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Health-related quality of life after interval cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with stage III ovarian cancer

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ABSTRACT

Introduction: The addition of hyperthermic intraperitoneal chemotherapy (HIPEC) to interval cytoreductive surgery (CRS) improves recurrence-free (RFS) and overall survival (OS) in patients with FIGO stage III ovarian cancer. We evaluated the effect of HIPEC on patient's health-related quality of life (HRQoL) in the OVHIPEC trial.

Materials and methods: OVHIPEC was a multicentre, open-label, randomized phase III trial for patients with stage III ovarian cancer. Patients were randomly assigned (1:1) to receive interval CRS with or without HIPEC with cisplatin. HRQoL was assessed using the EORTC QLQ-C30, and the ovarian (QLQ-OV28) and colorectal cancer (QLQ-CR38) modules. HRQoL questionnaires were administered at baseline, after surgery, after end of treatment, and every three months thereafter. HRQoL was a secondary endpoint, with the prespecified focus on the QLQ-C30 summary score and symptom scores on fatigue, neuropathy and gastro-intestinal symptoms. HRQoL was analysed using linear and non-linear mixed effect models.

Results: In total, 245 patients were randomized. One-hundred-ninety-seven patients (80%) completed at least one questionnaire. No significant difference over time in the QLQ-C30 summary scores was observed between the study arms (p-values for linear and non-linear growth: $p > 0.133$). The pattern over time for fatigue, neuropathy and gastro-intestinal symptoms did not significantly differ between treatment arms.

Conclusion: The addition of HIPEC to interval CRS does not negatively impact HRQoL in patients with stage III ovarian cancer who are treated with interval CRS due to the extent of disease. These HRQoL

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results, together with the improvement in RFS and OS, support the viability of HIPEC as an important treatment option in this patient population.

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1. Introduction

Ovarian cancer accounts for 3.6% of cancers in women worldwide, is the eighth cause of death from cancer in women, and has the highest mortality rate of all gynaecologic cancers in the western world [1,2]. Despite contemporary treatment with cytoreductive surgery (CRS) and intravenous (IV) platinum-based chemotherapy, about 80% of patients with advanced stage disease experience a recurrence within two years. Prognosis is best for patients in whom no macroscopic residual disease remains after surgery [3,4].

Intraperitoneal (IP) delivery of chemotherapy enhances drug delivery at the peritoneal surface, and is of interest in patients with ovarian cancer. Previous trials evaluating adjuvant IP chemotherapy in combination with IV chemotherapy after primary CRS, showed improved recurrence-free and overall survival [5,6]. However, this is an intensive treatment requiring multiple hospitalizations, with a high incidence of gastro-intestinal symptoms, fever, infections, and pain [6,7]. Catheter-related problems and increased toxicity limit the broad uptake of IP chemotherapy in clinical practice [8,9]. Hyperthermic Intraperitoneal administration of Chemotherapy (HIPEC) is an alternative modality for IP delivery of chemotherapy during surgery, that may resolve these concerns and reduce toxicity.

The OVHIPEC-trial was a randomized phase III trial that demonstrated a recurrence-free and overall survival benefit of the addition of HIPEC to interval CRS in patients with stage III ovarian cancer [10]. Patients recruited into this trial were ineligible for primary surgery because of extensive disease, but responded sufficiently to three cycles of neo-adjuvant chemotherapy to allow optimal or complete interval CRS. The addition of HIPEC to interval CRS prolonged total surgery time by 146 min and total hospital stay by two days, but did not increase the incidence of adverse events [10].

Patient-reported outcomes, including self-assessment of symptoms and side effects, and health-related quality of life (HRQoL) have been increasingly recognized as relevant parameters in the evaluation of new medical treatments [11]. We assessed the effect of the addition of HIPEC on the patients' symptom burden and HRQoL in the OVHIPEC trial.

2. Materials and methods

2.1. Participants

The OVHIPEC trial was a multicentre, randomized, open-label, phase III trial conducted in the Netherlands and Belgium. If eligible, patients with International Federation of Gynaecology and Obstetrics (FIGO) stage III ovarian, fallopian tube, or peritoneal cancer were enrolled for three cycles of neo-adjuvant chemotherapy with interval CRS because of the extent of disease or incomplete primary CRS. Full eligibility criteria have been published elsewhere [10]. The local ethical committees of all participating centres approved the study protocol. All participating

patients provided written informed consent and agreed to complete questionnaires as part of their consent.

