HIPEC for ovarian cancer

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HIPEC for ovarian cancer

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Faculteit der Geneeskunde

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CHAPTER 1

General introduction

Parts of this chapter appear in the following article:
S.N. Koole, W.J. van Driel, and G.S. Sonke

Hyperthermic intraperitoneal chemotherapy for ovarian cancer: the heat is on.
Cancer 2019;Supplement 24:4587-93

Incidence and survival

Ovarian cancer is in the top 10 of cancer diagnoses in females worldwide. In 2018, almost 300,000 women were diagnosed globally and 185,000 women died of ovarian cancer, accounting for 4.4% of all cancer related deaths.[1, 2] Although the global incidence of epithelial ovarian cancer slightly decreased over the past decade, the number of Dutch patients is fairly stable at around 1,100 each year.[3-5] Most patients present with non-specific abdominal discomfort. The lack of specific symptoms and screening methods often precludes early diagnosis and about 70-80% of women with ovarian cancer present with International Federation for Gynecology and Obstetrics (FIGO) stage III or IV disease, in which disease has spread to the upper abdomen or beyond.[6, 7] Ten-year survival of women with advanced disease is only 10-15% and did not improve in the past 20 years.[8, 9]

Treatment strategies

Surgery has been the cornerstone of treatment of FIGO stage III and IV ovarian cancer since decades. The objective of surgery is a complete resection of all macroscopically visible disease. Cytoreductive surgery includes hysterectomy, bilateral oophorectomy, and infra- and supra-colic omentectomy. Tumor deposits at other sites should also be completely removed. Ovarian cancer frequently spreads to the peritoneum of all intra-abdominal structures, and en-bloc peritoneal resection together with all involved structures might be required. Extensive surgery including bowel resection, peritonectomy, and stripping of the diaphragm may be required for complete cytoreduction.

Systemic chemotherapy with carboplatin area under the cure (AUC) 5-6 and paclitaxel 175 mg/m^2 administered intravenously, every three weeks for six cycles is standard of care in front-line therapy of epithelial ovarian cancer.[10] Chemotherapy can be administered as adjuvant treatment after primary cytoreductive surgery or as neo-adjuvant treatment, followed by interval cytoreductive surgery. If upfront cytoreductive surgery is not feasible, interval cytoreductive surgery can be performed following three cycles of neo-adjuvant chemotherapy in order to spare vital structures, reduce tumor burden and increase the chances of complete cytoreduction. Interval cytoreduction is then followed by adjuvant 3 cycles of chemotherapy.[11-13] Patients with high-grade serous tumors that harbor pathogenic BRCA1/2 mutations are candidate for maintenance therapy with poly (adenosine diphosphate [ADP]–ribose) polymerase (PARP)-inhibitor following chemotherapy.[14]

Despite macroscopically complete cytoreductive surgery, extensive chemotherapy, and maintenance PARP inhibition in selected patients, the vast majority of patients with advanced stage epithelial ovarian cancer dies from recurrent disease.[8, 9, 15-19] The peritoneal surface is the primary site of disease recurrence in most patients, highlighting the need for treatment strategies that specifically target the peritoneum.

Intraperitoneal chemotherapy

Intraperitoneal administration of chemotherapy specifically targets remaining microscopic disease after complete cytoreduction. Intravenous administration of chemotherapy often hinders therapeutic drug concentrations in intraperitoneal tumor depositions.[20] In vitro research showed that intraperitoneal administration of chemotherapy does

results in therapeutic intracellular drug concentrations, with a penetration depth of 1-3 mm.[21, 22] Accordingly, randomized trials, meta-analyses, and real-world data all show that administration of the right dose of adjuvant intraperitoneal chemotherapy after cytoreduction improves overall survival and progression-free survival in patients with advanced ovarian cancer.[23, 24] Controversies regarding the concept of intraperitoneal treatment, the design of the randomized studies, and increased toxicity (e.g., catheter related complications, renal dysfunction, gastro-intestinal dysfunction, and infections and pain) prevent this treatment from being widely adopted in clinical practice.[24, 25] In an attempt to reduce toxicity of intra-peritoneal chemotherapy, dose reductions from 100 mg/m^2 to 75 mg/m^2 and carboplatin instead of cisplatin have been evaluated without success, despite the addition of bevacizumab.[26]

Hyperthermic intraperitoneal chemotherapy

Hyperthermic intraperitoneal chemotherapy (HIPEC) is an alternative way to target microscopic peritoneal tumor deposits and is performed as a single procedure at the end of the cytoreductive surgery. Hyperthermia has a direct cytotoxic effect on tumor cells and induces heat-shock proteins that serve as receptors for natural killer-cells, leading to apoptosis and inhibiting angiogenesis.[27-29] Hyperthermia also causes depletion of BRCA1 and BRCA2 protein and thus and impairs *BRCA1/2* protein function. As a result, tumor cells are disabled to repair double-strand breaks through homologue recombination, thereby sensitizing these tumors to the platinum containing or alkylating chemotherapy that is introduced during HIPEC.[30-32] HIPEC is thus an attractive option after microscopically remaining disease after complete cytoreduction for tumors with a tendency to spread to the peritoneal surface, and such as ovarian cancer and colorectal cancer.

Towards the end of the 20th century, HIPEC made its entry for treatment of colorectal cancer.[33] HIPEC was also hypothesized to be attractive for patients with advanced ovarian cancer, given the frequency of peritoneal recurrences and initial platinum chemo-sensitivity. We performed a phase III, randomized, multicenter trial to investigate whether the addition of HIPEC to interval cytoreductive surgery improves recurrence-free and overall survival.

Chapter 2 describes the first randomized evidence on treatment with HIPEC for patients with ovarian cancer in the frontline setting. The OVHIPEC trial was an open-label trial and the primary endpoint was investigator-assessed recurrence-free survival. CT-scans and serum CA-125 measurements were performed at regular intervals for patients in both treatment arms, but establishments of disease recurrences might have been biased by the open-label design of the trial. Therefore, we collected all available CT-scans of patients that participated in the trial and performed central assessment of recurrence-free survival based on CT-scan images in **chapter 3**. In addition, we tested the hypothesis that HIPEC specifically targets the peritoneal surface by analyzing the site of disease recurrence.

Patient-reported outcomes, side effects, health-related quality of life and patients' satisfaction with care have been increasingly recognized as relevant parameters in the evaluation of new medical treatments. We assessed the effect of the addition of HIPEC on the patients' symptom burden and health-related quality of life in the OVHIPEC trial

in **chapter 5**. We present de results of a Markov model for cost-effectiveness analyses for this new treatment modality in **chapter 6** to support clinical implementation and reimbursement decisions.

Prognostic factors and biomarkers

Before and during treatment, diagnostic measures can provide insight into important prognostic factors that predict disease-free and overall survival, and predictive factors for treatment effect. Standard diagnostic workup for patients with FIGO stage III/IV ovarian cancer includes gynecological examination, transvaginal ultrasound, serum CA-125 measurement, thoracic and abdominal computed tomography (CT) scan and, if possible, cytological or histological confirmation of the disease. Serum CA-125 measurements and CT-scans during treatment help evaluate treatment response and can subsequently predict clinical outcome. **Chapter 3** reports the results of centrally assessed baseline imaging studies and radiological response to neo-adjuvant chemotherapy as prognostic and predictive marker of outcome after HIPEC.

The ability to adequately administer standard doses of chemotherapy is another possible prognostic factor.[14, 34-37] Chemotherapy toxicity often leads to decline of the patients' clinical fitness, dose reductions and treatment delays, all related to poor outcome. Significant weight loss and loss of skeletal muscle mass during treatment are possibly related to treatment toxicity and patient outcome.[38] We tested loss of skeletal muscle mass as independent prognostic factor in ovarian cancer patients participating in the OVHIPEC trial in **chapter 4**.

Mutational analysis of tumor tissue samples also increasingly become important predictive and prognostic tools in patients with ovarian cancer. Around 90% of ovarian cancers are of carcinomas, and these can be divided into five histological subtypes: high-grade serous (88%), high-grade endometrioid (2.5%), clear cell (4.5%), mucinous (1%), and low-grade serous or endometrioid carcinomas (5%).[7,39,40] Each of these subtypes has a different mutational background and assumed etiology. Up to 50% of patients with high-grade serous ovarian cancer are homologous recombination deficient due to germline or somatically acquired breast cancer gene 1 or 2 (*BRCA1* or *BRCA2*) mutations, epigenetic inactivation of *BRCA1*, or defects in the homologous recombination pathway such as *RAD51* and *ATM*.[41, 42] During homologous recombination, one of the mechanisms in the repair of double-strand breaks, *BRCA1, BRCA2, RAD51* and its homologs are important for single-strand DNA reattachment.[43-45] Hereditary or somatic mutations in *BRCA1, BRCA2*, or one of the other homologs cause homologue recombination deficiency. This results in activation of error-prone double-strand break repair mechanisms such as nonhomologous end joining, leading to genomic instability.[45, 46] Patients diagnosed with high-grade serous ovarian cancer have an approximately 20% likelihood of an inherited *BRCA1* or *BRCA2* mutation.[47] Since platinum agents induce DNA double-strand breaks, tumors harboring a *BRCA* mutation are more sensitive to platinum agents.[14, 48, 49]

A method to not only identify tumors with *BRCA1/2* mutations, but identify all tumors that fail homologue-recombination, is done by analyzing genome-wide copy-number aberration data. This is used to visualize genomic scar signatures of defective DNA repair in tumors.[50, 51]

So called copy-number variation profiles can be grouped to being *BRCA*-like or non-BRCA-like. Selection of tumors that are deficient in homologous recombination is increasingly recognized as a relevant marker for treatment selection in ovarian cancer. We developed an HRD-classifier in order to select tumors with *BRCA1*-like signatures, and validated it within the OVHIPEC-1 trial population (**chapter 7**). To test the hypothesis that patients with tumors that harbor aberrations related to homologous recombination deficiency are particularly sensitive to HIPEC, we estimated the effect of HIPEC in patients who participated in the phase 3 OVHIPEC-1 trial and stratified the results by BRCAm and HRD status in **chapter 8**.

The general discussion in **chapter 9** elaborates on the strengths and pitfalls of these results and shows an insight in current developments in treatment of patients with advanced ovarian cancer. It moreover covers directions for future research in order to properly select patients for treatment with HIPEC, and to further establish its working mechanism. **Chapter 10** summarizes the results of the thesis.

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CHAPTER 2

Hyperthermic intraperitoneal chemotherapy in ovarian cancer

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Abstract

Background Treatment of newly diagnosed advanced-stage ovarian cancer typically involves cytoreductive surgery and systemic chemotherapy. We conducted a trial to investigate whether the addition of hyperthermic intraperitoneal chemotherapy (HIPEC) to interval cytoreductive surgery would improve outcomes among patients who were receiving neoadjuvant chemotherapy for stage III epithelial ovarian cancer.

Methods In a multicenter, open-label, phase 3 trial, we randomly assigned 245 patients who had at least stable disease after three cycles of carboplatin (area under the curve of 5 to 6 mg per milliliter per minute) and paclitaxel (175 mg per square meter of body-surface area) to undergo interval cytoreductive surgery either with or without administration of HIPEC with cisplatin (100 mg per square meter). Randomization was performed at the time of surgery in cases in which surgery that would result in no visible disease (complete cytoreduction) or surgery after which one or more residual tumors measuring 10 mm or less in diameter remain (optimal cytoreduction) was deemed to be feasible. Three additional cycles of carboplatin and paclitaxel were administered postoperatively. The primary end point was recurrence-free survival. Overall survival and the side-effect profile were key secondary end points.

Results In the intention-to-treat analysis, events of disease recurrence or death occurred in 110 of the 123 patients (89%) who underwent cytoreductive surgery without HIPEC (surgery group) and in 99 of the 122 patients (81%) who underwent cytoreductive surgery with HIPEC (surgery-plus-HIPEC group) (hazard ratio for disease recurrence or death, 0.66; 95% confidence interval [CI], 0.50 to 0.87; P = 0.003). The median recurrence-free survival was 10.7 months in the surgery group and 14.2 months in the surgery-plus-HIPEC group. At a median follow-up of 4.7 years, 76 patients (62%) in the surgery group and 61 patients (50%) in the surgery-plus-HIPEC group had died (hazard ratio, 0.67; 95% CI, 0.48 to 0.94; P = 0.02). The median overall survival was 33.9 months in the surgery group and 45.7 months in the surgery-plus-HIPEC group. The percentage of patients who had adverse events of grade 3 or 4 was similar in the two groups (25% in the surgery group and 27% in the surgery-plus-HIPEC group, P = 0.76).

Conclusions Among patients with stage III epithelial ovarian cancer, the addition of HIPEC to interval cytoreductive surgery resulted in longer recurrence-free survival and overall survival than surgery alone and did not result in higher rates of side effects.

Introduction

Ovarian cancer is associated with the highest mortality of all gynecologic cancers in the western world. The majority of patients receive a diagnosis of advanced disease that has spread beyond the ovaries to the peritoneal surface. The most effective treatment for advanced disease involves a maximum effort to reduce the tumor burden through surgery followed by six cycles of intravenous chemotherapy with carboplatin and paclitaxel. Alternatively, interval cytoreductive surgery is performed after three cycles of chemotherapy.[1-4] Intraperitoneal delivery of chemotherapy enhances drug delivery at the peritoneal surface and may improve outcomes by eliminating residual microscopic peritoneal disease more efficiently than intravenous administration of chemotherapy.

Combination treatment with intravenous and intraperitoneal chemotherapy has been shown to prolong overall survival after primary cytoreduce tive surgery among patients with stage III ovarian cancer.[5-7] Catheter-related problems, increased demands on the patient, and gastrointestinal and renal side effects have hampered the adoption of this approach in most countries. Delivery of the intraperitoneal chemotherapy at the end of surgery can circumvent most of these drawbacks while maintaining its advantages. Intraperitoneal chemotherapy during surgery that can be delivered under hyperthermic conditions is termed hyperthermic intraperitoneal chemotherapy (HIPEC). Hyperthermia increases the penetration of chemotherapy at the peritoneal surface and increases the sensitivity of the cancer to chemotherapy by impairing DNA repair. Hyperthermia also induces apoptosis and activates heat-shock proteins that serve as receptors for natural killer cells, inhibits angiogenesis, and has a direct cytotoxic effect by promoting the denaturation of proteins.[8-11] The addition of HIPEC to interval cytoreductive surgery for the treatment of ovarian cancer is feasible, but efficacy data from randomized trials are lacking.[12] We report the results of a randomized, open-label, phase 3 trial of interval cytoreductive surgery with or without HIPEC in patients with International Federation of Gynecology and Obstetrics stage III ovarian, fallopian tube, or peritoneal cancer who had at least stable disease after three cycles of neoadjuvant chemotherapy with carboplatin and paclitaxel.

Methods

Trial Oversight

The trial was designed by an executive committee that included lead investigators and a statistician. Approval for the trial protocol was obtained from the relevant institutional review boards. Data were collected by the Netherlands Comprehensive Cancer Organisation. Final data collection and analysis were performed by personnel at the data coordinating center at the Department of Biometrics, the Netherlands Cancer Institute, Amsterdam. The first author wrote the initial draft of the manuscript. All the authors contributed to subsequent revisions of the draft, agreed to submit the manuscript for publication, and vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol. There were no agreements regarding confidentiality between the sponsor and either the authors or the participating institutions.

Patients

Eligible patients had newly diagnosed stage III epithelial ovarian, fallopian tube, or peritoneal cancer and were referred for neoadjuvant chemotherapy because their

abdominal disease was too extensive for primary cytoreductive surgery or because surgery had been performed but was incomplete (i.e., after surgery, one or more residual tumors measuring >1 cm in diameter were present). Eligibility criteria also included a World Health Organization performance-status score of 0 to 2 (on a scale of 0 to 5, with higher numbers indicating decreasing performance), normal blood counts, and adequate renal function. All the patients provided written informed consent before enrollment.

Trial Design

We performed a multicenter, randomized, open-label, phase 3 trial to assess the efficacy and safety of interval cytoreductive surgery with HIPEC as compared with interval cytoreductive surgery without HIPEC. Patients who had received three cycles of neoadjuvant chemotherapy with carboplatin (area under the curve of 5 to 6 mg per milliliter per minute) and paclitaxel (175 mg per square meter of body-surface area) could be registered in the trial before the interval cytoreductive surgery took place. Randomization was performed at the time of surgery in cases in which complete or optimal cytoreduction was anticipated. Complete cytoreductive surgery was defined as surgery that resulted in no visible disease (residual disease classification, R-1), optimal cytoreductive surgery as surgery that resulted in the presence of one or more residual tumors measuring less than 2.5 mm (R-2a) or 2.5 to 10 mm in diameter (R-2b), and incomplete cytoreductive surgery as surgery that resulted in the presence of one or more residual lesions measuring more than 10 mm in diameter. For logistic reasons, at two of the eight participating centers, a diagnostic laparoscopy was performed before surgery to evaluate whether complete or optimal surgery was feasible. At the time of surgery, patients were randomly assigned, in a 1:1 ratio, to undergo interval cytoreductive surgery either with HIPEC (surgery-plus-HIPEC group) or without HIPEC (surgery group). 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 to 5 vs. 6 to 8).

The trial was conducted at eight hospitals at which medical personnel had experience in administering HIPEC in patients with peritoneal disease from colon cancer or from pseudomyxoma peritonei. HIPEC was administered at the end of the cytoreductive surgical procedure with the use of the open technique. In brief, the abdomen was filled with saline that circulated continuously with the use of a roller pump through a heat exchanger. By circulation of the heated saline, an intraabdominal temperature of 40°C (104°F) was maintained. Perfusion with cisplatin at a dose of 100 mg per square meter and at a flow rate of 1 liter per minute was then initiated (with 50% of the dose perfused initially, 25% at 30 minutes, and 25% at 60 minutes). The perfusion volume was adjusted such that the entire abdomen was exposed to the perfusate. The HIPEC procedure took 120 minutes in total, including the 90-minute perfusion period. At the end of the perfusion, drains were used to empty the abdominal cavity as completely as possible. To prevent nephrotoxicity, sodium thiosulphate was administered at the start of perfusion as an intravenous bolus (9 g per square meter in 200 ml), followed by a continuous infusion (12 g per square meter in 1000 ml) over 6 hours. Urine production was maintained at a minimum of 1 ml per kilogram per hour during hyperthermic perfusion and for 3 hours after surgery.

Patients received an additional three cycles of carboplatin and paclitaxel after surgery. During follow-up, physical examinations and measurement of the serum cancer antigen 125 (CA-125) level were repeated every 3 months for 2 years and then every 6 months until 5 years after the completion of chemotherapy. Computed tomography was performed at 1, 6, 12, and 24 months after the last cycle of chemotherapy. Patients completed health-related quality-of-life questionnaires — the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (QLQ-C30), Quality of Life Questionnaire–Ovarian Cancer Module (QLQ-OV28), and Quality of Life Questionnaire–Colorectal Cancer Module (QLQ-CR38) — with- in 2 weeks before randomization, before the fourth cycle of chemotherapy, 1 week after completion of chemotherapy, and during follow-up at 3, 6, 9, 12, 15, 18, 21, and 24 months.

End Points

The primary end point was recurrence-free survival, which was defined as the time from randomization to disease recurrence or progression or death from any cause, whichever occurred first. Disease progression was defined according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, or on the basis of an increase from baseline in the CA-125 level, whichever one of these two criteria was met first, as recommended by the Gynecologic Cancer InterGroup (GCIG) - (see the Supplementary Appendix).[13, 14] Secondary end points included overall survival, the side-effect profile, and health-related quality of life; no correction for multiple testing was performed. Data on recurrence-free survival and overall survival were censored at the date of the last contact for the patients who remained alive and had no evidence of disease. The cutoff date for data was set at March 31, 2017.

