally receiving adjuvant HIPEC with systemic chemotherapy, compared to 63.2% in the control arm (Fig 2). As the Kaplan-Meier curves of both arms crossed at 14 months, two HRs were estimated by using Cox regression with a time-dependent covariate. The HR before 14 months was 1.202 ($P = .557$) and the HR after 14 months was 0.841 ($P = .624$). No significant difference was found to indicate a change in the effect over time. There were no differences in any outcome of the QoL analyses (Data Supplement [Suppl File S2]) between the two groups.

DISCUSSION

This long-term outcome analysis of the COLOPEC trial revealed similar 5-year OS rates in patients with c/pT4N0-2M0

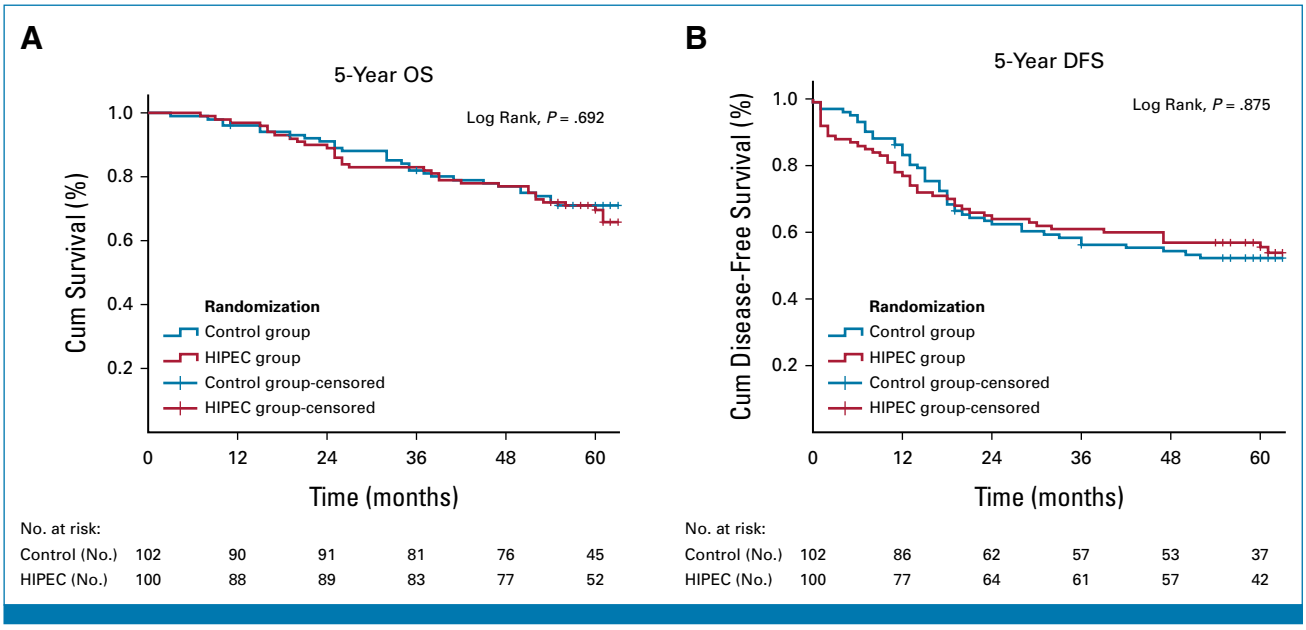

FIG 1. (A) Five-year OS. (B) Five-year DFS. DFS, disease-free survival; HIPEC, hyperthermic intraperitoneal chemotherapy; OS, overall survival.

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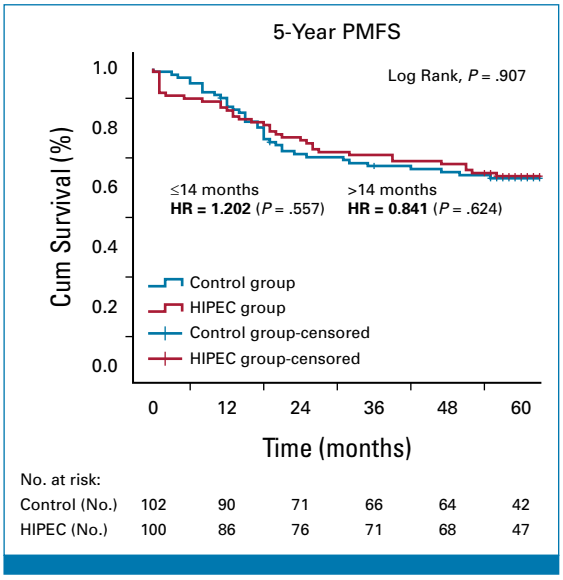