2.2. Study design and procedures

Neoadjuvant chemotherapy consisted of carboplatin (area under the curve [AUC] of 5–6 mg/ml/min) and paclitaxel (175 mg/m² of body-surface area [BSA]). Peroperative randomization was performed during interval CRS in cases in which complete or optimal cytoreduction was anticipated. Patients were randomly assigned (1:1) to receive interval CRS either with or without HIPEC. Randomization was performed with the use of a minimization procedure, with stratification according to previous surgery (yes vs. no), the hospital in which the surgery was being performed, and the number of involved regions in the abdominal cavity (0–5 vs. 6–8). For logistical reasons, two of the eight participating centres performed a diagnostic laparoscopy before surgery to evaluate whether complete or optimal surgery was feasible: in these cases randomization took place after laparoscopy.

HIPEC was administered at the end of the cytoreductive surgical procedure with the use of the open technique. The abdomen was filled with saline and the perfusion fluid was heated by continuous circulation through a heat exchanger, after which perfusion with cisplatin (100 mg/m² of BSA) was initiated (full method described elsewhere) [10]. The HIPEC procedure took 120 min in total, including 90-min perfusion time. To prevent nephrotoxicity in patients treated with HIPEC, sodium thiosulphate was administered at the start of perfusion as an intravenous bolus, followed by continuous infusion over a period of 6 h. Urine production was regulated during and 3 h after surgery. After HIPEC, patients had a 1-day stay in the intensive care unit per protocol. Three additional cycles of carboplatin and paclitaxel were administered after surgery. During follow-up, regular physical examinations, and measurement of the serum cancer antigen 125 (CA125) level were repeated every three months for two years, and then every six months until five years after the completion of chemotherapy, for both treatment arms. An abdominal CT scan was made after completion of treatment, and at six, 12 and 24 month follow-up.

2.3. Outcomes

HRQoL was a secondary endpoint of the OVHIPEC trial, with the pre-specified focus on the QLQ-C30 summary score and symptom scales for fatigue, neuropathy and gastro-intestinal symptoms. The results pertaining to recurrence-free survival, overall survival, and safety have been published previously [10].

2.4. Health-related quality of life (HRQoL) assessments

HRQoL was assessed with the European Organization for Research and Treatment of Cancer (EORTC) core questionnaire (EORTC QLQ-C30 version 3.0), and the ovarian and colorectal cancer questionnaire modules (QLQ-OV28 and QLQ-CR38, respectively).

The QLQ-C30 is a 30-item questionnaire that includes five multi-item functional scales (physical, role, cognitive, emotional, and social), three multi-item symptom scales (fatigue, nausea and vomiting, and pain), five single-item symptom scales (dyspnoea, insomnia, appetite loss, constipation, and diarrhoea), a question on financial impact; and a two-item global quality of life scale [12]. An overall QLQ-C30 summary score can also be calculated [13].

The QLQ-OV28 is a 28-item ovarian cancer-specific questionnaire module designed to supplement the QLQ-C30 [14]. It comprises three multi-item functional scales (body image, attitude to disease/treatment, and sexual functioning), and five multi-item ovarian cancer-associated symptom scales (abdominal/gastrointestinal symptoms, peripheral neuropathy, other chemotherapy side-effects, and hormonal/menopausal symptoms). Because CRS for ovarian cancer patients involves major abdominal surgery, including colonic surgery in some patients, we also administered the EORTC QLQ-CR38, which addresses symptoms relevant for patient groups undergoing abdominal surgery. It includes 38 items, organized into four functional scales (body image, sexual functioning, sexual enjoyment, and future perspective), and eight colorectal cancer-related symptom scales (micturition problems, gastro-intestinal symptoms, chemotherapy side-effects, problems with defecation, stoma-related problems, female sexual problems, and weight loss) [15].

The three HRQoL questionnaires have a one-week recall period and a four-point response scale (1 = “not at all”, 4 = “very much”), with the exception of the global QoL scale which has a seven-point response format. A linear transformation is used to calculate scale scores, ranging from 0 to 100. For functional scales, higher scores represent higher levels of functioning. For symptom scales, higher scores indicate more symptom burden [16]. Missing values within a subscale were replaced by the average score of the completed items in the same scale for each individual, provided that at least 50% of the items in that scale had been completed [16]. Administration of the HRQoL questionnaires was planned according to the trial schedule: within four weeks prior to randomization (baseline), before start of adjuvant chemotherapy, at the end of treatment, and every three months in follow-up, until two years of follow-up were completed.