Statistical Analysis

We determined that a sample of 245 patients with sufficient follow-up for observation of 192 events of disease recurrence, disease progression, or death would provide the trial with 80% power to detect 50% longer median recurrence-free survival (27 months vs. 18 months, with a hazard ratio for disease recurrence, disease progression, or death of 0.67)[5] in the surgery-plus-HIPEC group than in the surgery group, at an overall two-sided type I error rate of 0.05. A prespecified interim analysis for efficacy was performed after data from 50% of the required sample were available. The significance level for the final analysis was set at 0.048 to preserve an overall significance level of 0.05. Analyses of recurrence-free and overall survival were based on the intention-to-treat population and were stratified according to previous surgery (yes vs. no), the hospital in which the surgery was being performed, and the number of involved areas in the abdominal cavity. Kaplan–Meier estimates were compared with the use of stratified log-rank tests. Hazard ratios and the corresponding 95% confidence intervals were estimated with the use of Cox proportional-hazards models. Exploratory analyses of recurrence-free survival and overall survival were prespecified for subgroups defined according to previous surgery (yes vs. no) and number of involved regions of the abdominal cavity and were performed post hoc for subgroups defined according to the patients' age (<65 vs. ≥65 years), tumor histologic type (high-grade serous vs. other), and previous laparoscopy (yes vs. no). Hazard ratios for the subgroup analyses are provided with 99% confidence intervals. Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events,

version 4.0. In the safety analysis, we included data from all patients who received the assigned treatment. We used mixed-effects growth-curve modeling to evaluate linear and nonlinear changes from baseline in health-related quality of life over time; this modeling adjusted for nonignorable missing data from quality-of-life questionnaires that were not completed.

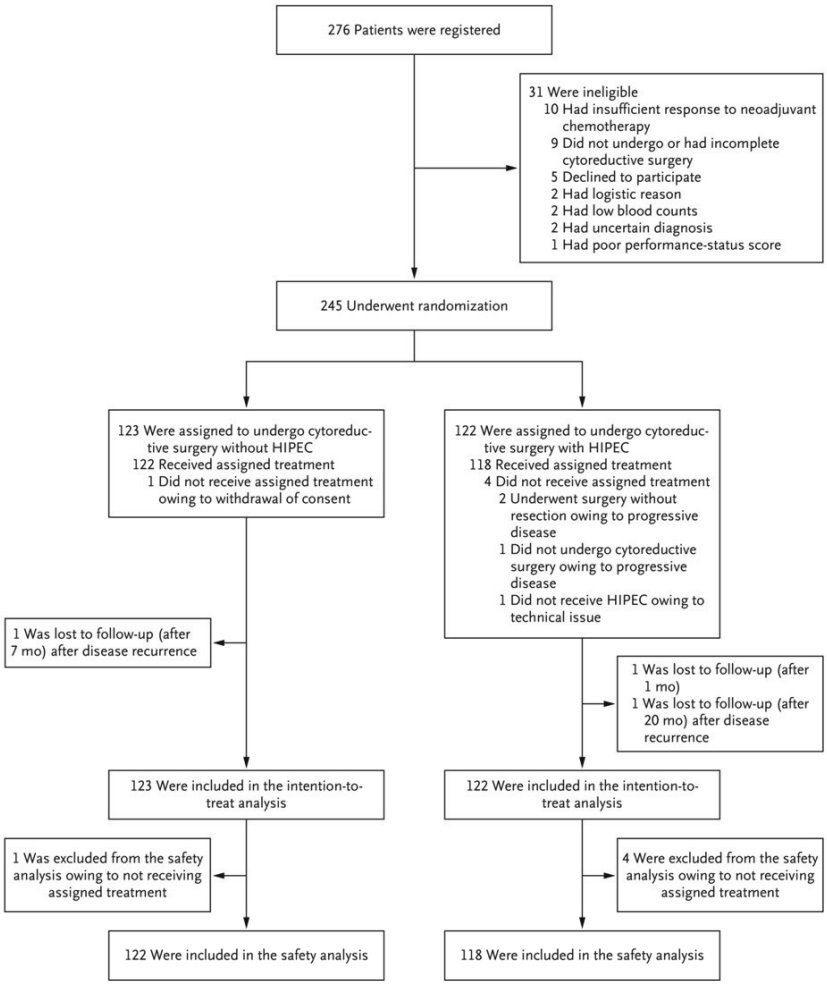

Figure 2.1. Enrollment, randomization, and follow-up.
The patient who was randomly assigned to the surgery group but did not undergo cytoreductive surgery owing to withdrawal of consent allowed the use of all her registered data before the time of withdrawal. Incomplete cytoreductive surgery was defined as surgery that resulted in the presence of one or more residual lesions measuring more than 10 mm in diameter. The 245 patients in the intention-to-treat population were followed until death or loss to follow-up.

Results

Patients

During the period from April 2007 through April 2016, a total of 245 women were enrolled at eight participating centers in the Netherlands and Belgium. The minimum number of events required for analysis of the primary end point was reached in April 2016, and efficacy data were updated in March 2017. Information on the enrollment, randomization, treatment, and follow-up of the patients is shown in Figure 2.1. Demographic and baseline disease characteristics and surgical and treatment information for the two trial groups are shown in Table 2.1.

Table 2.1. Baseline characteristics and surgery characteristics*

	Surgery (N=123)	**Surgery + HIPEC (N=122)**
Baseline characteristics		
Age – yr		
Median (Quartile 1 – Quartile 3)	63 (56 – 66)	61 (55 – 66)
Histology – no. (%)†		
High grade serous	107 (87)	112 (92)
High grade endometrioid	1 (<1)	1 (<1)
Carcinosarcoma	4 (3)	1 (<1)
Mucinous	2 (2)	1 (<1)
Clear cell carcinoma	5 (4)	0 (0)
Low grade serous	2 (2)	4 (3)
Low grade endometrioid	0 (0)	2 (2)
Metastasis gastrointestinal tumor	1 (<1)	0 (0)
Unknown	1 (<1)	1 (<1)
Prior surgery – no. (%)		
Yes	12 (10)	12 (10)
No	111 (90)	110 (90)
Number of regions affected at start of interval cytoreductive surgery – no. (%)‡		
0-5	83 (67)	83 (68)
6-8	40 (33)	39 (32)

Table 2.1. Baseline characteristics and surgery characteristics - continued*

Treatment characteristics		
Residual disease after surgery – no. (%)		
R-1: no visible tumor, complete CRS	82 (67)	84 (69)
R-2a: tumor nodules ≤2.5mm	24 (20)	22 (18)
R-2b: tumor nodules >2.5mm and ≤10mm	14 (11)	13 (11)
Tumor nodules >10mm, suboptimal CRS	1 (0.8)	0 (0)
No resection§	1 (0.8)	2 (2)
No surgery performed	1 (0.8)	1 (0.8)
Bowel resections – no. (%)		
No bowel resection performed	93 (76)	93 (76)
Bowel resection with ileo-/colostomy	13 (11)	21 (17)
Bowel resection without ileo-/colostomy	17 (14)	8 (7)
Duration of operation – minutes		
Median (Quartile 1 – Quartile 3)	192 (153 – 251)	338 (299 – 426)
Days hospitalized – no. of days ‖		
Median (Quartile 1 – Quartile 3)	8 (7 – 10)	10 (8 – 12)
Time between surgery and first adjuvant chemo-therapy cycle – no. of days		
Median (Quartile 1 – Quartile 3)	30 (25 – 41)	33 (28 – 41)
Number of cycles adjuvant chemotherapy – no. (%)		
0	7 (6)	5 (4)
1	2 (2)	0 (0)
2	3 (2)	2 (2)
3	111 (91)	115 (94)

* There were no significant differences between the trial groups in any of the variables listed in this table. Among patients who had a bowel resection, the rate of ileostomy or colostomy was significantly higher after HIPEC (21/29 vs 12/30), p-value 0.04. Percentages may not sum to 100 because of rounding, HIPEC denotes hyperthermic intraperitoneal chemotherapy, and IQR interquartile range.

† Histologic type was determined on the basis of centrally reviewed pathological assessment.

‡ At the start of surgery, the number of regions involvedwith disease was assessed as described by Verwaal et al.[15]

§ Surgery was performed, but no resection was possible.

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

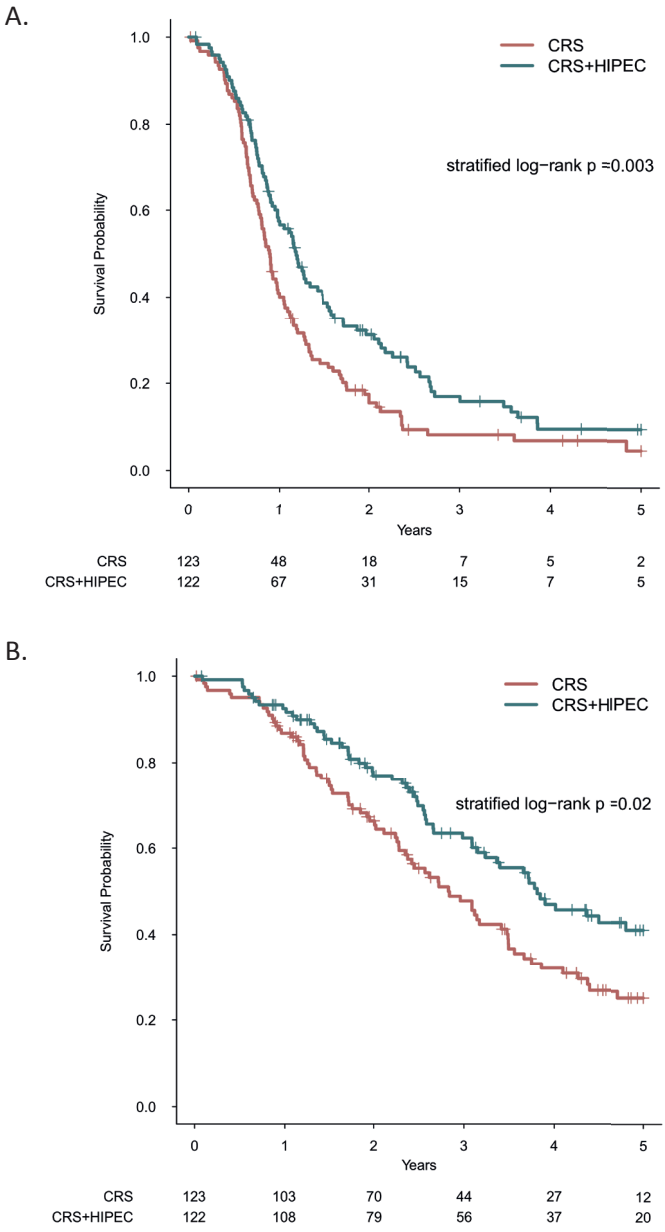

Figure 2.2. Kaplan–Meier estimates of recurrence-free survival and overall survival.
Panel A shows Kaplan–Meier estimates of recurrence-free survival among patients in the intention-to-treat population. Events of disease recurrence or death were observed in 110 patients (89%) in the surgery group and in 99 patients (81%) in the surgery-plus-HIPEC group.
Panel B shows Kaplan–Meier estimates of overall survival among patients in the intention-to-treat population. A total of 76 patients (62%) in the surgery group and 61 (50%) patients in the surgery-plus-HIPEC group died.

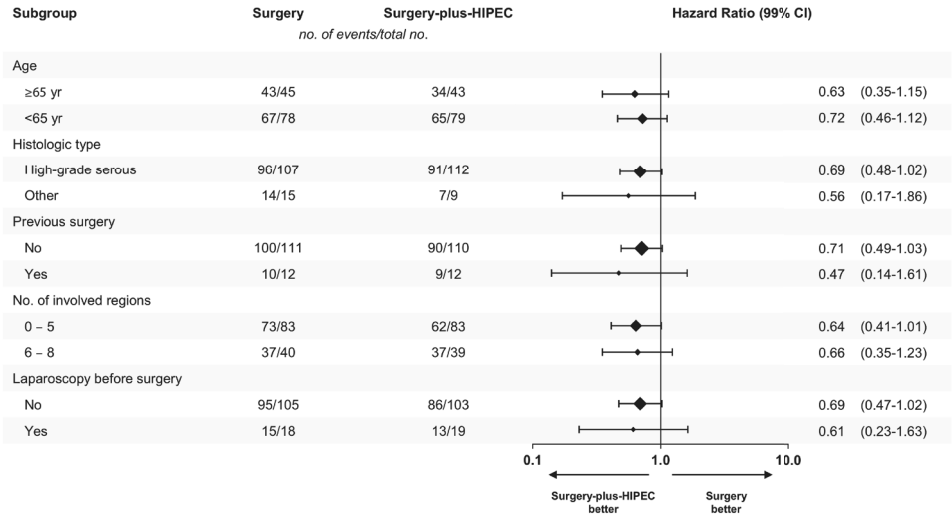

Figure 2.3. Panel A. Prespecified subgroup analyses of recurrence-free survival.
Histologic data were missing (i.e., no tumor sample was available for review) for one patient in each group. Histologic type was determined on the basis of centrally reviewed pathological assessment. Previous surgery and the number of involved regions in the abdominal cavity were used as stratification factors at randomization. All the patients had received neoadjuvant chemotherapy. The size of each diamond is proportional to the amount of data available.

Efficacy

After a median follow-up of 4.7 years, 209 of the 245 patients (85%) had had an event of disease recurrence or death; 137 of the 245 patients (56%) had died. In total, 83% of the recurrences were detected on the basis of imaging, irrespective of whether the patient had an increase from baseline in the CA-125 level, and 17% were detected on the basis of an increase in the CA-125 level alone. In the intention-to-treat analysis, 110 of the 123 patients (89%) in the surgery group and 99 of the 122 patients (81%) in the surgery-plus-HIPEC group had an event of disease recurrence or death (hazard ratio, 0.66; 95% confidence interval [CI], 0.50 to 0.87; stratified P = 0.003) (Fig. 2.2A). The median recurrence-free survival was 3.5 months longer in the group that underwent cytoreduction surgery with HIPEC than in the group that underwent surgery alone (14.2 months vs. 10.7 months). The probability of recurrence-free survival at 3 years was 8% in the surgery group (95% CI, 4 to 16) and 17% in the surgery-plus-HIPEC group (95% CI, 11 to 26). Subgroup analyses of recurrence-free survival (Fig. 1.3A) and overall survival (Fig. 2.3B) showed that the effect of HIPEC was consistent across the levels of prespecified stratification factors and post hoc subgroups. A total of 76 of the 123 patients (62%) in the surgery group and 61 of the 122 (50%) patients in the surgery-plus-HIPEC group died (hazard ratio, 0.67; 95% CI, 0.48 to 0.94; stratified P = 0.02) (Fig. 2.2B). The median overall survival was 33.9 months in the surgery group and

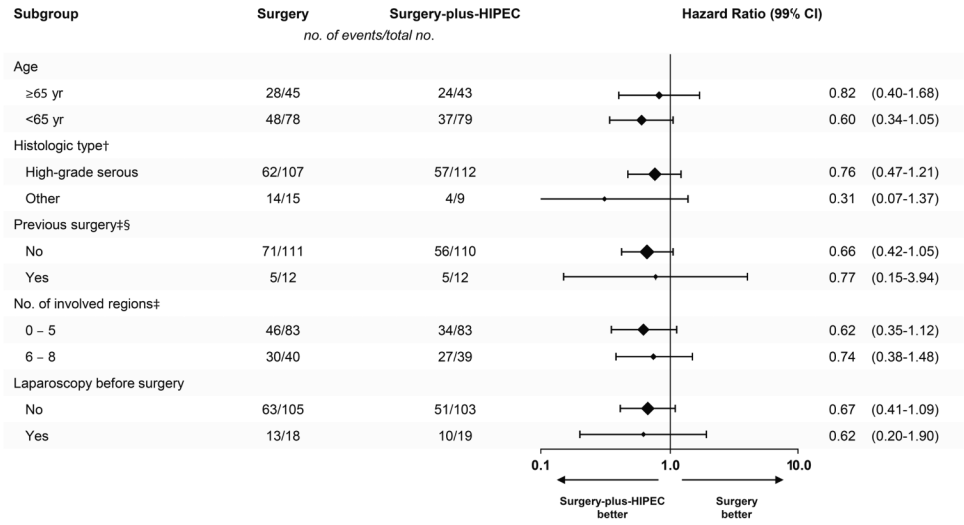

Figure 2.3. Panel B. Prespecified subgroup analyses of overall survival.
Histologic data were missing (i.e., no tumor sample was available for review) for one patient in each group. Histologic type was determined on the basis of centrally reviewed pathological assessment. Previous surgery and the number of involved regions in the abdominal cavity were used as stratification factors at randomization. All the patients had received neoadjuvant chemotherapy. The size of each diamond is proportional to the amount of data available.

45.7 months in the surgery-plus-HIPEC group. The probability of overall survival at 3 years was 48% (95% CI, 39 to 58) in the surgery group and 62% (95% CI, 54 to 72) in the surgery-plus-HIPEC group.

Safety and Health-Related Quality of Life

The median duration of surgery was 192 minutes (interquartile range, 153 to 251) in the surgery group and 338 minutes (interquartile range, 299 to 426) in the surgery-plus-HIPEC group. More than 95% of the patients in each group had at least one adverse event of any grade between randomization and 6 weeks after completion of the last cycle of chemotherapy. No significant differences between the two groups were noted in the incidence of adverse events of any grade. Adverse events of grade 3 or 4 were reported in 30 patients (25%) in the surgery group and in 32 patients (27%) in the surgery-plus-HIPEC group (P = 0.76). In both groups, the most common events of grade 3 or 4 were abdominal pain, infection, and ileus (Table 2.2). One patient in the surgery group died within 30 days after undergoing surgery. A total of 59 patients — 30 in the surgery group and 29 in the surgery-plus-HIPEC group — underwent bowel resection. Among the patients who underwent bowel resection, a colostomy or ileostomy was performed more commonly among patients in the surgery-plus-HIPEC group (21 of 29 patients [72%]) than among those in the surgery group (13 of 30

patients [43%]) (P = 0.04). The median total length of hospital admission was 8 days in the surgery group and 10 days in the surgery-plus- HIPEC group, including 1 day in the intensive care unit (ICU), as required by the protocol. The median time between the completion of surgery and the restart of chemotherapy after surgery was similar in the two groups — 30 days in the surgery group and 33 days in the surgery-plus-HIPEC group.
Rates of completion of all three cycles of chemo- therapy after surgery were also similar in the two groups (90% and 94% in the surgery and surgery-plus-HIPEC groups, respectively). A total of 11 patients in the surgery group and 9 in the surgery-plus-HIPEC group had recurrent disease but received no further therapy. We observed no significant differences between the two groups in health-related quality-of-life outcomes over time.