FIG 2. Five-year PMFS. HIPEC, hyperthermic intraperitoneal chemotherapy; HR, hazard ratio; PMFS, peritoneal metastases-free survival.

colon cancer who were randomly assigned to either adjuvant HIPEC in addition to systemic chemotherapy or adjuvant systemic chemotherapy alone. In addition, no significant differences in DFS and 5-year PMFS were observed. Our findings are in line with the primary end point analysis that showed no significant difference in 18-month PMFS between both groups, knowing that PM is an important determinant of patients' long-term prognosis and often occurs relatively early after the primary resection.

Other trials investigating the effect of adjuvant HIPEC are still ongoing; the Spanish HIPECT4 trial investigates simultaneous adjuvant HIPEC during primary tumor resection using mitomycin-C during 60 minutes in patients with cT4N0-2M0 staged colon cancer on the basis of CT imaging.[7] Preliminary results are promising regarding 3-year locoregional recurrence (97% *v* 87%; $P = .025$ and HR = 0.21; 95% CI, 0.05 to 0.95; $P = .04$), but this did not translate into survival benefit so far.[11] Recently, a new trial protocol (the CHECK study) was published, which will determine the effect of adjuvant HIPEC with mitomycin-C and CO2 agitation.[8] But just like the French PROPHYLOCHIP trial that investigated second-look surgery plus HIPEC versus surveillance in patients at high risk of developing colorectal PM, this trial also includes patients with resected synchronous peritoneal or ovarian metastases.[12] In our opinion, therapy in such patients should no longer be regarded as prophylactic but rather as therapeutic for proven macroscopic PM.

It might be that exposure to oxaliplatin during a single rinse with a duration of 30 minutes is not enough to eliminate malignant cells. Oxaliplatin exhibits a clear temperature dose-effect relationship in treatment-resistant CMS-4 colorectal cell lines with higher temperatures and longer duration of exposure being more effective.[13] Interestingly, a recent experimental study demonstrated that organoids derived from PM from patients with colorectal cancer were resistant to 30-minute exposure to clinically relevant doses of oxaliplatin.[14] This may imply that not the concept of adjuvant HIPEC was proven to be ineffective in the current trial, but rather the use of short-duration intraperitoneal oxaliplatin. Mitomycin-C and/or longer duration of HIPEC might be more effective as suggested by the HIPECT4 trial, but only based on a surrogate end point.[11] In addition, timing of HIPEC relative to primary tumor resection might be important as well, given the theory of entrapment of tumor cells in postoperative adhesions that make them potentially inaccessible during staged HIPEC. Finally, the trial cannot exclude a small risk reduction in peritoneal recurrence rate because of sample size.

Future trials should include drugs and appropriate regimens with proven efficacy for PM with adequate timing and length of exposure. Otherwise, research focus can be shifted to improving current treatment strategies and early detection rather than prophylactic intraperitoneal chemotherapy. The risk of developing metachronous PM may also be reduced by performing complete mesocolic excision, which showed prolonged DFS when compared with conventional colon resection in a large population-based study.[15] In addition, upcoming induction chemotherapy for locally advanced colon cancer could reduce the risk of PM by improving radicality of resections.[16] Finally, the COLOPEC 2 trial is currently including patients with pT4 colon cancer to investigate the added value of a second-/third-look laparoscopy during follow-up for the purpose of early detection and treatment of PM and the subsequent impact on 5-year survival.[17]

In conclusion, long-term follow-up of the COLOPEC trial did not show any survival benefit of adjuvant HIPEC with high-dose oxaliplatin for 30 minutes, mainly using a staged approach, in patients with T4 or perforated colon cancer. Adjuvant HIPEC to reduce the risk of PM in patients with colon cancer should thus still be performed in trial setting only.[18]

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APPENDIX. COLOPEC COLLABORATORS GROUP

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