2.5. Statistical analyses

A HRQoL-specific statistical analyses plan was developed at initiation of the trial. First the questionnaire completion rate was evaluated. The HRQoL questionnaires were analysed based on the intention-to-treat principle (i.e., all randomized patients were compared according to the treatment to which they were allocated). Questionnaires completed after disease recurrence, and those completed after data cut-off for follow-up (March 31, 2017) were excluded from the analyses [10]. Baseline questionnaires were defined as those completed before randomization, but one week after administration of the last neo-adjuvant chemotherapy cycle. Questionnaire completion results were summarized in six different time points. Because of variability in the timing of the questionnaire completion between patients, time from randomization to the completion date of each assessment (in weeks) was used as a continuous variable in the mixed effect model.

The data were analysed using a linear and non-linear growth curve modelling approach, based on maximum likelihood estimation with random intercept and slope [17]. This approach takes the within-person and between-person variability into account, and deals adequately with missing data [18]. To test non-linear growth trajectories we included higher order polynomial trends (i.e., quadratic or cubic slopes) to the model. To test if the non-linear

growth trajectory was appropriate, we compared the Bayesian Information Criterion (BIC) and the Akaike's Information Criterion (AIC).

Subjects were divided into groups depending on their missing data pattern. To analyse the missing data-pattern, the observation period was divided into three time points to create the dummy-coded variables: (1) before randomization; (2) between randomization and 20 weeks of follow-up; and (3) after 20 weeks of follow-up. Effects of non-ignorable drop-out patterns on choice of covariance structure (identity, unstructured, compound symmetry and autoregressive covariance structure) were evaluated based on the fit of the respective models using BIC and AIC, and compared between treatment groups. After testing the covariance structure, the treatment arm was added as variable to test differences between the two arms. Overall group differences and between-group differences in change over time were accompanied by effect sizes (ES), which are calculated using the t -test values $((2 \cdot t) / (\sqrt{df}))$ [19]. An ES of 0.20 was considered small, 0.50 moderate and clinically significant, and an ES of 0.80 was considered large [20,21].

3. Results

Between April 2007, and April 2016, a total of 245 patients were randomly assigned; 123 to the interval CRS group and 122 to the interval CRS and HIPEC group. A total of 197 of the 245 randomized patients (80%) completed at least one HRQoL questionnaire, of whom 91 (46%) were treated with CRS, and 106 (54%) with CRS and HIPEC. Within the group of patients with one or more questionnaires, the mean number of questionnaires completed was 3.1 and ranged from one to eight. Baseline and treatment characteristics were well balanced between the two treatment groups for both the total trial sample and the HRQoL sample (Table 1). The number of completed HRQoL questionnaires included is shown in Table 2. A total of 613 questionnaires were analysed; 269 (44%) completed by patients treated with interval CRS, and 344 (56%) completed by patients treated with interval CRS and HIPEC. Completed questionnaires not fitting the criteria for analyses were excluded (Fig. 1). The dummy-coded patterns for non-ignorable dropout did not differ significantly between groups ($p = 0.508$). The non-ignorable dropout pattern did not affect any of the tested models, and was therefore excluded from the model.

No significant between-group differences were observed over time (treatment by time interaction) for the QLQ-C30 summary score (p -value for linear and non-linear growth: >0.133). For the total HRQoL sample, the QLQ-C30 summary scores declined shortly after surgery ($p = 0.015$; $ES = -0.23$), then improved until approximately one year after surgery ($p = 0.001$; $ES = 0.33$), and finally started to decline again ($p < 0.001$; $ES = 0.35$) (Fig. 2).

Similarly, there were no statistically significant differences observed between groups over time for the other primary HRQoL outcomes: symptoms of fatigue (C30), neuropathy (OV28) and gastro-intestinal complaints (CR38). For the total HRQoL sample, fatigue decreased linearly over time ($p < 0.001$; $ES = -0.63$). The overall trajectory for neuropathy showed an increase in the first postoperative period, during the adjuvant chemotherapy treatment ($p < 0.001$; $ES = 0.54$), a decrease 15–20 weeks after surgery ($p < 0.001$; $ES = -0.53$), and a further gradual increase during follow-up ($p < 0.001$; $ES = 0.47$) (Fig. 3). Gastro-intestinal symptoms first decreased slightly ($p = 0.001$; $ES = -0.31$), and then increased during follow-up ($p = 0.009$; $ES = 0.25$) (Fig. 4).