Table 2.2. Adverse events from randomization to 6 weeks after the end of treatment*

	Surgery (N=122)		Surgery + HIPEC (N=118)	
	Any grade	Grade 3-4†	Any grade	Grade 3-4
	Number of events (%)			
Infection‡	14 (11)	3 (2)	21 (18)	7 (6)
Abdominal pain	70 (57)	7 (6)	71 (60)	6 (5)
Ileus	4 (3)	2 (2)	9 (8)	5 (4)
Pain	28 (23)	2 (2)	39 (33)	4 (3)
Thromboembolic event§	2 (2)	2 (2)	7 (6)	4 (3)
Pulmonary event ‖	8 (7)	1 (1)	11 (9)	3 (3)
Dyspnea	13 (11)	0	8 (7)	3 (3)
Electrolyte disturbance¶	6 (5)	1 (1)	7 (6)	3 (3)
Gastrointestinal anastomotic leak	3 (2)	2 (2)	3 (3)	3 (3)
Nausea	70 (57)	3 (2)	74 (63)	2 (2)
Fatigue	37 (30)	0	44 (37)	2 (2)
Cardiac	6 (5)	2 (2)	8 (7)	2 (2)
Neuropathy	33 (27)	1 (1)	37 (31)	1 (1)
Vomiting	47 (39)	1 (1)	32 (27)	1 (1)
Anemia	7 (6)	6 (5)	5 (4)	1 (1)
Pneumonia	1 (1)	1 (1)	2 (2)	1 (1)
Post-operative hemorrhage	4 (3)	1 (1)	2 (2)	1 (1)
Hypotension	11 (9)	1 (1)	1 (1)	1 (1)
Sepsis	2 (2)	2 (2)	1 (1)	1 (1)
Constipation	32 (26)	1 (1)	23 (19)	0
Alopecia	19 (16)	0	22 (19)	0
Diarrhea	11 (9)	0	16 (14)	0
Fever	10 (8)	0	14 (12)	0
Dizziness	15 (12)	0	9 (8)	0
Gastroparesis	2 (2)	2 (2)	1 (1)	0
Intestinal perforation	2 (2)	2 (2)	0	0

* Shown are the adverse events of any grade that occurred in at least 10% of the patients in either trial group, along with all grade 3 or 4 events that occurred in at least two patients. The data from five patients who did not undergo cytoreductive surgery (one patient) or did not receive HIPEC as assigned (four patients) were not included in the analysis of adverse events

† In one patient, a grade 5 event occurred; the patient died after having a colonic perforation that resulted in septic shock.

‡ Events of infection excluded pneumonia.

§ Thromboembolic events included venous thrombosis, pulmonary embolism, cerebrovascular event and transient ischemic attack.

‖ Pulmonary events included hypoxia and respiratory distress.

¶ Electrolyte disturbances include hyponatremia, hypernatremia, hypokalemia, hypercalcemia, hypomagnesemia and hypophosphatemia.

Discussion

After standard treatment for ovarian cancer, the peritoneal surface is the primary site of disease recurrence. Previous trials that compared six cycles of intraperitoneal chemotherapy plus intravenous chemotherapy with intravenous chemotherapy alone after complete or optimal primary cytoreductive surgery showed that survival was 16 months longer after exposure to chemotherapy at the peritoneal surface than after intravenous chemotherapy alone.[5, 6, 16] Nevertheless, the uptake of postoperative intravenous chemotherapy plus intraperitoneal chemotherapy in clinical practice is limited by increased side effects, including catheter-related complications, and the inconvenience of administering therapy intraperitoneally.[7, 17] In the current trial, we evaluated HIPEC as a single administration of intraperitoneal chemotherapy during surgery to overcome the side effects and inconvenience of serial adjuvant intraperitoneal chemotherapy and to improve the distribution of heated chemotherapy in the abdominal cavity.

Although randomized trials support the use of HIPEC in colorectal cancer,[15, 18-20] previous evidence of a beneficial effect of HIPEC in primary ovarian cancer has been limited to single-group trials and retrospective cohorts.[12, 14] In one previous trial involving patients with recurrent ovarian cancer who were randomly assigned to undergo cytoreductive surgery either with or without HIPEC, a significant survival benefit was observed among the patients who received HIPEC.[21] However, the randomization process was not clearly described, and primary end points were not clearly defined.[22] Our trial provides data from patients who were randomly assigned to undergo surgery with HIPEC or without HIPEC for the primary treatment of advanced ovarian cancer. Our findings indicate that the addition of HIPEC to complete or optimal interval cytoreductive surgery resulted in longer median recurrence-free survival, by 3.5 months, and longer median overall survival, by 11.8 months, than surgery alone. The effect was consistent across the levels of pre-specified stratification factors and other baseline characteristics. All the patients in our trial received neoadjuvant chemotherapy. Postoperative care was similar in the two trial groups, with the exception of the care that the patients received during the 1-day stay in the ICU after HIPEC that was pre-specified in the protocol. The administration of HIPEC had little effect on safety, and the incidence of postoperative complications, the incidence and type of grade 3 or 4 adverse events, and health-related quality-of-life outcomes did not differ significantly between the surgery-plus-HIPEC group and the surgery group. The reinitiation of intravenous chemotherapy after surgery was not delayed in either trial group, and no effect of HIPEC on the number of cycles of chemotherapy administered was observed. A single administration of intraperitoneal chemotherapy under hyperthermic conditions differs from repeated postoperative administration of intra-peritoneal chemotherapy with respect to pharmacokinetics and pharmacodynamics, which could explain the lower rate of systemic side effects seen with a single administration of intraperitoneal chemotherapy than with a postoperative intravenous or intraperitoneal chemotherapy regimen.[17]

Additional trials are needed to determine the ways in which HIPEC differs from postoperative intravenous or intraperitoneal chemotherapy and whether HIPEC is also effective after primary cytoreductive surgery. The overall percentage of bowel resections performed was similar in the two groups, but the percentage of patients who underwent a colostomy or an

ileostomy after surgery was significantly higher in the surgery-plus-HIPEC group than in the surgery group (72% vs. 43%, P = 0.04). Because there is no evidence that HIPEC for ovarian cancer is associated with a higher rate of anastomotic leakage than the rate without HIPEC, this difference in the rate of colostomy or ileostomy could reflect the surgeons' preference. Randomization in our trial took place at the time of surgery in cases in which complete or optimal cytoreduction was anticipated. The institutional review board at each trial center approved this procedure, which ensured equality of prognosis between the trial groups at the actual time of the trial intervention, although for logistic reasons, randomization was performed before the interval surgery at two of the centers on the basis of the results of a diagnostic laparoscopy that was performed to determine whether complete or optimal surgery was feasible. When HIPEC is added to the surgical treatment, the duration of surgery is extended by 2 hours and a perfusionist is needed. Additional standard costs are incurred owing to the additional 2 hours of surgical time, the disposable products that are needed to administer HIPEC, the use of the HIPEC machine, and the 1-day stay in the ICU. Our trial involved patients with prognostically unfavorable stage III ovarian cancer who were ineligible for primary cytoreduction owing to extensive abdominal disease. As a result, survival in the control group of our trial was shorter than that Oncology Group (GOG)–172 trial, which included only patients who were eligible for primary cytoreduction.[5]

The recurrence-free survival in our trial was also influenced by the definition of the primary end point, which included elevation of the CA-125 level as determined on the basis of GCIG criteria. When the protocol was designed, measurement of the CA-125 level during follow-up was part of routine clinical practice. However, if the definition of the primary end point had been based on clinical symptoms rather than on measurement of the CA-125 level, the estimated rate of recurrence would have been lower and the absolute prolongation of median recurrence-free survival might have been greater.[23] The median overall survival was 12 months longer among the patients who received HIPEC than among those who did not receive HIPEC, whereas the median recurrence-free survival was 3.5 months longer with HIPEC than without HIPEC. However, the relative effects of HIPEC on recurrence-free survival and on overall survival were remarkably similar, with hazard ratios of 0.66 for recurrence-free survival and 0.67 for overall survival. The discrepancy between similar relative effects in overall survival and recurrence-free survival and a larger absolute benefit in overall survival than recurrence-free survival reflects the higher rate of disease recurrences than deaths. This finding was also shown in the GOG-172 trial, in which the difference between the trial groups in recurrence-free survival and in overall survival was 5.5 months and 15.9 months, respectively, both in favor of the intraperitoneal chemotherapy group. The number of patients in the control group of the Gynecologic who received no therapy for recurrent disease in the surgery group was similar to that in the surgery-plus-HIPEC group and cannot explain the difference in absolute benefit between recurrence-free survival and overall survival.

In conclusion, our results indicate that among women with advanced ovarian cancer, HIPEC plus complete or optimal interval cytoreductive surgery resulted in longer survival than cytoreductive surgery alone.

Trial registration
ClinicalTrials.gov number, NCT00426257; EudraCT number, 2006-003466-34

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Supplementary files chapter 2

Methods

Gynecologic Cancer InterGroup (GCIG) criteria for progression according to CA-125

The primary endpoint was recurrence-free survival defined as the time from randomization to disease recurrence or progression on the basis of the Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1, a rise in CA-125 level according to the Gynecologic Cancer InterGroup criteria (GCIG), or death from any cause, whichever occurred first.[13]

Evaluation of progression according to CA-125, described by the GCIG

Progression or recurrence based on serum CA 125 levels will be defined on the basis of a progressive serial elevation of serum CA 125 according to the following criteria:

- Patients with elevated CA-125 pretreatment and normalization of CA-125 must show evidence of CA-125 greater than, or equal to, 2 times the upper limit of the reference range on 2 occasions at least 1 week apart or
- Patients with elevated CA-125 before treatment, which never normalizes, must show evidence of CA-125 greater than, or equal to, 2 times the nadir value on 2 occasions at least 1 week apart or
- Patients with CA-125 in the reference range before treatment must show evidence of CA-125 greater than, or equal to, 2 times the upper limit of the reference range on 2 occasions at least 1 week apart.
- CA 125 progression will be assigned the date of the first measurement that meets the criteria as noted. Patients are not evaluable by CA 125 if they have received mouse antibodies (unless the assay used has been shown not to be influenced by human antimouse antibody) or if there has been medical and/or surgical interference with their peritoneum or pleura (eg, paracentesis) during the previous 28 days.

A patient may be declared to have recurrent disease on the basis of either the objective RECIST 1.1 criteria or the CA 125 criteria. The date of progression will be the date of the earlier of the 2 events if both are documented.

Results

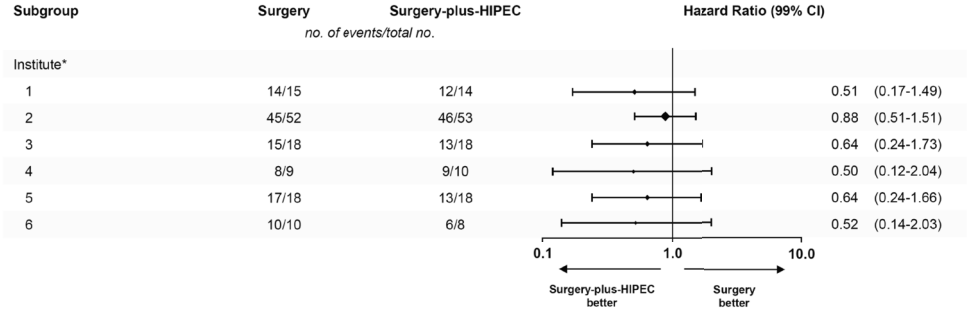
Study statistics

The database for this analysis was closed on April 5, 2017. The study has been closed with 276 registered patients, of whom 245 were randomized. The first patient was randomized on April 27, 2007 and the last patient on April 18, 2016.

The median follow-up of the sample was 4.7 years (respectively 4.8 years for CRS and 4.6 years for CRS+HIPEC). Patients were stratified by primary suboptimal cytoreductive surgery (yes vs. no), institute and the number of abdominal cavity regions involved at the time of interval surgery (0-5 versus 6-8).

Supplementary figures

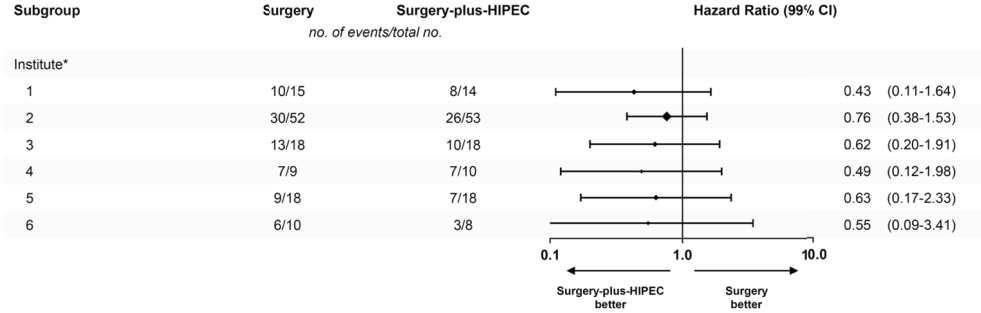
Figure S2.1. Forest plot for recurrence-free survival per site



* Two institutes included only 1 patient and could therefore not be included in subgroup analyses

† Overall result was based on the intention-to-treat sample

Figure S2.2. Forest plot for overall survival per site



* Two institutes included only 1 patient and could therefore not be included in subgroup analyses

† Overall result was based on the intention-to-treat sample

CHAPTER 3

Central radiology assessment of the randomized phase 3 open-label OVHIPEC-1 trial in ovarian cancer

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Abstract

Introduction Hyperthermic intraperitoneal chemotherapy (HIPEC) improved investigator-assessed recurrence-free survival and overall survival in patients with stage III ovarian cancer in the phase III OVHIPEC-1 trial. We analyzed whether open-label design affected the results of the trial by central blinded assessment of recurrence-free survival and tested if HIPEC specifically targets the peritoneal surface by analyzing the site of disease recurrence.

Methods OVHIPEC-1 was an open-label, multicenter, phase III trial that randomized 245 patients after three cycles of neoadjuvant chemotherapy to interval cytoreduction with or without HIPEC using cisplatin (100mg/m^2). Patients received three additional cycles of chemotherapy after surgery. Computed Tomography (CT)-scans and serum CA-125 measurements were performed during chemotherapy, and during follow-up. Two expert radiologists reviewed all available CT-scans. They were blinded for treatment allocation and clinical outcome. Central revision included RECIST 1.1 measurements and peritoneal cancer index scorings at baseline, during treatment, and during follow-up. Time to centrally-revised-recurrence was compared between study arms using Cox proportional-hazard models. Subdistribution models compared time to peritoneal recurrence between arms, accounting for competing risks.

Results CT-scans for central revision were available for 231 patients (94%) during neo-adjuvant treatment and 212 patients (87%) during follow-up. Centrally-assessed median recurrence-free survival was 9.9 months in the surgery group and 13.2 months in the surgery+HIPEC group (hazard ratio for disease recurrence or death, 0.72; 95%-confidence interval, 0.55-0.94; P=0.015). The improved recurrence-free survival and overall survival associated with HIPEC were irrespective of response to neoadjuvant chemotherapy and baseline peritoneal cancer index. Cumulative incidence of peritoneal recurrence was lower after surgery+HIPEC, but there was no difference in extra-peritoneal recurrences.

Discussion Centrally assessed recurrence-free survival analysis confirms the benefit of adding HIPEC to interval cytoreductive surgery in patients with stage III ovarian cancer, with less peritoneal recurrences. These results rule out radiological bias caused by the open-label nature of the study.

Introduction

Ovarian cancer is one of the leading causes of cancer deaths in women in the Western world.[1] The majority of patients presents with advanced disease that has spread to the peritoneal surface and beyond (International Federation of Gynaecological Oncology [FIGO] stage III-IV disease). Standard treatment generally consists of complete cytoreductive surgery followed by six cycles of chemotherapy with carboplatin and paclitaxel.[2, 3] In case of extensive disease precluding upfront complete cytoreductive surgery, treatment starts with neoadjuvant chemotherapy followed by interval cytoreductive surgery and an additional three cycles of adjuvant chemotherapy.[4, 5] Despite maximal treatment, around 70% of patients with advanced ovarian cancer relapse within two years and ten year survival rates have not improved over the past three decades.[6, 7]

The peritoneal surface is the primary site of disease recurrence in the vast majority of patients with ovarian cancer. In vitro research showed that intraperitoneal delivery of chemotherapy increases intracellular concentrations of cytostatic agents in the peritoneum compared to intravenous chemotherapy.[8] Randomized trials, systematic reviews and real-life data showed recurrence-free and overall survival benefit after intraperitoneal chemotherapy combined with intravenous chemotherapy (IP/IV) in patients with advanced stage ovarian cancer.[9-12] Adoption of IP/IV chemotherapy in general practice was hampered by a higher incidence of catheter related complications and logistical hurdles.[12] In an attempt to reduce toxicity of intra-peritoneal chemotherapy, dose reductions from 100 mg/m^2 to 75 mg/m^2 and, using carboplatin instead of cisplatin have been evaluated without success, despite the addition of bevacizumab.[13]

Hyperthermic intraperitoneal chemotherapy (HIPEC) is an alternative approach for intraperitoneal chemotherapy delivery, in which heated chemotherapy is administered into the abdominal cavity at the end of the cytoreductive procedure. OVHIPEC-1 was a multicenter, open-label, randomized phase III trial that showed statistically significant and clinically meaningful improvement in patient outcome with the addition of HIPEC to interval cytoreductive surgery.[14] Primary endpoint of the trial was investigator assessed recurrence-free survival, which may have been affected by the open-label design of the trial. Here, we report the results of the blinded centrally-assessed recurrence-free survival analysis and exploratory subgroup analyses of HIPEC benefit based on radiological response to neo-adjuvant chemotherapy and peritoneal cancer index scores. In addition, we analyzed the site of disease recurrence in both study arms.

Methods

Patients and treatment

The study design and procedures were published previously.[14] In short, 245 patients with with stage III ovarian cancer who had undergone neoadjuvant chemotherapy were randomized (1:1) to receive interval cytoreductive surgery with or without HIPEC using cisplatin 100mg/m^2. These patients were not candidate for primary surgery due to the extent of disease, and they had at least had stable disease after three cycles of neoadjuvant chemotherapy with carboplatin (area under the curve [AUC] 5-6 mg) and paclitaxel 175 mg/m^2. Randomization was performed intra-operatively and was stratified by 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). All patients received an additional three cycles of carboplatin and paclitaxel after surgery. All patients provided written informed consent before trial registration. In accordance with the journal's guidelines, we will provide our data for the reproducibility of this study in other centers if requested.
During follow-up, physical examinations and measurement of the serum cancer antigen 125 (CA-125) level were repeated every three months for two years, and every six months thereafter until at least five years after the completion of chemotherapy or until recurrence occurred. Computed tomography (CT)-scans were performed at one, six, 12, and 24 months after the last cycle of chemotherapy.

The primary endpoint of the trial was recurrence-free survival as assessed by the local investigator based on the assessments as stated in the protocol and defined as the time from randomization to first evidence of disease recurrence or death from any cause, whichever came first. Disease recurrence was defined according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, or based on an increase in the CA-125 level, as recommended by the Gynecologic Cancer InterGroup (GCIG).[15] Main secondary endpoint was overall survival, defined as time from randomization to death from any cause. Data on recurrence-free survival and overall survival were censored at the date of the last contact for the patients who remained alive and had no evidence of disease. The data cutoff was set at March 31, 2017.

Data collection
We collected CT-scans at diagnosis, during neoadjuvant chemotherapy, and during follow-up from all patients that were randomized in the OVHIPEC-1 trial. Scans were anonymized and coded. Central revision was performed with cross-section verification by two experienced gynecologic radiologists (CF, ML). In case of observer discrepancies, inter-observer concordance was reached based on discussion. Both radiologists were blinded for treatment allocation and clinical outcome. Each radiologist recorded findings using a standardized scoring form that included RECIST measurements[15], peritoneal cancer index [16], extra-peritoneal disease locations, involvement of lymph nodes, presence of ascites, and presence of omental involvement. Lymph nodes with a minimum size on short-axis of 10 mm, and up to 5 target lesions were measured in at least one dimension.
The FIGO substage was determined on the baseline CT-scan before the start of neo-adjuvant chemotherapy. [17] Response during neo-adjuvant chemotherapy was defined according to the GCIG criteria and RECIST 1.1, as was disease recurrence during follow-up. [15, 18] The recurrence date was set on the date of the first evidence of recurrence or progression, and could be based on radiological evidence, CA-125 rise, clinical symptoms or other diagnostic methods, such as ultrasound or pathology reports.[15] In some cases, the date of disease recurrence was based on CA-125 or clinical symptoms without the availability of a CT-scan within 4 weeks.