No significant between-group differences over time were observed for any of the other scales of the QLQ-C30, QLQ-OV28 or QLQ-CR38, with the exception of appetite loss, which showed a statistically significant, but not a clinically significant greater

Table 1
Baseline and treatment characteristics.*

	Intention to treat population		HRQoL population	
	Interval CRS (N = 123)	Interval CRS and HIPEC (N = 122)	Interval CRS (N = 91)	Interval CRS and HIPEC (N = 106)
Baseline characteristics				
Median age – yr (IQR)	63 (56–66)	61 (55–66)	63 (56–67)	62 (55–67)
Previous surgery – no. (%)				
Yes	12 (10)	12 (10)	11 (12)	11 (10)
No	111 (90)	110 (90)	80 (88)	95 (90)
No. of involved regions (%)				
0–5	83 (67)	83 (68)	63 (69)	73 (69)
6–8	40 (33)	39 (32)	28 (31)	33 (31)
Treatment characteristics				
Residual disease after surgery – no. (%)				
R-1, no visible tumour, complete cytoreduction	82 (67)	84 (69)	61 (68)	74 (70)
R-2a, tumour nodules ≤2.5 mm	24 (20)	22 (18)	19 (21)	18 (17)
R-2b, tumour nodules >2.5 mm and ≤10 mm	14 (11)	13 (11)	8 (9)	12 (11)
Tumour nodules >10 mm, incomplete cytoreduction	1 (1)	0 (0)	1 (1)	0 (0)
No resection ^a	1 (1)	2 (2)	1 (1)	1 (1)
No surgery performed	1 (1)	1 (1)	0 (0)	0 (0)
Bowel resections – no. (%)				
No bowel resection performed	93 (76)	93 (76)	66 (73)	80 (75)
Bowel resection without ileo-/colostomy	17 (14)	8 (7)	15 (16)	7 (7)
Bowel resection with ileo-/colostomy	13 (11)	21 (17)	10 (11)	19 (18)
Median duration of surgery – min (IQR)	192 (153–251)	338 (299–426)		
Median duration of hospitalization – days (IQR) ^b	8 (7–10)	10 (8–12)	8 (7–10)	10 (8–12)
Median time between surgery and start of first cycle of adjuvant chemotherapy – days (IQR)	30 (25–41)	33 (28–41)	30 (25–41)	33 (28–41)

CRS denotes cytoreductive surgery, HIPEC denotes hyperthermic intraperitoneal chemotherapy, IQR interquartile range.

*There were no significant differences between the trial groups in any of the variables listed in this table.

P-value for bowel resections with ileo-/colostomy (13/123 vs. 21/122, $p=0.19$).

Percentages may not sum to 100 because of rounding.

^a Surgery was performed, but no resection was possible.

^b The median duration of hospitalization included a 1-day stay in the intensive care unit after HIPEC, as specified in the protocol.

Table 2
Summary of questionnaire completion in each time period.

	No. of questionnaires		
	Interval CRS	Interval CRS and HIPEC	Total
Baseline	49	58	107
Between surgery and EOT, during adjuvant chemotherapy	56	69	125
Follow-up 0–15 weeks after EOT	71	72	143
Follow-up 16–30 weeks after EOT	48	71	119
Follow-up 31–45 weeks after EOT	34	47	81
Follow-up 46 weeks – 1 year after EOT	11	27	38
	269	344	613

CRS denotes cytoreductive surgery, HIPEC denotes hyperthermic intraperitoneal chemotherapy, EOT denotes end of treatment.

decrease in patients treated with HIPEC ($p=0.019$; $ES=-0.20$). Other outcomes from the HRQoL questionnaires are reported in supplementary appendix A.

4. Discussion

The addition of HIPEC to interval CRS in patients with stage III ovarian cancer results in significant recurrence-free and overall survival benefit [10]. Because of the more intensive nature of surgery including HIPEC, concern has been voiced about a potential increase in adverse events and compromised HRQoL [22]. Based on physician-rated data, we observed comparable percentages of patients with grade three or four adverse events in the group treated with interval CRS and HIPEC as compared to interval CRS alone (27% and 25%, respectively, $p=0.76$) [10]. The current results, based on patient-reported outcomes, indicate comparable HRQoL and

symptom burden between patients treated with interval CRS and HIPEC and those treated with interval CRS without HIPEC. Although appetite loss was reported more frequently by patients treated with HIPEC, this was however not clinically significant based on the effect size.

Previous studies reporting HRQoL after treatment with HIPEC for various peritoneal malignancies including ovarian cancer, indicated that this treatment is safe and that side effects affecting HRQoL typically resolve within the first year after treatment [22–24]. We observed similar results in our trial; functioning scores and overall HRQoL decreased during adjuvant treatment, but recovered quickly after end of treatment, with similar patterns in the two treatment arms. Also, symptom scores of the patients in our trial who underwent CRS and HIPEC were largely similar to those in the CRS group, and to previously reported scores of patients with ovarian cancer treated with HIPEC [24,25].

Fig. 1. Consort diagram for the HRQoL component of the OVHIPEC trial

HRQoL: health-related quality of life, CRS: cytoreductive surgery, HIPEC: hyperthermic intraperitoneal chemotherapy, EOT: end of treatment.

Fig. 2. Trajectories of the QLQ-C30 summary score for both trial arms

Trajectories are pictured with 95% pointwise Confidence Intervals. CRS: cytoreductive surgery, HIPEC: hyperthermic intraperitoneal chemotherapy, QLQ-C30: the EORTC Quality of Life core Questionnaire. For the C30 summary scale, higher scores represent higher levels of functioning.

Fig. 3. Trajectories of QLQ-OV28 Neuropathy scores for both trial arms

Trajectories are pictured with 95% pointwise Confidence Intervals. CRS: cytoreductive surgery, HIPEC: hyperthermic intraperitoneal chemotherapy, QLQ-OV28: the EORTC disease-specific questionnaire module for ovarian cancer. For the symptom scales on neuropathy higher scores indicate more symptom burden.

In our trial, the number of patients with bowel resections was similar in both arms (30 patients (24%) in the interval CRS group, 29 patients (24%) in the interval CRS and HIPEC group). The number of patients with a colostomy was slightly higher in the HIPEC group (13 patients [11%] in the interval CRS group vs. 21 patients [17%] in the interval CRS and HIPEC group, $p=0.19$) [10]. Previous studies looking into the HRQoL of patients with colostomies showed higher symptom burden, which should be considered in daily practice [26,27].

Our study had several limitations that should be noted. First, compliance with the planned schedule of HRQoL questionnaire

administration was suboptimal, and better in the arm treated with HIPEC. This is possibly due to open-label bias, because patients in the investigational arm, and their treating physicians, might have been more conscientious in completing questionnaires. Second, although at least one completed questionnaire was available for 80% of patients, and baseline and surgical characteristics were well balanced between groups, bias due to selective missing data cannot be completely ruled out. It is for this reason that we examined potential patterns of missing data when fitting the models. Third, we only analysed data of questionnaires completed up to time of disease recurrence. Since the group treated with interval CRS-only

Fig. 4. Trajectories of QLQ-CR38 Gastro-intestinal symptom scores for both trial arms

Trajectories are pictured with 95% pointwise Confidence Intervals. CRS: cytoreductive surgery, HIPEC: hyperthermic intraperitoneal chemotherapy, QLQ-CR38: the EORTC disease-specific questionnaire module for colorectal cancer. For the symptom scales on gastro-intestinal symptoms, higher scores indicate more symptom burden.

progressed significantly earlier, this might have resulted in further imbalance between arms. Fourth, the observed difference in appetite-loss between the two treatment arms, should be interpreted with caution because of multiple testing. Fifth, because questionnaires were not always completed at specific timepoints, time from randomization to the completion date of each assessment was used as a continuous variable in the analyses of questionnaires. Therefore, only estimates of the model (see Figs. 2–4) rather than mean scores at specific time points could be calculated, thus precluding the possibility of comparing the absolute differences between groups. However, the use of mixed model analyses minimized the effect of some of these methodological limitations (e.g. missing data), and yielded a reliable picture of the differences in the trajectory of HRQoL scores between the groups over time.

The strengths of this HRQoL investigation lie in its prospective, randomized design with large numbers of patients. It is, to the best of our knowledge, the first such study carried out in patients with stage III ovarian cancer, comparing HRQoL in patients treated with interval CRS and HIPEC to patients treated with interval CRS alone.

In conclusion, this study revealed no clinically relevant differences in HRQoL outcomes over time between patients with stage III ovarian cancer who were treated with interval CRS and HIPEC and those treated with interval CRS. Given the previously reported improvement in median recurrence-free and overall survival without impairment in toxicity, these HRQoL analyses lend support to the viability of HIPEC as an important treatment option in this setting.

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Declarations of interest

None of the authors report any conflicts of interest.

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Appendix A. Supplementary data

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