Statistics
Baseline characteristics including FIGO substage, previous surgery, number of regions affected at start of treatment, mean pre-operative peritoneal cancer index on CT-scan, and

radiological response during neoadjuvant treatment were listed for both treatment arms. Median RFS based on central revision was calculated using Kaplan-Meier estimates and compared using the log-rank test. Hazard ratios and the corresponding 95% confidence intervals (CI) were estimated with Cox proportional-hazards models. The primary site of disease recurrence was scored as a categorical variable, and compared using competing-risk subdistribution as proposed by Fine and Gray.[19]

Exploratory subgroup analyses of centrally assessed recurrence-free survival and overall survival were performed for pre-operative peritoneal cancer index-scores and radiological response during neoadjuvant chemotherapy. Hazard ratios and corresponding 99% confidence intervals were estimated using Cox proportional-hazard models, with associated p-values for interaction. Time-dependent Receiver Operating Curves (ROC) were calculated for the peritoneal cancer index scores on the first and second CT-scan and for the decrease of peritoneal cancer index scores during neoadjuvant chemo, related to overall survival. The cut-off values for peritoneal cancer indexes were based on the medians, because of area under the curves under 0.60 for all three valuables (supplementary figure 1 and supplementary table 1). All analyses were performed using International Business Machines (IBM) Statistical Package for the Social Sciences (SPSS) version 25 and R software (version 3.5.0).

Results

A total of 948 CT-scans were available for central review. All 245 patients had at least one CT-scan available for central review (Figure 3.1). Two-hundred-thirty-one patients (94%) had CT-scans available before and after neo-adjuvant chemotherapy. For 212 patients (87%) all CT-scans were available during neo-adjuvant chemotherapy and during follow-up. The total number of available CT-scans during follow-up slightly differed across treatment arms, as early recurrences were more frequent in the absence of HIPEC (figure 3.1, supplementary table 3.2b).

On central review, six patients were upstaged to FIGO stage IV disease, based on suspected lesions in liver and/or spleen (two patients) or enlarged paracardial lymph nodes (four patients) (table 3.1). On central review, no patient had progressive disease during neoadjuvant chemotherapy, 134 (55%) had stable disease, and 89 (36%) had a partial response (table 1). No radiological complete response was observed. The mean peritoneal cancer index score decreased from 17 (standard deviation [SD] 5.8) before chemotherapy to 12 (SD 5.1) after two cycles of neoadjuvant chemotherapy (paired-sample t-test p-value: <0.001). PCI at baseline and after two cycles were similar between the study arms due to the randomization.

Table 3.1. Baseline characteristics

	CRS		CRS + HIPEC	
	N=123		N=122	
FIGO, Nr. (%)				
IIIA	1	1%	0	0%
IIIB	12	10%	13	11%
IIIC	102	83%	102	84%
IVB	4	3%	2	2%
missing	4	3%	5	4%
PCI score, mean (SD)				
CT-scan at baseline	17.2	5.4	17.2	5.8
CT-scan during NACT	12.3	5.1	11.8	5.2
mean decrease in PCI	-4.8	4.0	-5.7	4.8
Radiological response during NACT according to RECIST 1.1 (%)				
complete response	0		0	
partial response	40	33%	49	36%
stable disease	71	58%	63	52%
progressive disease	0		0	
unmeasurable	12	10%	10	8%
- because of incomplete primary surgery:	8/12		4/10	

NACT, neo-adjuvant chemotherapy; PCI, peritoneal cancer index, SD; standard deviation

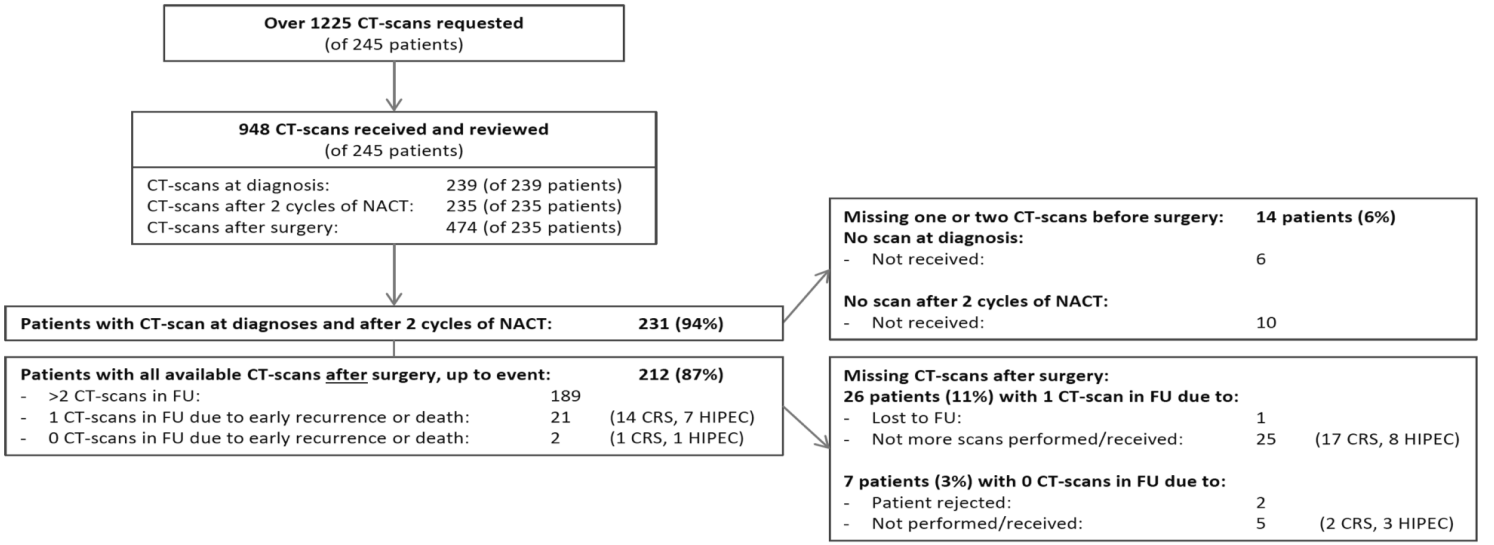

Figure 3.1. CONSORT diagram for availability of CT-scans and missing CT-scans

Death, or centrally reviewed events of recurrence occurred in 112/123 (91%) of the patients in the surgery alone group, and in 102/122 (84%) of the patients in the surgery plus HIPEC group (table 2). Centrally assessed median RFS was 9.9 months in the surgery group and 13.2 months in the surgery plus HIPEC group (hazard ratio for disease recurrence or death, 0.72; 95% CI, 0.55 to 0.94; P = 0.015 (figure 3.2). In exploratory subgroup analyses, the benefit of HIPEC on centrally assessed RFS and OS was irrespective of baseline peritoneal cancer index, peritoneal cancer index after two cycles of neoadjuvant chemotherapy, and radiologic response to neoadjuvant chemotherapy according to RECIST 1.1 (Figure 3.3A and 3.3B).

Table 3.2. Events of recurrent disease for patients included in the OVHIPEC trial

	CRS N=123		**CRS+ HIPEC** N=122	
Event of recurrence or death (central revision)*	**112**	**91%**	**102**	**84%**
unequivocal new lesion on CT	68	55%	50	41%
progression of lesions compared to previous CT†	21	17%	28	23%
recurrence based on clinical symptoms/CA-125 rise‡	15	12%	17	14%
recurrence without available CT-scan	5	4%	4	5%
death without recurrence	3	2%	3	3%
No recurrence	**11**	**9%**	**20**	**16%**

* if recurrence was based on clinical symptoms/CA-125 rise and a CT-scan within 4 weeks was available, this scan was also evaluated in this table

† date of progression was declared using the date of the initial scan

‡ or without availability of CT-scan within 4 weeks

Table 3.3. Site of recurrence disease in central revision

	CRS N=123		**CRS+ HIPEC N=122**	
Event of recurrence or death (central revision)*	**112**	**91%**	**102**	**84%**
peritoneal recurrence	82	73%	66	65%
- peritoneal recurrence only	*44*	*39%*	*39*	*38%*
- peritoneal and extra-peritoneal disease	*38*	*34%*	*27*	*26%*
extra-peritoneal recurrence only	7	6%	12	12%
recurrence based on clinical symptoms/CA-125 rise†	15	12%	17	14%
recurrence without available CT-scan	5	4%	4	5%
death without recurrence	3	2%	3	3%
No recurrence	**11**	**9%**	**20**	**16%**

* if recurrence was based on clinical symptoms/CA-125 rise and a CT-scan within 4 weeks was available, this scan was also evaluated in this table

† or without availability of CT-scan within 4 weeks

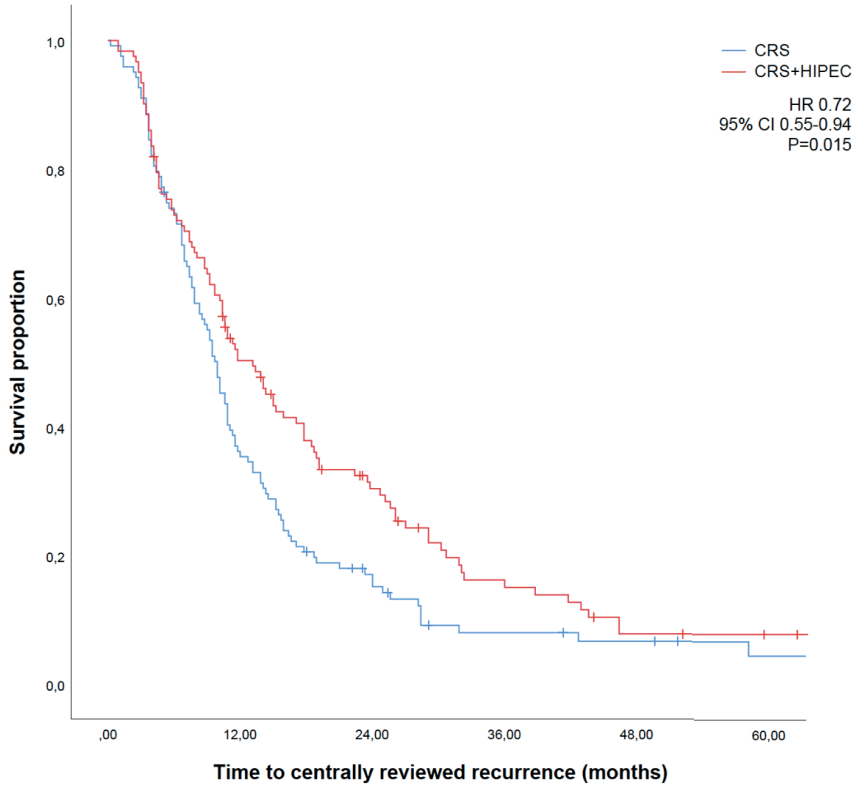

Figure 3.2. Recurrence-free survival curve based on centrally revised recurrences

Location of recurrence per treatment arm is listed in table 3. The cumulative incidence of peritoneal or extra-peritoneal recurrences was centrally reviewed. These analyses show significantly fewer peritoneal recurrences over time after treatment with interval CRS plus HIPEC (HR 0.72; 95% CI 0.52 to 0.99; Gray's test p = 0.046; figure 3.4A). There was no difference in the incidence of extra-peritoneal recurrences over time (HR 0.85; 95% CI 0.55 to 1.30; Gray's test p = 0.45; figure 3.4C). The most common location of extra-peritoneal disease was in enlarged lymph nodes on CT-scan (supplementary table 3.3). Sensitivity analyses in which recurrences based on CA-125, symptoms or recurrences without availability of CT-scan were considered either peritoneal or extra-peritoneal did not affect these results (figure 3.4B and 3.4D).

Subgroup	CRS	CRS + HIPEC	Hazard Ratio (99% CI)	p-value
	no. of events/total no.			
PCI baseline scan				
0-16	50/57	39/52	0.73 (0.42-1.27)	0.948
17-39	52/62	53/68	0.59 (0.35-0.98)	
PCI after 2 cycles of NACT				
0-11	45/56	38/56	0.75 (0.42-1.32)	0.461
12-39	57/63	51/60	0.58 (0.35-0.96)	
Response to NACT according to RECIST 1.1				
PR	31/40	35/49	0.86 (0.45-1.62)	0.536
SD	64/71	52/63	0.62 (0.38-1.00)	

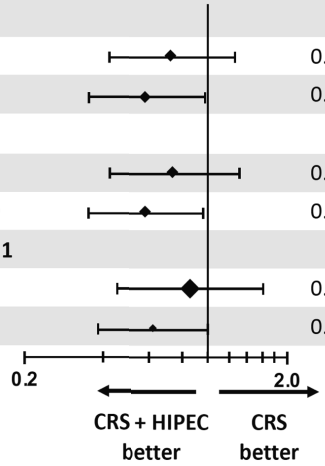

Figure 3.3. Panel A. Forest plot for exploratory subgroup analysis for the effect of HIPEC on recurrence-free survival

Subgroup	CRS	CRS + HIPEC	Hazard Ratio (99% CI)	p-value
	no. of events/total no.			
PCI baseline scan				
0-16	35/57	27/52	0.68 (0.35-1.32)	0.966
17-39	39/62	33/68	0.60 (0.32-1.10)	
PCI after 2 cycles of NACT				
0-11	27/56	28/56	0.89 (0.44-1.78)	0.137
12-39	45/63	31/60	0.58 (0.32-1.07)	
Response to NACT according to RECIST 1.1				
PR	22/40	22/49	0.71 (0.33-1.51)	0.438
SD	45/71	32/63	0.67 (0.37-1.21)	

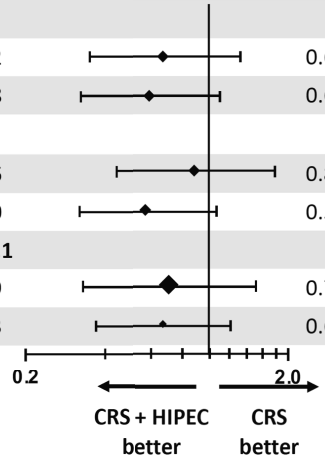

Figure 3.3. Panel B. Forest plot for exploratory subgroup analysis for the effect of HIPEC on overall survival

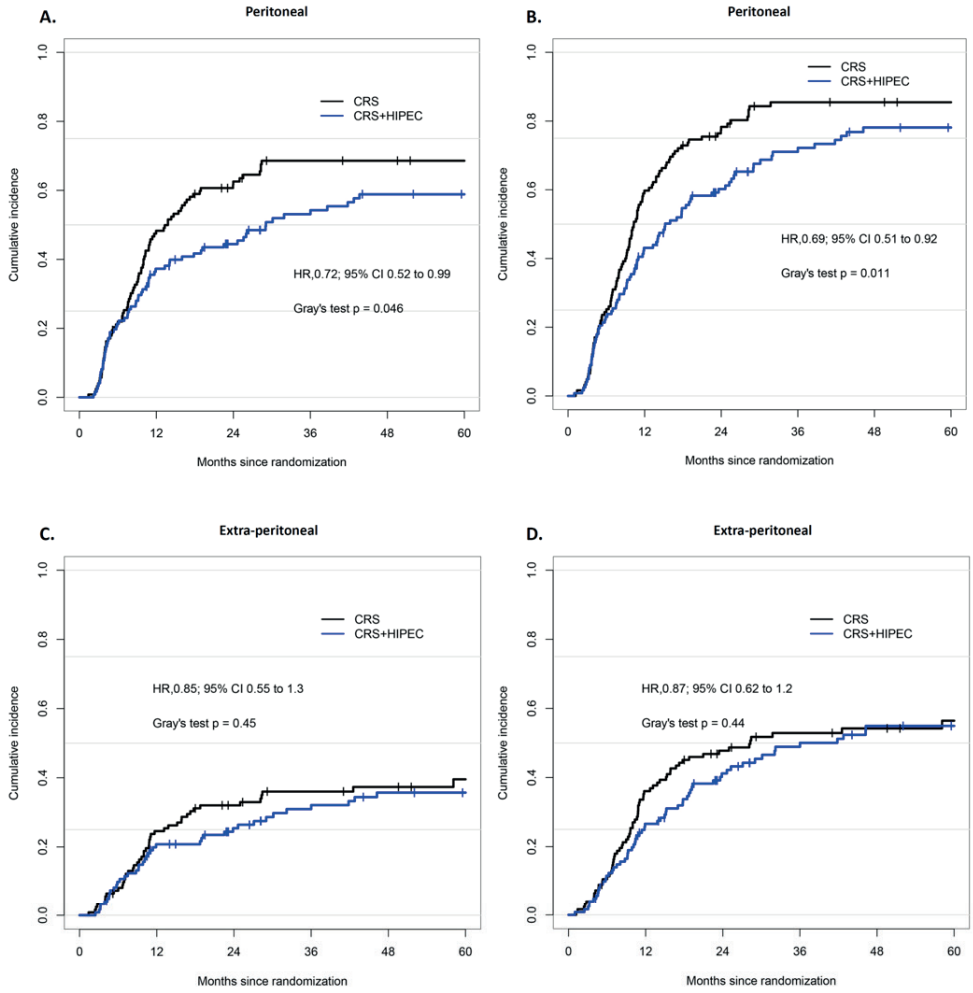

Figure 3.4. Cumulative incidence for peritoneal and extra-peritoneal recurrences based on central review, including sensitivity analysis for recurrences based on CA-125 rise, symptoms, or without availability of CT-scan.

Discussion

The multicenter, open-label phase III OVHIPEC-1 trial showed that the addition of HIPEC to interval cytoreductive surgery improves recurrence-free survival and overall survival in patients with FIGO stage III ovarian cancer by reducing the cumulative incidence of peritoneal recurrences.[14] The open-label design of the trial is potentially a source of bias in the assessment of recurrence-free survival as the primary outcome measure. This central blinded review of all imaging studies performed confirmed the earlier reported investigator-assessed recurrence-free survival benefit. The benefit of HIPEC based on central assessment (HR=0.72) was largely similar as the previously reported investigator-assessed primary endpoint of the study (HR 0.66), highlighting that the open-label design did not affect the assessment of recurrence-free survival.

The OVHIPEC-1 trial randomized patients during surgery once a (near-)complete cytoreduction was anticipated. This randomization process was approved by the hospitals' ethics boards and ensured equal distribution of baseline characteristics at surgery. Nevertheless, random imbalances may exist despite randomization and we previously showed that these imbalances in well-known prognostic factors in ovarian cancer were small and insignificant.[14, 20-22] These factors included age, histologic subtype, and prior surgery. In the present analyses, we provide further detail regarding findings at baseline imaging in both study arms. The majority of patients was diagnosed with FIGO stage IIIC ovarian cancer. Central revision was suspect for stage IV disease at baseline CT-scan in six patients (2%), essentially balanced across the study arms. As HIPEC is intended to provide high exposure to chemotherapy in tumor cells at the peritoneal surface, a meaningful effect in stage IV patients who have extra-peritoneal disease is not expected. Thus, the inclusion of stage IV patients may have slightly diluted the true effect of HIPEC in stage III patients, although this effect will have been very small given the very small number of stage IV patients.

The peritoneal cancer index was scored on CT-scan at baseline, and during neoadjuvant chemotherapy. As expected, mean peritoneal cancer index decreased during neoadjuvant chemotherapy, from a mean of 17 to a mean of 12, in both arms. Radiological response to neoadjuvant chemotherapy according to RECIST 1.1 was also similar in both treatment arms. In agreement with the eligibility criteria, no patient had evidence of disease progression during neo-adjuvant treatment. The effect of HIPEC was consistent across the levels of exploratory subgroups, including low and high baseline peritoneal cancer index and response to neo-adjuvant treatment. Although only patients with (near-)complete interval cytoreductive surgery were included in the OVHIPEC study, the radiological peritoneal cancer index at baseline ranged from 0-33 and from 0-31 after two cycles of neo-adjuvant chemotherapy. This observation indicates the variety of involvement of peritoneal disease. Complete cytoreduction remains the aim of surgery, and the additive value of HIPEC does not rely on peritoneal disease load upfront, but presumably microscopically remaining disease at the end. The effect of HIPEC was also consistent across the levels of pre-defined subgroups, including previous incomplete primary surgery (yes vs. no), the hospital in which the surgery was performed, and the number of involved regions in the abdominal cavity (0-5 vs. 6-8).[14]

This central review has some limitations. First, CT scans were planned at one, six, 12 and 24 months after the last cycle of chemotherapy or in case of a CA-125 rise or clinical symptoms. In clinical practice and according to national guidelines, screening for disease recurrences is not usually performed but triggered by symptoms. As a result, early, asymptomatic recurrences have been detected reducing the observed recurrence-free period in both arms. Second, the OVHIPEC-1 trial randomized patients after three cycles of neo-adjuvant chemotherapy, more than three months after the initial diagnosis. These three months should be taken into account when comparing the median recurrence-free and overall survival estimates to those in other trials that randomized patients with stage III ovarian cancer before the start of treatment.[20] Third, the number of CT-scans during follow-up was slightly lower in the surgery group than in the surgery plus HIPEC group. The lower number of CT-scans in the surgery group is often caused by early recurrences occurring after surgery without HIPEC, and only in few cases due to protocol violations.

Our analysis supports a targeted effect of HIPEC at the peritoneal surface as fewer peritoneal recurrences occur after HIPEC (Gray's test p-value 0.046), while the number of extra-peritoneal recurrences is similar with and without HIPEC (Gray's test p-value 0.45). These findings are in line with a case-control study that also showed fewer peritoneal recurrences after HIPEC.[23] HIPEC is thus a particular effective approach to target microscopic residual peritoneal disease as the penetration of systemic chemotherapy in tumor cells at the peritoneal surface is poor.[24]

In conclusion, the benefit of HIPEC was confirmed in a central blinded assessment of the OVHIPEC-1 trial's imaging results. This effect is independent of the response to systemic chemotherapy and extent of initial peritoneal involvement. HIPEC targets ovarian cancer cells at the peritoneal surface and specifically prevents peritoneal central recurrences when added to complete or near-complete interval cytoreductive surgery.

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Supplementary files chapter 3

Supplementary table 3.1: values of area under the curve ROC analysis for PCI score on overall survival

Test variable	AUC year 1	AUC year 2	AUC year 3
PCI at baseline	0.53	0.49	0.49
PCI after two cycles of NACT	0.56	0.55	0.59

Supplementary table 3.2a: availability of CT-scans per arm

Suppl table 2a: Availability of CT-scans per arm	**CRS (N=123)**	**CRS+HIPEC (N=122)**	**Total (N=245)**
CT-scans at diagnosis	119 (97%)	120 (98%)	239 (97%)
CT-scans after 2 cycles of NACT:	119 (97%)	116 (94%)	235 (96%)
- Patients with both scans before surgery	116 (94%)	115 (94%)	231 (94%)
CT-scans after surgery	220	254	474
Total	**458**	**489**	**947**

Supplementary table 3.2b: number of CT-scans in follow-up, per arm

Suppl table 3.2b: Nr. of scans in FU per arm	**CRS (N=123)**	**CRS+HIPEC (N=122)**	**Total (N=245)**
Patients with 5 CT-scans after surgery	0	1 (<1%)	1 (<1%)
Patients with 4 CT-scans after surgery	1 (<1%)	6 (5%)	7 (3%)
Patients with 3 CT-scans after surgery	11 (9%)	19 (16%)	30 (12%)
Patients with 2 CT-scans after surgery	76 (62%)	75 (62%)	151 (62%)
Patients with 1 CT-scans after surgery :			
- due to early progression or death	14 (11%)	7 (6%)	21 (9%)
- 1 CT scan: lost to FU	0	1 (<1%)	1 (<1%)
- 1 CT-scan: other missing (not received/ not performed)	17 (14%)	8 (7%)	25 (10%)
Patients with 0 CT-scans after surgery:			
- due to early progression or death	1 (<1%)	1 (<1%)	2 (<1%)
- 0 CT-scans: patient rejected scans in FU	1 (<1%)	1 (<1%)	2 (<1%)
- 0 CT-scans: missing (not received/not performed)	2 (2%)	3 (2%)	5 (2%)
Patients with all available CT-scans after surgery, up to event	103 (85%)	109 (89%)	212 (87%)

Supplementary table 3.3. Location of extra-peritoneal disease

	CRS N=45		CRS + HIPEC N=39	
Enlarged lymph nodes	29	64%	24	62%
Parenchymal metastasis (liver or spleen)	8	18%	9	23%
Lymph nodes + parenchymal metastasis	3	7%	2	5%
Abdominal wall	3	7%	3	8%
Pleural effusion	2	4%	0	
Brain	0		1	3%

CHAPTER 4

No influence of sarcopenia on survival of ovarian cancer patients in a prospective validation study

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Abstract

Background Decrease in skeletal muscle index (SMI) during neo-adjuvant chemotherapy has been associated with worse outcome in patients with advanced ovarian cancer. To validate these findings, we tested if a decrease in SMI was a prognostic factor for a homogenous cohort of patients who received neoadjuvant chemotherapy in the randomized phase 3 OVHIPEC-trial.

Methods CT-scans were performed at baseline and after two cycles of neo-adjuvant chemotherapy in stage III ovarian cancer patients. The SMI (skeletal muscle area in cm^2 divided by body surface area in m^2) was calculated using SliceOMatic software. The difference in SMI between both CT-scans (ΔSMI) was calculated. Cox-regression analyses were performed to analyze the independent effect of a difference in SMI (ΔSMI) on outcome. Log-rank tests were performed to plot recurrence-free (RFS) and overall survival (OS). The mean number of adverse events per patient were compared between groups using t-tests.

Results Paired CT-scans were available for 212 out of 245 patients (87%). Thirty-four of 74 patients (58%) in the group with a decrease in ΔSMI and 73 of 138 of the patients (53%) in the group with stable/increase in ΔSMI had died. Median RFS and OS did not differ significantly (p=0.297 and p=0.764) between groups. Patients with a decrease in SMI experienced more pre-operative adverse events, and more grade 3-4 adverse events.

Conclusion Decreased SMI during neo-adjuvant chemotherapy was not associated with worse outcome in patients with stage III ovarian cancer included in the OVHIPEC-trial. However, a strong association between decreasing SMI and adverse events was found.

Introduction

Epithelial ovarian cancer shows the highest mortality rate of all gynaecologic cancers in the western world.[1] The majority of patients is diagnosed with advanced stage disease, (FIGO ≥III).[2] For advanced stage patients, 10-year survival is only 10-15%, and survival has not improved over the past 20 years.[3] Standard treatment consists of maximum cytoreductive surgery (CRS) combined with chemotherapy consisting of carboplatin and paclitaxel. If complete primary CRS is not feasible, interval CRS might be performed after three cycles of neo-adjuvant chemotherapy.[4-6] Achieving a complete cytoreduction is the most important prognostic factor, in addition to the ability to complete six cycles of carboplatin and paclitaxel and the clinical condition of the patient.[7, 8] The clinical condition is reflected by multiple factors and besides subjective scores, such as the World Health Organization (WHO) performance score, we lack an objective measure of patient fitness. Sarcopenia might be such a measure, and might be predictive for treatment completion and outcome in patients with advanced stage ovarian cancer.

Sarcopenia is the loss of, or low, skeletal muscle mass.[9] The skeletal muscle mass of patients with cancer can be accurately quantified using a single lumbar CT image by the so-called skeletal muscle index (SMI).[10] Loss of skeletal muscle mass is associated with higher rates of chemotoxicity and impaired overall survival (OS) in ovarian cancer patients.[11-13] In an analysis of a retrospective cohort of 123 patients published by Rutten et al., loss of skeletal muscle mass during neoadjuvant chemotherapy was shown to be associated with worse outcome. However, multivariable analyses taking into account completeness of surgery, response to chemotherapy, and toxicity were not performed.[13] Although previous studies reported worse outcome in patients with ovarian cancer and either a low baseline SMI or a decrease in SMI during treatment, it is uncertain whether SMI is an independent prognostic factor or a measure of extensive disease and treatment burden and poor performance.[14-16] The aim of this study was to validate earlier results by Rutten et al. in the most homogenous cohort of ovarian cancer patients reported to date. We analyzed whether a decrease in SMI during neoadjuvant chemotherapy was associated with worse outcome in a cohort of patients with similar extent of disease; stage III epithelial ovarian cancer, and similar performance scores.

Methods

Patients and treatment

For this study, CT-scans were collected from patients included in the OVHIPEC trial.[17] This multicenter randomized phase III trial included 245 newly-diagnosed patients with stage III epithelial ovarian, fallopian tube, or peritoneal cancer between April 2007 and April 2016. Full eligibility criteria are presented elsewhere.[17] All patients received three cycles of intravenous chemotherapy (carboplatin [area under the curve 5-6 mg/ml per minute] and paclitaxel [175mg/m^2]) prior to interval cytoreductive surgery, because of extent of disease, or because of incomplete primary CRS (residual tumor > 1cm in diameter). Patients were eligible for inclusion in case of at least stable disease after two cycles of neoadjuvant chemotherapy. Randomization was performed during interval cytoreductive surgery when complete or optimal (no visible, or <1cm visible tumor remaining) CRS was anticipated. Patients were randomized to receive either interval CRS with or without HIPEC using

cisplatin 100mg/m^2. An additional three cycles of adjuvant intravenous carboplatin were administered after CRS for all patients. CT-scans were performed at diagnosis: before start of neoadjuvant chemotherapy, after 2 cycles of neoadjuvant chemotherapy, at the end of adjuvant chemotherapy, and at 6, 12, and 24 months after the last cycle of chemotherapy. Grade 1-5 toxicity was scored from baseline to 30 days after end of therapy, using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. All patients provided informed consent for participation. The trial protocol was approved by the institutional review board of the Netherlands Cancer Institute. The trial was registered in the international database: ClinicalTrials.gov Identifier: NCT00426257.

Body composition analysis

To analyze whether pre-operative sarcopenia and/or a skeletal muscle depletion were associated with worse outcome, CT-scans performed at baseline (timepoint 1) and after 2 cycles of neo-adjuvant chemotherapy (timepoint 2) were selected. The axial slide at the third lumbar level (L3), with the best representation of the bilateral transverse process was selected from each portal venous phase CT-scan. The axial CT-scan at the L3 level was used for evaluation of total skeletal muscle (SM). Predefined and previously validated cut-offs of -29 to +150 Hounsfield Units (HU)[18] for SM were used to demarcate tissue using SliceOmatic software (v5.0, Tomovision, Montreal, Canada). Evaluation of the demarcations was performed by one of two observers (JU & JB), both blinded for clinical characteristics, outcome and allocated treatment arm. An example of how tissues were delineated with SliceOmatic is shown in figure 4.1. The Skeletal Muscle Index (SMI) was calculated using the surface area of SM in cm^2 and the stature of the patient (squared height) in m^2. All data were coded and processed anonymously.

Changes in SMI from timepoint 1 to timepoint 2 were expressed as a percentage. To account for variations in time between the sequential CT-scans, the change in SMI was calculated as a percentage of change per 100 days. In order to do so, the change in SMI between the scan at timepoint 1 and timepoint 2 was divided by the number of days between the scans, and subsequently multiplied by 100. This is referred to as ΔSMI. A measurement error of 2% was adopted based on previously reported accuracy of CT for muscle and fat tissue analysis.[10] Patients with a decrease of >2% of SMI in 100 days were defined as the SMI-loss group. The 2% cutoff was also used by Rutten et al.[13] Other patients were defined as SMI-stable or increase.[10, 13]

Only CT-scans that were performed up to 10 weeks before start of chemotherapy, up to interval CRS surgery were selected. Scans at timepoint 1 had to be performed ten weeks to 1 day before start of neo-adjuvant chemotherapy. Scans at timepoint 2 had to be performed more than three weeks after start of neo-adjuvant chemotherapy but before interval CRS.

Statistical analyses

Comparisons between the SMI-loss and SMI-stable/increase group were performed with the t-test for continuous variables and the Pearson's chi-square test for categorical variables. Pre-operative toxicity was scored before start of chemotherapy, during neoadjuvant chemotherapy, or between neoadjuvant chemotherapy and surgery. Toxicity was divided into CTCAE grade 1-2 or grade 3-5 toxicity. The mean number of events per patient were presented and compared between groups using a t-test for independent samples. The

Welch t-test was used to compare the total number of pre-operative adverse events. Survival was compared for sarcopenic patients at timepoint 1 and timepoint 2, and for the SMI-loss group and the SMI-stable or increase group. Analyses of overall survival (OS) and recurrence-free survival (RFS) were performed using Kaplan-Meier estimates and log-rank tests. RFS was defined as the time from randomization to first-recurrence or death, whichever occurred first, as was defined by the GCIG criteria.[19] Univariable and multivariable cox regression analyses was performed for analyzing the effect of the different treatment arms on outcome, with ΔSMI and treatment arm (HIPEC or no HIPEC) as associated variables. Subgroup analyses were performed for interval CRS and interval CRS + HIPEC groups for OS and RFS. Statistical significance for all comparisons was determined at $p<0.05$. All analyses were performed with the statistical software package SPSS v.25.0 (IBM Corp, Chicago, IL, USA).

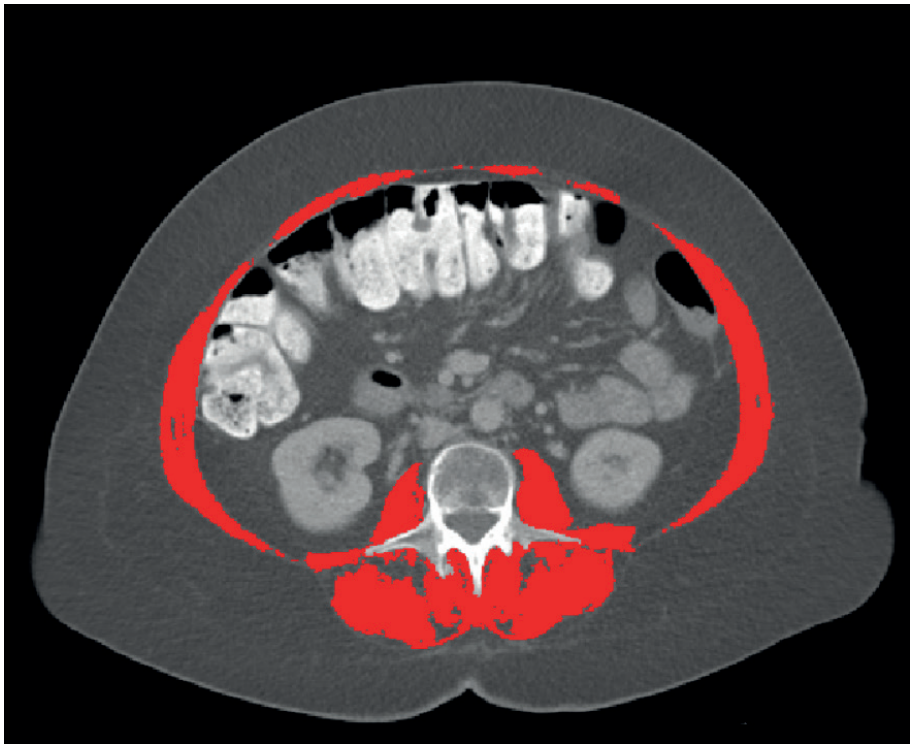

Figure 4.1. Abdominal axial CT scan of an ovarian cancer patient taken at the third lumbar level. Total skeletal muscle area in red.

Results

Paired CT-scans at baseline and after two cycles of neo-adjuvant chemotherapy were available for 221 out of 245 patients (90.2%). For 24 patients, CT-scans were not provided by the participating centers. Mean time between CT-scan 1 and CT-scan 2 was 60 days (SD 15.7). Mean time between cycles of neo-adjuvant chemotherapy and the interval CRS are presented in the supplementary material, table S4.1. The SMI and ΔSMI could not be calculated for nine patients (4.1%) because CT-scans were of insufficient quality or incomplete. The median SMI was 39.5 (range 27.5-57.9) at timepoint 1 and 38.1 (range 26.4-55.4) at timepoint 2. Means with SD of the SMI at timepoint 1 and 2, and ΔSMI are presented in supplementary table S4.2. The ΔSMI could be calculated for 212 patients. The mean ΔSMI was -5.9% (SD 11.8%), ranging from -31.6% to 46.9%. ΔSMI was lower than -2% in 138 patients and was stable or increased (higher than -2%) in 74 patients.

Baseline characteristics for all patients with SMI measurements are presented in table 4.1 and 4.2. The mean BMI in the SMI stable/ increase group was 20.9 (SD 3.6), and 19.7 (SD 3.1) in the SMI decrease group (p=0.025). Slightly more patients with a decrease in SMI were treated with HIPEC (n=74 (53.6%)), compared to the group with stable/increased SMI (n=29 (39.2%) p=0.045). Median OS was 41 months (95% confidence interval [CI] 36.1-45.9), and median RFS was 12 months (95% CI 10.6-13.4).

Toxicity and sarcopenia

Between enrollment and surgery, pre-operative toxicity was scored. A total of 1265 events were registered before interval cytoreductive surgery. The majority of the events was a CTCAE grade 1-2 event (1208/1265; 95.5%) (table 4.3). Within the group of patients with a decrease in SMI, a total of 893 events (70.6%) were reported, compared to 372 (29.4%) events in the stable/increase SMI group (p=0.008). The overall mean number of pre-operative events per patient was 6.2 (SD 3.9). The percentage of grade 3-4 events was higher in the group with a decrease in SMI (5.3%) than the percentage in the group with stable or increased SMI (2.6%). The mean number of pre-operative events was significantly higher: 6.7 (SD 3.9) in the group of patients whose SMI decreased versus 5.3 (SD 3.1) in the group with a stable or increased SMI (p=0.019) (table 4.3). Specific grade 3-4 toxicities are listed in supplementary table S4.5, and were mostly related to chemotherapy or cancer-related adverse events such as pulmonary embolisms.

Table 4.1. Patient and treatment characteristics

	Total cohort	SMI decrease >2%	SMI stable or SMI increase	
	N=212	N=138	N=74	P-value
Age, mean years (SD)	60.9 (8.1)	60.9 (8.2)	61.0 (7.8)	0.883
FIGO, Nr. (%)				
III	221 (100)	138 (100)	74 (100)	
Histological type (%)				0.469
High-grade serous	191 (90.1)	125 (90.6)	66 (89.2)	
Other	19 (9.0)	11 (8.0)	8 (10.8)	
Unknown	2 (0.9)	2 (1.4)	0	
BMI, mean kg/m^2 (SD)*				0.025
Baseline	20.5 (3.5)	20.9 (3.6)	19.7 (3.1)	
Weight, mean kg (SD)*				0.076
Baseline	68.9 (12.9)	70.1 (13.2)	66.8 (12.2)	
Primary incomplete debulking, Nr. (%)				0.884
yes	18 (8.5)	12 (8.7)	6 (8.1)	
no	194 (91.5)	126 (91.3)	68 (91.9)	
Outcome interval CRS, Nr. (%)†				0.936
R1	146 (68.9)	95 (68.8)	51 (68.9)	
R2a	40 (18.9)	26 (18.8)	14 (18.9)	
R2b	22 (10.4)	14 (10.1)	8 (10.8)	
Suboptimal	1 (0.5)	1 (0.7)	0	
No resection	1 (0.5)	1 (0.7)	0	
No surgery	2 (0.9)	1 (0.7)	1 (1.4)	
Treatment with HIPEC, Nr (%)				0.045
HIPEC	103 (48.6)	74 (53.6)	29 (39.2)	
No HIPEC	109 (51.4)	64 (46.4)	45 (60.8)	
Six cycles of chemotherapy completed, Nr. (%)				0.895
Yes	197 (92.9)	128 (92.8)	69 (93.2)	
No	15 (7.1)	10 (7.2)	5 (6.8)	

* based on known values

† R1: no visible tumor, complete cytoreduction; R2a: tumor nodules ≤2.5 mm; R2b: tumor nodules >2.5 mm and ≤10 mm; suboptimal: tumor nodules >10 mm, incomplete cytoreduction

Table 4.2. CT-scans and body composition characteristics

	Total cohort	SMI decrease >2%	SMI stable or SMI increase	
	N=212	**N=138**	**N=74**	**P-value**
Nr. of days between scan 1-2, mean (SD)				
	60.3 (15.7)	60.1 (16.0)	60.6 (15.3)	0.841
Nr. of days between start neoadjuvant chemotherapy and scan 2, mean (SD)*				
	36.8 (8.0)	36.66 (7.5)	37.1 (9.0)	0.727
SMI, mean cm^2/m^2 (SD)				
Baseline	39.5 (5.4)	40.7 (5.3)	37.4 (4.0)	<0.001
After 2 cycles of NACT	38.1 (5.0)	37.8 (5.0)	38.6 (5.0)	0.252
% of change (range)	-5.9%	-12.3	6.0%	<0.001
	(-31.6% to 46.9%)	(-31.6% to -2.3%)	(-2.0%-46.9%)	
SMRA, mean HU (SD)*				
Baseline	36.0 (7.8)	35.7 (7.6)	36.5 (8.2)	0.464
After 2 cycles of NACT	36.6 (7.5)	35.6 (7.2)	38.5 (7.7)	0.007
OS, median months (95% CI)	41 (36.11-45.89)	41 (34.18-47.82)	41 (35.54-46.46)	0.764
RFS, median months (95% CI)	12 (10.63-13.37)	11 (9.49-12.51)	13 (10.24-15.76)	0.297

Table 4.3. association of decrease in SMI with adverse events

	Total cohort	SMI decrease >2%	SMI stable or SMI increase	P-value
	N=203	N=133	N=70	
Mean number of adverse events pre-operative (SD)*				
Gr1-2	5.9 (3.7)	6.4 (3.9)	5.2 (3.1)	0.044
Gr3-4	0.3 (0.7)	0.4 (0.8)	0.1 (0.4)	<0.001
Mean N of events pre-op per pt	6.2 (3.9)	6.7 (4.2)	5.3 (3.1)	0.019
Total number of adverse events pre-operative*				
Total Gr1-2 (range per patient)	1208 (0-22)	846 (0-22)	362 (1-13)	0.018
Total Gr3-4 (range per patient)	57 (0-4)	47 (0-4)	10 (0-2)	0.016
Total nr of events (range per patient)	1265 (1-25)	893 (1-25)	372 (1-13)	0.008

* based on known values

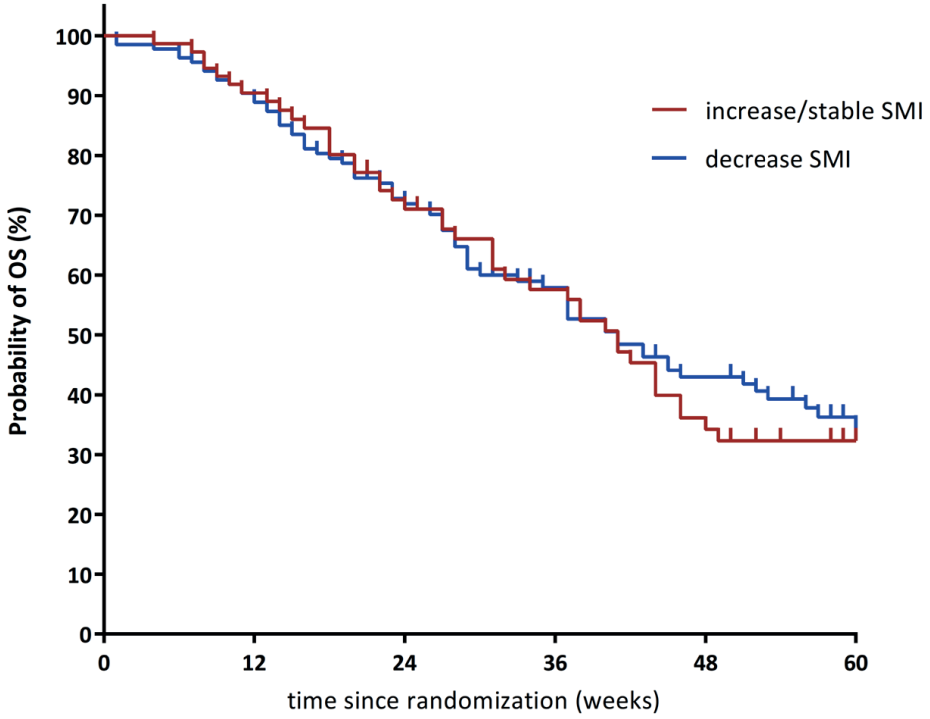

Figure 4.2. Kaplan-Meier survival analysis. SMI; skeletalmuscle index, plotted is an increase vs. decrease in SMI and the association with overall survival.

P-value	0.764		
	Total N	**N of events**	**%**
ΔSMI >-2	74	43	58
ΔSMI =<-2	138	73	53
Overall	**212**	**116**	**55**

Sarcopenia and survival

After a median of 4.7 years of follow-up, 116 of 212 patients (55%) had died and 181 of 212 patients (85%) experienced an event of disease-recurrence or death. Survival analysis revealed that 43 of 74 patients (58%) with a more than 2% decrease in SMI versus 73 of 138 (53%) of the patients with a stable or increased SMI had died. Median overall survival did not differ significantly between these two groups (p=0.764, figure 4.2).

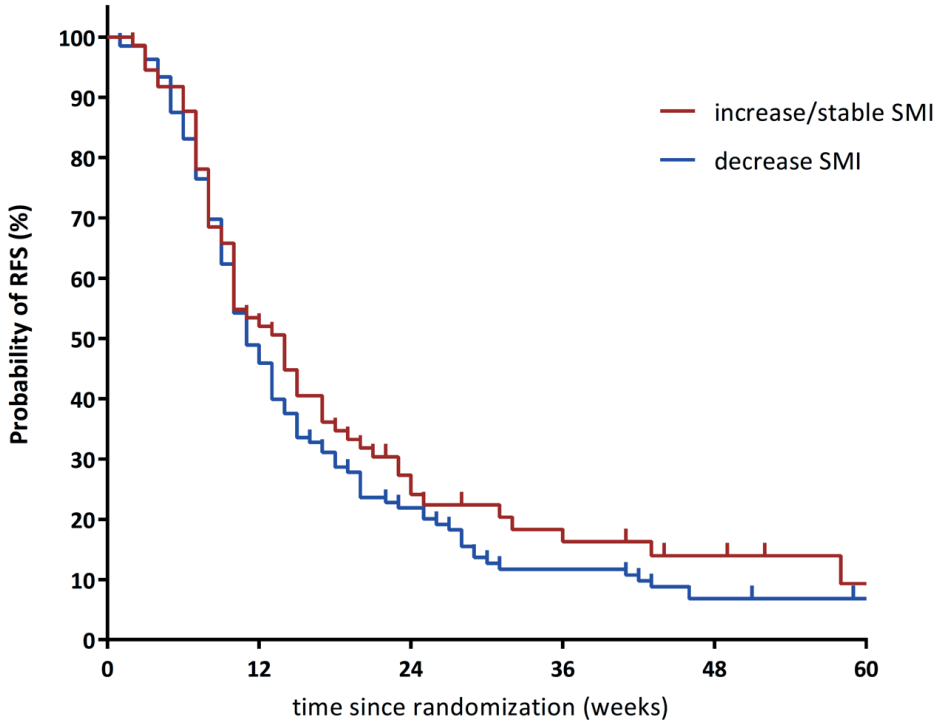

Figure 4.3. Kaplan-Meier survival analysis. SMI; skeletalmuscle index, plotted is an increase vs. decrease in SMI and the association with recurrence free survival.

P-value	0.297		
	Total N	**N of events**	**%**
ΔSMI >-2	74	61	82
ΔSMI =<-2	138	120	87
Overall	**212**	**181**	**85**

Sixty-one of 74 (82%) patients in the ΔSMI decrease group had disease recurrence, compared to 120 of 138 (87%) in the ΔSMI stable/increase group. Median recurrence-free survival was similar (p=0.297, figure 4.3). ΔSMI was also not associated with overall survival and recurrence-free survival after correcting for differences in baseline characteristics and treatment effect in multivariable analysis (supplementary tables S4.3 and S4.4, respectively).

Discussion

The primary goal of this study was to validate the previously published finding that a decline in SMI during neo-adjuvant chemotherapy in ovarian cancer patients was associated with worse OS.[13] Although a loss of skeletal muscle mass was detected in the present cohort, inclusion criteria allowed only for randomization of patients with prognostically favorable characteristics such as good response to chemotherapy or complete- or optimal cytoreduction. This selection of patients might have resulted in negative validation of the results as published by Rutten et al. Nevertheless, a strong association between decreasing SMI and adverse events was found.

Rutten et al. showed that ovarian cancer patients with a decrease in SMI (>2%/100 days) had a significant (p=0.004) survival disadvantage (median OS 916±99 days) as opposed to patients who showed stable or increased SMI (median OS 1431±470 days) [13]. The patient cohort presented by Rutten et al. is essentially different regarding a number of aspects: 1) patients were older (mean age 60.9 [present] vs. 66.5 [Rutten et al.]), 2) had higher FIGO stage (III [present] vs. III-IV [Rutten et al.]), 3) received more chemotherapy between CT-scans (2 [present] vs. 3 cycles [Rutten et al.]), and 4) had worse outcome of CRS (68% [present] vs. 45.5% [Rutten et al.] patients with complete debulking surgery). The present study included patients under the age of 76, who were fit for major surgery (ASA1-2 and WHO performance score 0-2), had adequate organ function, and had only FIGO stage III disease[17]. In addition, only patients with a complete or partial response, or stable disease after two cycles, were selected. However, the mean decrease of SMI in both cohorts was quite similar (5.9%/100 days present cohort vs. 5.2%/100 days in the Rutten et al. cohort).

During neo-adjuvant chemotherapy, patients with a decrease in SMI had a significantly higher number of toxicities of any grade (6.7, SD: 4.2 vs. 5.3; SD: 3.1, p=0.008) (table 4.3). This might indicate that skeletal muscle depletion is a measure of clinical fitness which impacts the patients' ability to receive treatment and thereby affects survival, rather than being an independent prognostic variable. Earlier findings already indicated that increased toxicity from chemotherapy is related to lower lean body mass, which results in reduced volume of distribution, protein binding, metabolism, and clearance of drugs[20]. The group of patients who lost skeletal muscle during chemotherapy had a slightly higher baseline BMI (20.9, SD 3.6) compared to the group of patients with stable/increased muscle mass (19.7, SD 3.1). It is not clear whether this slightly higher baseline BMI contributes to a greater decrease in skeletal muscle mass.[21]

The association between a decrease in SMI and outcome that was previously described [13]may be attributed to the fact that relatively frail patients were studied that did not meet the inclusion criteria for the OVHIPEC-1 trial, but had a poor outcome due to adverse events, dose modifications or incomplete surgery. The strong relationship with reported toxicities in the current study is in line with this explanation. One of the main shortcomings of the current survival analysis is that it was not powered for analysis of OS/RFS, or for any subgroup analyses. All participants in the OVHIPEC-1 trial were included for analysis with the assumption that sarcopenic patients were evenly distributed over both treatment arms. However, slightly more patients were treated with HIPEC in the group with a decrease

in SMI. Multivariate analysis for treatment arm (HIPEC vs. no HIPEC) and for ΔSMI were performed to evaluate the independent effect of ΔSMI without the potential mask by treatment with HIPEC (supplementary table S4.3 and S4.4). Skeletal muscle mass was not an independent prognostic factor for recurrence-free and overall survival in multivariable analysis. Due to its prospective nature, this cohort is the most homogeneous described to date, and important confounders for outcome (FIGO stage, performance score, and surgical treatment) which were present in previous studies have been eliminated. The strict inclusion criteria in the current study make it difficult to generalize our findings to the general ovarian cancer patient population. Assessment of SMI was performed according to accepted methods[10, 22, 23]. The effect of a decrease in SMI was assessed independently of treatment with HIPEC in multivariable analysis. Since a survival disadvantage was not detected for patients with skeletal muscle mass loss, it is expected that optimal resection of the tumor is of greater importance for OS than adverse body composition. Based on previous cohorts, the association between adverse body composition and OS might still be of importance in older patients, or patients in whom complete resection of the tumor is not feasible. Due to the nature of the selected cohort, however, these patients were not analyzed[14, 15, 24, 25]. Multivariate analyses that consider important prognostic variables such as treatment response, completeness of surgery, and toxicities could reveal if a decrease in body composition might be an independent predictor in other cohorts.

Conclusion

A change in SMI during 2 cycles of neoadjuvant chemotherapy was not associated with outcome within a large cohort of patients included in the OVHIPEC-1 trial. In the current population, with relatively good prognostic characteristics, a loss of skeletal muscle mass is not an independent predictor for survival. In this selection of patients, we observed a significant association of sarcopenia with reported toxicities. Whether loss of skeletal muscle mass is related to patient performance status, toxicity or treatment burden should be confirmed in future analyses.

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Supplementary files chapter 4

Table S4.1. Timing of CT-scans

	Mean (SD)	Range	
Time between Scan 1 and start NACT	2.92 (1.88)	0-9	Nr. of weeks prior to NACT
Time between Scan 1 and iCRS	13.98 (2.24)	9-22	Nr.of weeks prior to iCRS
Time between start NACT and Scan 2	4.89 (1.20)	3-9	Nr. of weeks after NACT
Time between Scan 2 and iCRS	5.34 (1.37)	2-10	Nr. of weeks prior to iCRS
Time between Scan 1 and Scan 2	60.55 (16.91)	31-121	Nr of days between scan 1-2

Table S4.2. Exploration of parameters

	Median	Mean	SE	SD	Range	33.33 percentile
SMI1 (N=212)	39.49	39.55	0.37	5.42	27.54-57.93	37.27
SMI2 (N=212)	38.31	38.08	0.34	4.98	26.44-55.40	35.79
DeltaSMI per 100 days (N=212)	-5.42%	-5.91%	0.81	11.77%	-31.61%-46.93%	
HU1 (N=220)	35.87	36.08	0.53	7.91	17.91-56.60	31.92
HU2 (N=221)	36.43	36.59	0.51	7.65	17.91-59.40	32.78

Table S4.3. Multivariable cox regression analyses for effect on overall survival

Risk factor	Univariate			Multivariate		
	HR	95%-CI	p-value	HR	95%-CI	p-value
ΔSMI	1.059	0.726-1.544	0.766	0.987	0.674-1.447	0.948
Treatment arm	0.668	0.462-0.965	0.032	0.667	0.459-0.968	0.033

HR; hazard ratio, 95%-CI; 95% confidence interval, SMI; skeletal muscle index

Table S4.4. Multivariable cox regression analyses for effect on recurrence-free survival

Risk factor	Univariate			Multivariate		
	HR	95%-CI	p-value	HR	95%-CI	p-value
ΔSMI	0.853	0.627-1.162	0.314	0.801	0.586-1.095	0.165
Treatment arm	0.697	0.550-0.935	0.016	0.675	0.501-0.908	0.010

HR; hazard ratio, 95%-CI; 95% confidence interval, SMI; skeletal muscle index

Table S4.5. Grade III and grade IV toxicity in both groups

	SMI decrease >2% N=133		SMI stable or SMI increase N=70	
Pulmonary embolism	8	6%	0	0%
Leukocytopenia/neutropenia	6	5%	2	3%
Cardiac symptoms	4	3%	1	1%
Peripheral neuropathy	4	3%	0	0%
Abdominal pain	3	2%	1	1%
Renal insufficiency	3	2%	0	0%
Fatigue	2	2%	1	1%
Abdominal distension (ascites)	2	2%	0	0%
Diarrhea	2	2%	0	0%
Dyspnea	2	2%	0	0%
Ileus	2	2%	0	0%
Thrombo-embolic event	2	2%	0	0%
Infection	1	1%	2	3%
Thrombocytopenia	1	1%	2	3%
Constipation	1	1%	0	0%
Dyspareunia	1	1%	0	0%
Liver function anormality	1	1%	0	0%
Loss of concentration	1	1%	0	0%
Syncope	1	1%	0	0%
Allergic reaction to paclitaxel	0	0%	1	1%
Total	47		10	

Figure S4.1. ROC curve for recurrence-free survival and different outcome variables

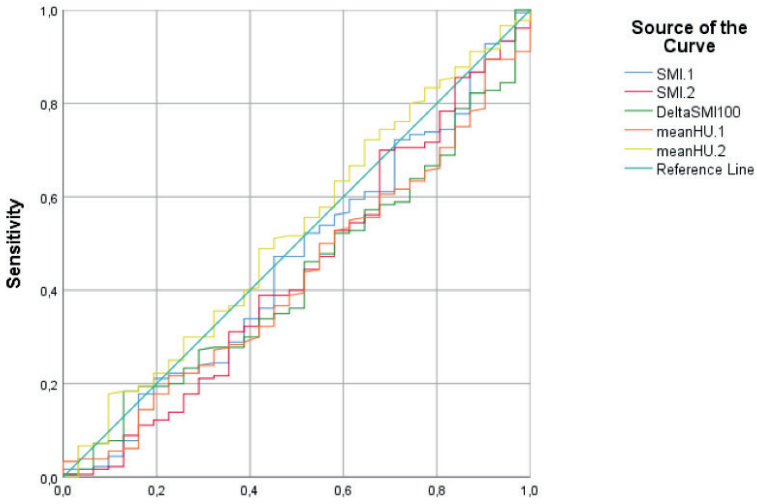
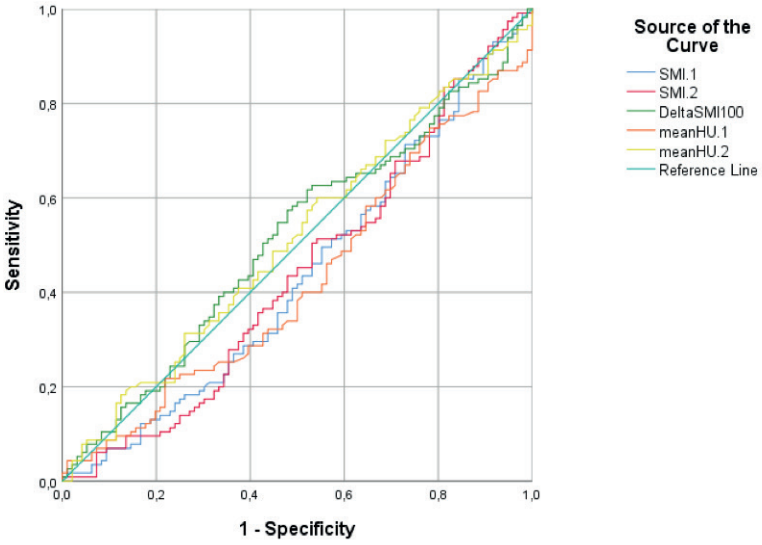


Figure S4.2. ROC curve for overall survival and different outcome variables



CHAPTER 5

Health-related quality of life after interval cytoreductive surgery with or without HIPEC

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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-1 trial.

Methods OVHIPEC-1 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 analyzed 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. These HRQoL results, together with the improvement in RFS and OS, support the viability of HIPEC as an important treatment option in this patient population.

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 gynecologic 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 therefore of interest in patients with ovarian cancer. Previous trials evaluating adjuvant IP chemotherapy in combination with IV chemotherapy as an addition to 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 symptoms such as nausea and vomiting. Catheter-related problems and increased toxicity limit the broad uptake of IP chemotherapy in clinical practice.[7, 8] 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-1 trial was a randomized phase III trial that demonstrated a recurrence-free and overall survival benefit for the addition of HIPEC to interval CRS in patients with stage III ovarian cancer.[9] 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 148 minutes and total hospital stay by two days but did not increase the incidence of adverse events.[9]

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.[10] We assessed the effect of the addition of HIPEC on the patients' symptom burden and HRQoL in the OVHIPEC-1 trial.

Methods

Participants

The OVHIPEC-1 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 described in chapter 2. 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.

Study design and procedures

Neoadjuvant chemotherapy consisted of carboplatin (area under the curve [AUC] of 5-6 mg/ml/min) and paclitaxel (175 mg/m^2 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 to 5 vs. 6 to 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 which case randomization then took place.

HIPEC was administered at the end of the cytoreductive surgical procedure with the use of the open technique. The abdomen was filled with saline, the perfusion fluid was heated by continuous circulation through a heat exchanger after which perfusion with cisplatin (100mg/m^2 of BSA) was initiated (full method described elsewhere).[9] The HIPEC procedure took 120 minutes in total, including 90-minute 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 six hours. Urine production was regulated during and three hours after surgery. After HIPEC, patients had a 1-day stay in the intensive care unit per protocol. All patients received three additional cycles of carboplatin and paclitaxel 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.

Outcomes

HRQoL was a secondary endpoint of the OVHIPEC-1 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 described in chapter 2.

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 (dyspnea, insomnia, appetite loss, constipation, and diarrhea), a question on financial impact; and a two-item global quality of life scale.[11] An overall QLQ-C30 summary score can also be calculated.[12]

The QLQ-OV28 is a 28-item ovarian cancer-specific questionnaire module designed to supplement the QLQ-C30.[13] 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 other 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).[14]

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 calculates scale scores, ranging from 0-100. For functional scales, higher scores represent higher levels of functioning. For symptom scales, higher scores indicate more symptom burden.[15] 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.[15] 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.

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 analyzed 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. 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 questionnaire administration

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 analyzed using a growth curve modeling approach, based on maximum likelihood estimation with random intercept and slope.[16] This approach takes the within and between-person variability into account, and deals adequately with missing data.[17] To test non-linear growth trajectories we included higher order polynominal trends (i.e., quadratic or cubic slopes) to the model. To test if the non-linear growth trajectory was appropriate, we used the Bayesian Information Criterion (BIC) and the Akaike's Information Criterion (AIC).

The missing-data pattern was analyzed using dummy-coded variables, which were added to the model. Subjects were divided into groups depending on their missing data pattern. To analyze the data-pattern, the observation period was divided into three time points: (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**t*)/(√*df*)).[18] An ES of 0.20 was considered small, 0.50 moderate and clinically significant, and an ES of 0.80 was considered large.[19, 20]

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 5.1). The number of completed HRQoL questionnaires included in the intention-to-treat-analysis is shown in table 5.2. A total of 613 questionnaires were analyzed; 269 (44%) completed by patients treated with interval CRS, and 344 (56%) completed by patients treated with CRS and HIPEC. Completed questionnaires not fitting the criteria for analyses were excluded (figure 5.1). 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.

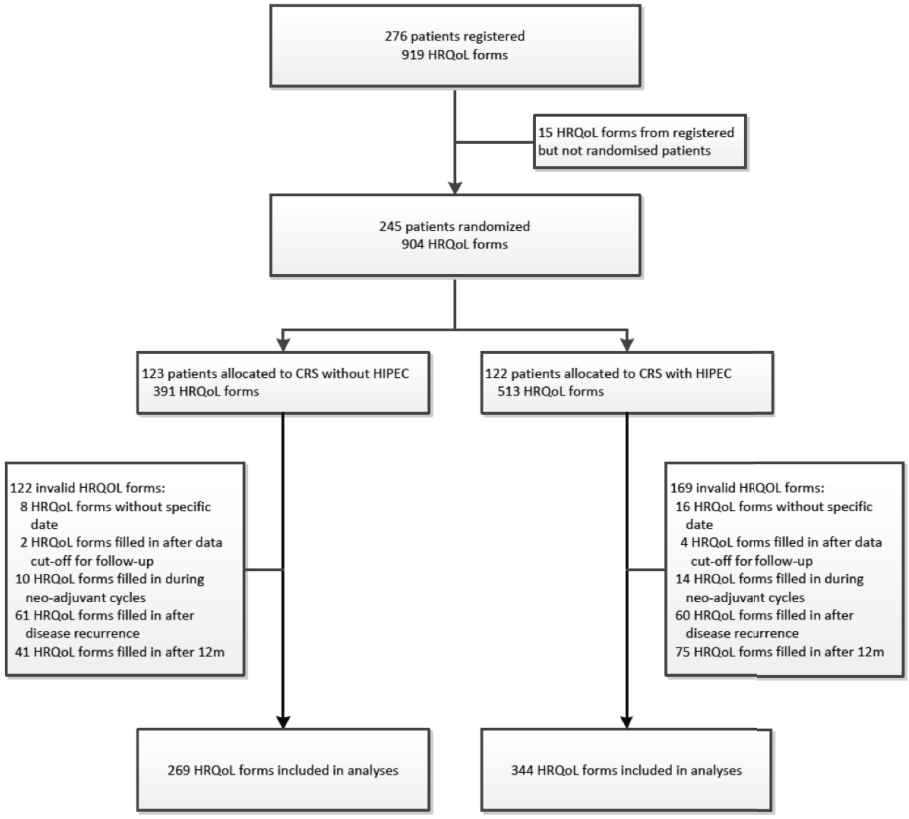

Figure 5.1. Consort diagram for the HRQoL component of the OVHIPEC-1 trial
HRQoL: health-related quality of life, CRS: cytoreductive surgery, HIPEC: hyperthermic intraperitoneal chemotherapy, EOT: end of treatment.

Table 5.1. Baseline and treatment characteristics*

	HRQoL population	
	Interval CRS (N=91)	**Interval CRS and HIPEC (N=106)**
Baseline characteristics		
Median age – yr (IQR)	63 (56-67)	62 (55-67)
Previous surgery – no. (%)		
Yes	11 (12)	11 (10)
No	80 (88)	95 (90)
No. of involved regions (%)		
0-5	63 (69)	73 (69)
6-8	28 (31)	33 (31)
Treatment characteristics		
Residual disease after surgery – no. (%)		
R-1, no visible tumour, complete cytoreduction	61 (68)	74 (70)
R-2a, tumour nodules ≤2.5 mm	19 (21)	18 (17)
R-2b, tumour nodules >2.5 mm and ≤10 mm	8 (9)	12 (11)
Tumour nodules >10 mm, incomplete cytoreduction	1 (1)	0 (0)
No resection†	1 (1)	1 (1)
No surgery performed	0 (0)	0 (0)
Bowel resections – no. (%)		
No bowel resection performed	66 (73)	80 (75)
Bowel resection without ileo-/colostomy	15 (16)	7 (7)
Bowel resection with ileo-/colostomy	10 (11)	19 (18)
Median duration of surgery– min (IQR)	190 (153 – 246)	342 (300 – 430)
Median duration of hospitalization – days (IQR)‡	8 (7 – 11)	10 (8 – 13)
Median time between surgery and start of first cycle of adjuvant chemotherapy - days (IQR)	30 (25 – 40)	33 (27 – 42)

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, with the exception of the rate of ileostomy or colostomy among the patients who had a bowel resection (13/30 vs. 21/29, p=0.04)

Within the total sample, there were no significant differences (13/123 vs. 21/122, p=0.19)

Percentages may not sum to 100 because of rounding

† Surgery was performed, but no resection was possible

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

Table 5.2. 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	71	127
Follow-up until 15 weeks after EOT	68	67	135
Follow-up 16-30 weeks after EOT	49	72	121
Follow-up 31-45 weeks after EOT	35	48	83
Follow-up 46 weeks -1 year after EOT	12	28	40
Sum	**269**	**344**	**613**

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

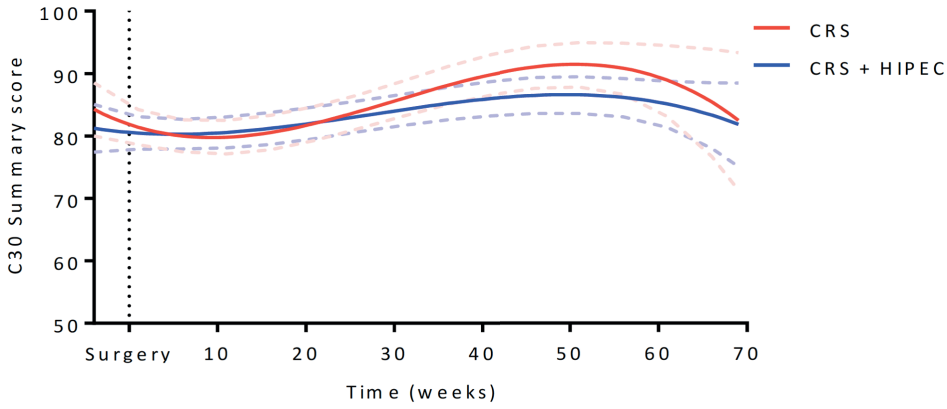

Figure 5.2. Trajectories of the QLQ-C30 summary score for both trial arms.
Trajectories are pictured with 95% pointwise Confidence Intervals. QLQ-C30: the EORTC Quality of Life core Questionnaire. For the C30 summary scale, higher scores represent higher levels of functioning.

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) (figure 5.2).

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) (figure 5.3). Gastro-intestinal symptoms first decreased slightly (*p*=0.001; ES=-0.31), and then increased during follow-up (*p*=0.009; ES=0.25) (figure 5.4). No significant between-group differences over time were observed for any of the other scales of the QLQ-C30, QLQ-OV28 or QLQ-C38, with the exception of appetite loss, which showed a statistically significant, but not a clinically significant greater decrease in patients treated with HIPEC (*p*=0.019; ES=-0.20).

Additional results from the QLQ-C30, the QLQ-OV28 or the QLQ-C38 questionnaires
In the total group, global quality of life (p=0.002), physical (p<0.001) and role functioning scales (p =0.001) decreased and then increased (p<0.001), without differences between arms. Scores for sexuality decreased over time (p=0.006). Scores for social functioning (p<0.001), body image (p=0.011), attitude (p<0.001) and future perspective (p<0.001) increased over time. Overall, symptoms for dyspnea (p=0.010), nausea/vomiting (p=0.001), abdominal problems (p=0.003), hair-loss (p<0.001) and chemotherapy side effects (p<0.001) significantly decreased over time. Scores for appetite loss showed a statistically significant, but not a clinically significant greater decrease in patients treated with HIPEC (p=0.019; ES=-0.20). The trend for appetite loss exhibited a linear decrease over time for the entire sample (p<0.001; ES=-0.43). For micturition, complaints decreased (p<0.001) after surgery but slightly increased during follow-up. No changes in emotional functioning, cognitive functioning, pain, insomnia, constipation, diarrhea or financial impact were observed over time.

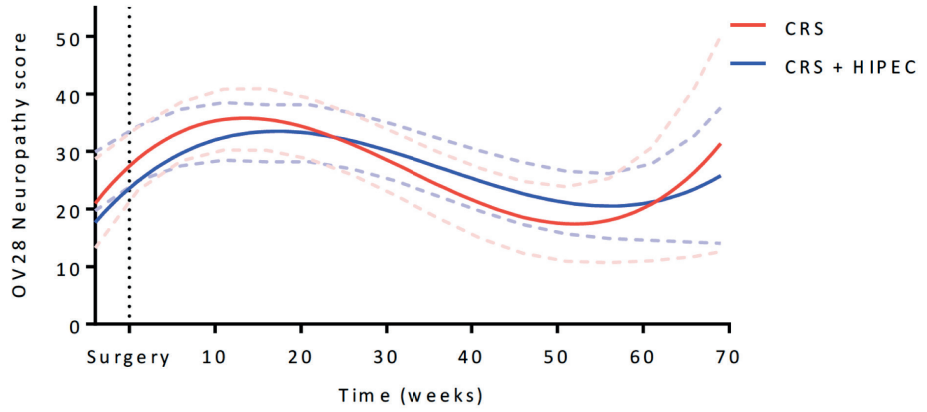

Figure 5.3. Trajectories of QLQ-OV28 Neuropathy scores for both trial arms. Trajectories are pictured with 95% pointwise Confidence Intervals. QLQ-OV28: the EORTC disease-specific questionnaire module for ovarian cancer. For the symptom scales on neuropathy higher scores indicate more symptom burden.

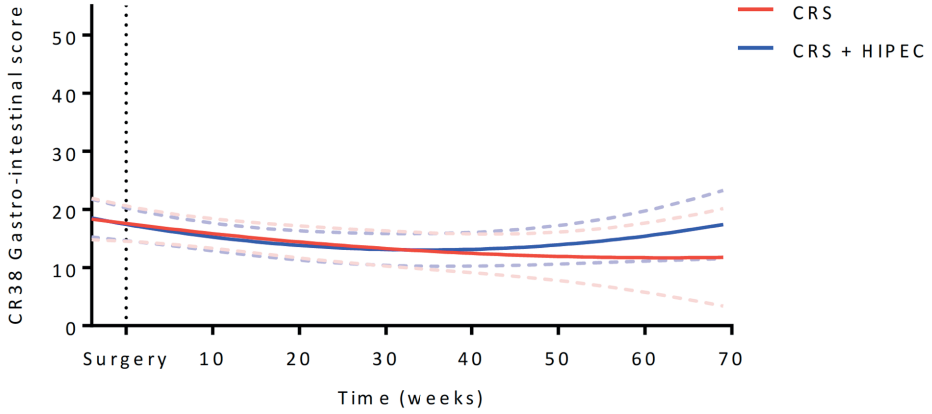

Figure 5.4. Trajectories of QLQ-CR38 Gastro-intestinal symptom scores for both trial arms. Trajectories are pictured with 95% pointwise Confidence Intervals. CRS: cytoreductive surgery, HIPEC: hyperthermic intraperitoneal chemotherapy, QLQ-CR38: the EORTC disease-specific questionnaire module for colorectal cancer. For the symptom scales on gastro-intestinal symptoms, higher scores indicate more symptom burden.

Discussion

The addition of HIPEC to interval CRS in patients with stage III ovarian cancer results in significant recurrence-free and overall survival benefit.[9] Because of the more intensive nature of surgery including HIPEC, concern has been voiced about a potential increase in adverse events and compromised HRQoL.[21] 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).[9] 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.[21-23] 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.[23, 24] 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).[9] Previous studies looking into the HRQoL of patients with colostomies showed higher symptom burden, which should be considered in daily practice.[25, 26]

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 progression. Since the group treated with interval CRS-only 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 figure 5.2, 5.3, and 5.4) 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 and in 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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CHAPTER 6

Cost-effectiveness of treatment with interval cytoreductive surgery and HIPEC for ovarian cancer

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Cost effectiveness of interval cytoreductive surgery with hyperthermic intraperitoneal chemotherapy in stage III ovarian cancer on the basis of a randomized phase III trial.
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Abstract

Background In the randomized open-label phase III OVHIPEC- 1trial, the addition of hyperthermic intraperitoneal chemotherapy (HIPEC) to interval cytoreductive surgery (CRS) improved recurrence-free and overall survival in patients with stage III ovarian cancer. We studied the cost-effectiveness analysis of the addition of HIPEC to interval CRS in patients with ovarian cancer.

Methods We constructed a Markov health-state transition model to measure costs and clinical outcomes. Transition probabilities were derived from the OVHIPEC- 1 trial by fitting survival distributions. Incremental cost-effectiveness ratio (ICER), expressed as euro per quality-adjusted life-year (QALY) was calculated from a Dutch societal perspective, with a time horizon of ten years. Univariable and probabilistic sensitivity analyses were conducted to evaluate the decision uncertainty.

Results Total healthcare costs were €70,046 (95% Credibility Interval [CrI], €64,016-€76,661) for interval CRS compared to €85,791 (95% CrI, €78,766-€93,935) for interval CRS+HIPEC. The mean QALY in the interval CRS group was 2.12 (95% CrI, 1.66-2.64), and 2.68 (95% CrI, 2.11-3.28) in the interval CRS+HIPEC group. The ICER amounted to €28,299/QALY. In univariable sensitivity analysis, the utility of recurrence-free survival and the number of days in the hospital affected the calculated ICER most.

Conclusion Based on the trial data, treatment with interval CRS and HIPEC in patients with stage III ovarian cancer is accompanied by a substantial gain in QALYs. The ICER is under the willingness-to-pay threshold in the Netherlands, indicating interval CRS and HIPEC is cost effective for this patient population. These results lend further support for reimbursing the costs of treating these patients with interval CRS and HIPEC in countries with comparable health care systems.

Introduction

Epithelial ovarian cancer has the highest mortality of all gynecologic tumors in the western world. Most patients are diagnosed with International Federation for Gynecology and Obstetrics (FIGO) stage III/IV disease.[1] The ten-year survival of women with advanced stage ovarian cancer is 10-15% and did not improve in the past 20 years.[2, 3] Despite treatment with maximal cytoreductive surgery (CRS) and platinum-based chemotherapy, around 70% of patients with advanced stage disease relapse within 18 months. Given this high number of recurrences, new approaches are needed to improve outcomes for these patients.

Since the peritoneal surface is the primary site of recurrence in ovarian cancer, administering chemotherapy directly in the abdominal cavity maximizes drug exposure. Local hyperthermia may have a direct cytotoxic effect and may increase drug sensitivity of tumor cells. We previously showed improved recurrence-free survival (RFS) and overall survival (OS) when hyperthermic intraperitoneal chemotherapy (HIPEC) was added to interval CRS in the multicenter randomized phase III OVHIPEC-1 trial in patients with stage III ovarian cancer.[4]

For wide implementation of this technique and adequate financial coverage, cost-effectiveness analysis (CEA) is essential. The objective of this study was to perform a CEA, calculating the incremental cost-effectiveness ratio (ICER) of treatment with interval CRS and HIPEC compared to interval CRS for patients with stage III ovarian cancer.

Methods

Patients and treatment

The patient data used in the model were extracted from the OVHIPEC- 1trial (chapter 2). In this multicenter randomized phase III trial, 245 patients with stage III ovarian cancer who received three neo-adjuvant chemotherapy cycles with carboplatin (area under the curve [AUC] 5-6mg) and paclitaxel 175mg/m^2, were randomized to receive interval CRS with or without HIPEC using cisplatin 100mg/m^2. One-hundred-twenty-two patients underwent interval CRS and HIPEC and 123 patients received interval CRS only. Data were available on the surgical procedure, the administered chemotherapy, hospital stay, additive diagnostic tests, and complications. Post-operative complications were determined and classified using the Common Terminology Criteria for Adverse Events (CTCAE) version 4, and grouped into toxicity grade 1-2 and grade 3-5.

Utility estimates

Patients in the OVHIPEC-1 trial completed health-related quality of life (HRQoL) questionnaires of the European Organization for Research and Treatment of Cancer (EORTC). No significant between-group differences were observed over time for the QLQ-C30 summary score in the OVHIPEC-1 trial. The questionnaires in the OVHIPEC-1 trial did not include preference-based questions to obtain utilities. Because of the lack of mapping algorithms for ovarian cancer to derive utility values from QLQ-C30 results, we derived utilities from Havrilesky et al. as was previously done for cost-effectiveness studies in ovarian cancer.[5] These utilities were based on time trade-off tasks performed by healthy women, women with ovarian cancer, and women previously treated for ovarian cancer. Nearly all patients were diagnosed with FIGO stage III-IV ovarian cancer. The utility for

disease-free survival of 0.83 reported by Havrilesky et al. is similar to utilities reported by other trials in advanced ovarian cancer. For both treatment arms in the OVHIPEC-1 trial, the utility for the disease-free health state from Havrilesky et al. was modified for the percentage of patients with grade 1-2 and grade 3-4 toxicities, and for the percentage of patients receiving a colostomy.[6] The risk of an adverse event or a colostomy was derived from the OVHIPEC-1 trial (table 6.1).

Costs estimates

Total treatment costs from diagnosis to recurrent disease were calculated based on the treatment schedule of the OVHIPEC-1 trial (table 6.1). Total costs included chemotherapy agents, diagnostic tests, outpatients visits, societal costs, costs for surgery, costs of hospital admission, costs of admission to the intensive-care unit (ICU), and estimated healthcare costs in case of toxicity. Costs of the most frequent grade 1-2 and 3-4 events in the OVHIPEC-1 trial were calculated, taking into account costs for supportive drugs, re-admission, and diagnostic tests. The number of hospitalization days, diagnostic tests, outpatient visits, and dosages and schedules for all administered regimens were based on the trial protocol, as described elsewhere. Costs were determined using multiple sources. Unit costs for inpatient hospital days, admission to the ICU, and costs for outpatient visits were derived from the Dutch National Health Care Institute (ZINL) cost manual.[7] Costs for chemotherapy and supportive drugs (i.e. analgesia and anti-emetic drugs), were derived from the Dutch online database for therapeutic agents.[8] Costs for imaging modalities, laboratory tests and pathology review were determined using the maximum tariffs set by the Dutch Healthcare Authority (NZa) in 2017.[9] For the estimation of the surgery costs, we used the mean costs for CRS for a patient with ovarian cancer in 2017 in the Netherlands, as reported by the Dutch Healthcare Authority (NZa). [9] Costs for hospitalization days were reported separately. Costs for surgery with HIPEC were based on the prolonged duration of surgery, use of additional material and equipment, and personnel costs. Societal costs were calculated using data from the ZINL cost manual and data provided by Statistics Netherlands.[7, 10, 11] The period of production loss was calculated using the friction costs method for predicting the replacement time for a sick employee.[7, 10] The average labor costs per working day were determined using the weighted average labor costs of full-time and part-time employees in the Netherlands. The friction costs are assumed to be 80% of wage costs. Costs for colostomies were based on internal cost calculations, and the ZINL cost manual.[7] Treatment of the most frequent CTCAE grade 1-2 and grade 3-4 toxicities were based on local protocols, and associated costs were derived from the Dutch online database for therapeutic agents.[8] All costs were retrieved in 2017 Euros, or calculated to 2017 Euros by inflation rate using the Consumer Price Index.[10]

Table 6.1. Treatment costs per patient

	Unit cost (€)	Units	Costs (€)	S.E. (€)	Subtotal (€)	Distribution	Ref.
Healthcare costs for both treatment groups							
Chemotherapy (6 cycles)							
Carboplatin (AUC 5-6) + paclitaxel (175 mg/m^2)*†	€ 1,064	6	**€ 6,566**			Fixed	8
Daycare	€ 315	6	**€ 1,893**			Fixed	7
Diagnostics‡							
Laboratory			**€ 572**			Fixed	9
Radiology			**€ 2,623**			Fixed	9
Pathology	€ 991	1	**€ 991**			Fixed	9
Outpatient visits and follow-up							
Consultations	€ 210	13	**€ 2,724**			Fixed	7
Others§	€ 42	7	**€ 297**			Fixed	7
Societal Costs|			**€ 4,359**			Fixed	7,10
Other Healthcare costs included in the model, for both treatment groups							
Toxicity††							
Toxicity Grade 1-2			**€ 80**	€ 8		Gamma	§§ 7,8
Toxicity Grade 3-4			**€ 4,200**	€ 420		Gamma	§§ 7,8
Colostomy			**€ 8,400**	€ 840		Gamma	§§ 7
Costs for treatment and subsequent care of disease recurrence‡‡			**€ 39,000**	€ 3,900		Gamma	§§ 7,8

Table 6.1. Treatment costs per patient - continued

	Unit cost (€)	Units (days)	Costs (€)	S.E. (€)	Subtotal (€)	Distribution	Ref.
Interval CRS (standard treatment arm)							
Surgery¶			**€ 9,000**	€ 900		Gamma	§§
Inpatient stay perioperative							
Ward stay	€ 825	8.4	**€ 6,934**			Fixed unit costs	7
ICU stay	€ 2,591	0.85	**€ 2,202**			Fixed unit costs	7
Subtotal					**€ 18,136**		
Interval CRS and HIPEC (intervention arm)							
Surgery¶			**€ 18,000**	€ 1,800		Gamma	§§
Therapeutic agents during HIPEC**			**€ 1,507**	€ 151			
Inpatient stay perioperative							
Ward stay	€ 825	11	**€ 9,080**			Fixed unit costs	7
ICU stay	€ 2,591	2.05	**€ 5,311**			Fixed unit costs	7
Subtotal					**€ 33,898**		

Costs are expressed in 2017 Euros. SEs for the costs were derived from internal cost calculations or estimated at a percentage of 10%.

* Assumes mean body surface area of 1.7 m^2, a weight of 70 kg and a glomerular filtration rate of 75 ml/min

† Includes materials and pre-medication (dexamethason 8 mg, clemastine 2 mg, and ranitidine 150 mg)

‡ Consists of costs for multiple blood sample evaluations, CT-scans, ultrasounds, X-rays, and the pathological analyses of biopsies and resection specimen. Because costs for laboratory tests and for radiology modalities were grouped, units could not be given.

§ Among which consultations by physiotherapists and dieticians

| Calculated with the following formula: = Friction period[8] x mean working hours[8] x production costs[6] x mean participation[8] x percentage of patients <65 year[4]. Price per unit could not be expressed

¶ Consists of costs for anesthetic care and diagnostics, cytoreductive surgery including abdominal uterus extirpation, removal of adnexa, omental tissue and, peritoneal disease, and an estimation of costs for surgical time, personnel costs, and in case of HIPEC costs for disposables and use of the HIPEC perfusion system

** Consists of costs for cisplatin and sodium thiosulfate

†† Costs for treatment of toxicities as reported previously in the OVHIPEC-trial

‡‡ Estimated costs for care at the event of recurrent disease, based on treatment with standard chemotherapy

§§ Based on internal calculation

Costs for disease recurrence

Because of alternative treatment strategies for relapsed ovarian cancer, costs were calculated for three different treatment scenarios: 1) standard chemotherapy (base-case); 2) carboplatin-gemcitabine-bevacizumab and maintenance bevacizumab for platinum sensitive disease; and 3) maintenance Poly(adenosine diphosphate [ADP]–ribose) polymerase (PARP)-inhibitors for high-grade serous recurrent disease. Standard chemotherapy was considered as treatment with carboplatin and paclitaxel, and/or gemcitabine and/or doxorubicin.

The first scenario accounts for the lowest possible costs, and is reported in the base-case analyses to represent the most conservative strategy. Mean costs for disease recurrence for all three scenarios were based on real-time data from patients in the Netherlands Cancer Institute. Average costs for standard chemotherapy (first scenario) were calculated taking into account the proportion of platinum-sensitive relapsed ovarian cancer in the OVHIPEC-1 trail: 69% had a platinum-sensitive relapse, and 31% had platinum-resistant relapsed ovarian cancer. Associated costs for all scenarios were derived from the ZINL cost manual, the Dutch Healthcare Authority (NZa), local costs and the Dutch online database for therapeutic agents.[7, 8, 9]

Model description

A Markov-model was built to analyze the cost-effectiveness of the addition of HIPEC to interval CRS. The model, constructed in Microsoft Excel version 2010 (Microsoft, Redmond, WA), consisted of three mutually exclusive health states: "recurrence-free survival", "disease recurrence" and "death" with the corresponding utility for each health state (figure 6.1). This study was carried out from a societal perspective in the Netherlands. The duration of each cycle in the model was three months. A ten-year time horizon was chosen because of the life expectancy of the population, and the reliability of the survival extrapolation.

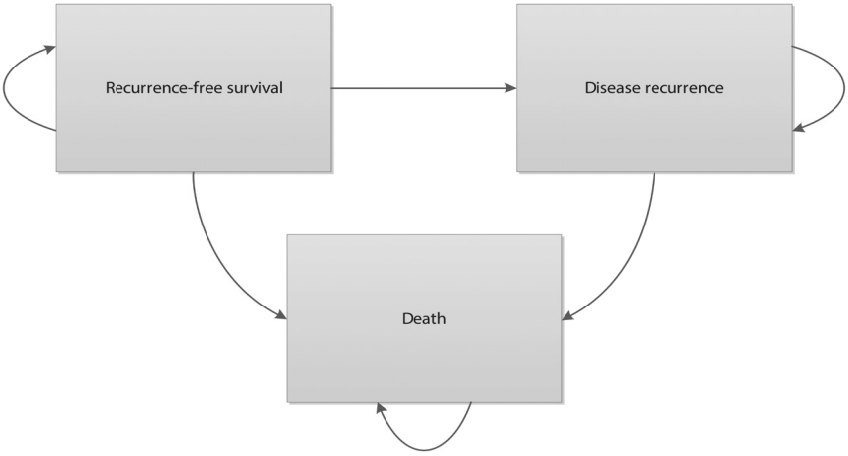

Figure 6.1. Schematic overview of the Markov model

Outcome probabilities
Survival data were extrapolated directly, using the exact patient-specific dates for disease recurrence and death from all patients included in the OVHIPEC-1 trial. The following parametric survival models were fitted: the Gompertz, exponential, log-logistic, log-normal, and Weibull distributions, according to the UK National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) guidelines.[11, 12] Based on the Akaike information criterion (AIC), visual comparison of the estimated parametric survival models and Kaplan-Meier plots of the data, and clinical knowledge of experts in our institute, the best model was selected (supplementary material, tables S6.1 and S6.2, and figures S6.1 and S6.2).The log-logistic distribution showed the best fit and was used for estimating survival and hazard rates of the observed 5-year follow-up period and for extrapolation beyond the observed time (supplementary material, figures S6.1 and S6.2). Standard errors of the estimated rates were obtained with 1000 bootstrapped samples. Probabilities for RFS and OS (*p*) per cycle (*t*) were calculated using hazard rates (*r*) for RFS and OS derived from the log-logistic model, using the following equation: $p = 1\text{-}\exp(\text{-}rt)$.

Markov Model
To calculate the incremental mean costs and quality adjusted life years (QALY)-difference between the two groups, we used bootstrapping with 1,000 replicas representing women at an age of 60, to derive an estimate and 95% confidence interval (CI) for each treatment arm. The chosen age was based on the mean age of patients in the OVHIPEC-1 trial. For each treatment arm, replicas entered the model at cycle 0, and remained in the same health state or transferred between health states at the end of each cycle, depending on probabilities for RFS or OS. Life years (LY) were calculated for both treatment arms. Subsequently, QALYs for both treatment arms were calculated based on probabilities for RFS, disease recurrence, grade 1-2 toxicity, grade 3-4 toxicity, and colostomies, with corresponding utilities and disutilities (table 6.2).[4, 5, 6] All cost and outcome data were discounted at a rate 4% and 1.5% per year respectively, according to the Dutch guidelines.[7, 13] We assumed that all patients with recurrent disease, regardless of treatment arm, would be treated according to current treatment guidelines. The primary outcome of the model was the incremental cost-effectiveness ratio (ICER). The ICER was calculated by dividing the mean incremental costs, by the mean incremental QALY.

Sensitivity analyses
We performed a series of sensitivity analyses to evaluate the robustness of the model and to address uncertainty in the estimation of variables. To determine which of the input parameters had the largest impact on the cost-effectiveness of interval CRS and HIPEC, one-way sensitivity analyses were performed, showing the effect of a deviation of 20% of each individual model-input parameter on the ICER. Results were distributed in a tornado diagram. A probabilistic sensitivity analysis (PSA) was carried out using a Monte Carlo Simulation, in which the simulation of 1,000 patients per treatment arm is repeated a thousand times. Gamma distribution was used for cost parameters, and beta distribution for parameters bounded between 0 and 1 (table 6.1). The corresponding ICERs for each of the iterations were illustrated in a cost-effectiveness plane. Cost-effectiveness acceptability curves (CEAC) were constructed to demonstrate the probability of cost-effectiveness. In CEAC-analysis,

the "willingness to pay" (WTP) threshold for a certain health benefit is set against the probability of not breaching the threshold. In the Netherlands, the informal threshold for the WTP lies at €80,000 per QALY.[14]
To show the effect of increasing costs in the relapsed setting, a scenario analysis was performed using estimated costs of treatment with carboplatin-gemcitabine-bevacizumab, and for treatment with maintenance PARP-inhibitors for high-grade serous disease.

Table 6.2. Survival and outcome probabilities and health-state utilities

	Mean	S.E.	Distribution	Reference
Probabilities interval CRS (standard treatment)				
Toxicity Grade 1/2	0.71	0.04	Beta	4
Toxicity Grade 3/4	0.25	0.04	Beta	4
Colostomy	0.11	0.03	Beta	4
ICU stay (days)	0.85	0.25	Gamma	4
Hospital ward stay (days)	8.4	0.39	Gamma	4
Probabilities interval CRS and HIPEC (investigational treatment)				
Toxicity Grade 1/2	0.71	0.04	Beta	4
Toxicity Grade 3/4	0.27	0.04	Beta	4
Colostomy	0.17	0.03	Beta	4
ICU stay (days)	2.05	0.40	Gamma	4
Hospital ward stay (days)	11.00	1.11	Gamma	4
Health-State Utilities for both treatment groups				
Recurrence-free survival	0.83	0.06	Beta	5
Toxicity grade 1-2	0.60	0.08	Beta	5
Toxicity grade 3-4	0.49	0.09	Beta	5
Recurrent disease, toxicity grade 3-4	0.47	0.09	Beta	5
Stoma Disutility	-0.11	0.05	Beta	6

Standard errors (SE) belonging to the utilities were calculated using reported standard deviations and sample sizes. SEs for survival probabilities, complication rates and hospitalization days were derived from the OVHIPEC-trial.

Results

Patients and survival

Demographic and baseline characteristics, treatment information, and patient outcome data of patients in the OVHIPEC-1 trial are shown in chapter 2. The hazard ratio (HR) for RFS or death was 0.66 (95% CI, 0.50 to 0.87; P = 0.003). The HR for OS was 0.67 (95% CI, 0.48 to 0.94; P = 0.02).[4]

Base case results

The mean total healthcare costs of interval CRS and HIPEC were €85,791 (95% Credibility Interval [CrI], €78,766-€93,935) compared to €70,046 (95% CrI, €64,016-€76,661) for interval CRS, resulting in a mean incremental costs of €15,745 (95% CrI, €5,829-€25,927) when adding HIPEC. Treatment with interval CRS and HIPEC lead to mean life years (LY) of 5.07 (95% CrI, 4.80-5.34) compared to a mean of 4.07 (95% CrI, 3.83 -4.33) LY for patients treated with interval CRS only. This resulted in costs per LY gained of €15,746 when adding HIPEC. Adjusting for HRQoL, the mean QALYs in the interval CRS and HIPEC group was 2.68 (95% CrI, 2.11 -3.28), whereas the mean QALYs in the interval CRS group was 2.12 (95% CrI, 1.66-2.64). This resulted in an incremental cost-effectiveness ratio (ICER) of €28,299/QALY over the first five years for patients treated with interval CRS and HIPEC.

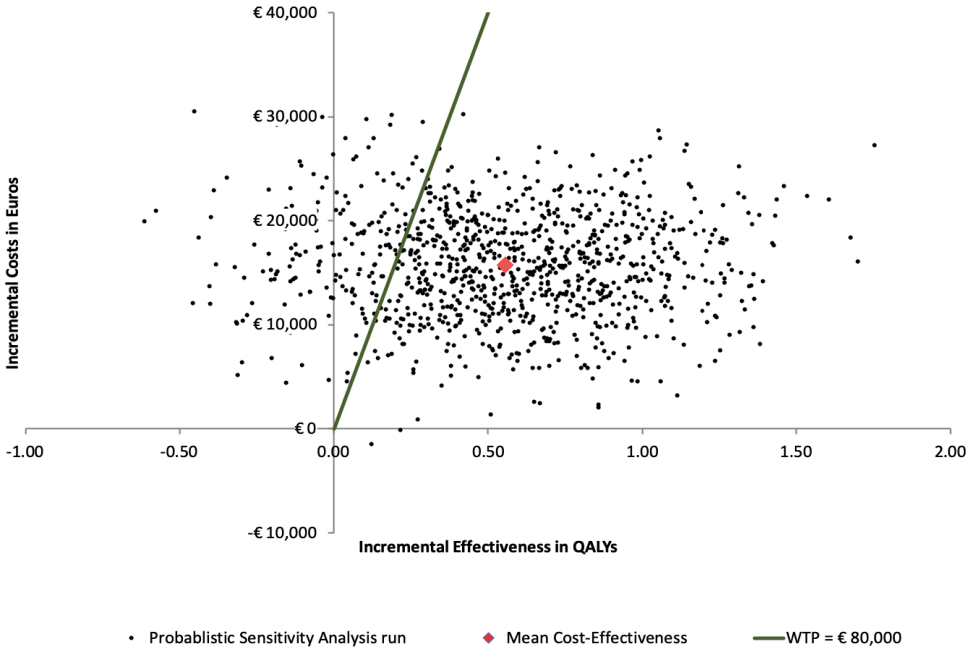

Figure 6.2. Cost-effectiveness plane for the incremental costs in euros compared with the incremental effectiveness in quality-adjusted life-years (QALYs), treatment with interval cytoreductive surgery, and hyperthermic intraperitoneal chemotherapy compared with treatment with interval cytoreductive surgery. Costs are expressed in 2017 euros (€). The willingness-to-pay (WTP) threshold of €80,000 per QALY is pictured.

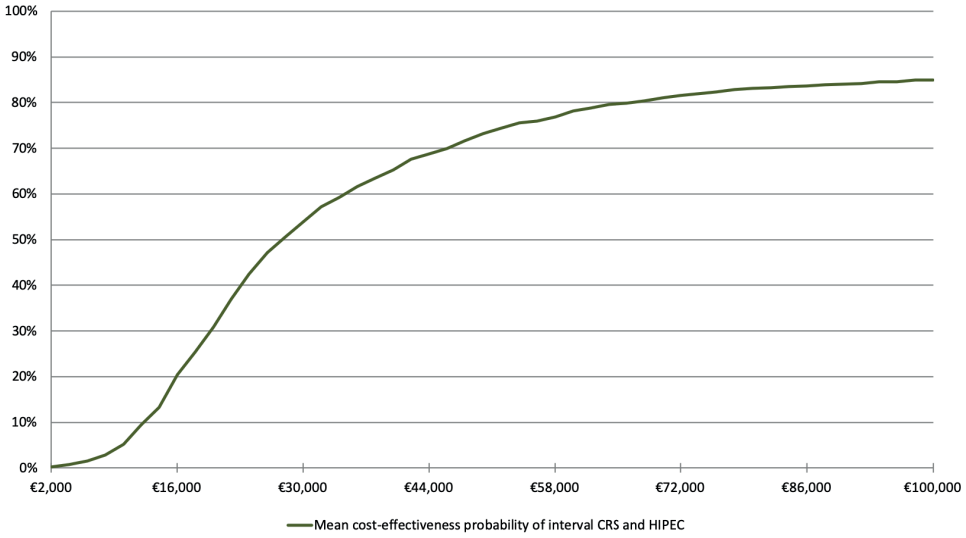

Figure 6.3. Cost-effectiveness acceptability curve showing the probability of interval cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) being cost effective given a certain willingness-to-pay threshold per quality-adjusted life-year in euros (€). Costs are expressed in 2017 euros.

Probabilistic sensitivity analysis

The ICERs for the 1000 samples in the probabilistic sensitivity analysis are shown in the scatter plot (figure 6.2). Eighty-three percent of the points were under the €80,000-per-QALY level, and 92% of tested ICERs are in the northeastern quadrant. The cost-effectiveness acceptability curve is shown in figure 6.3 for varying values of WTP per QALY.

Results for the additional treatment scenarios after disease recurrence are listed in table 6.3. With the increase of costs for the treatment of relapsed ovarian cancer, mean incremental costs for initial treatment with HIPEC decreases, resulting in decrease of the calculated ICER.

Univariable sensitivity analysis

The results of the univariable sensitivity analysis are shown in the tornado diagram (figure 6.4). The parameters with the greatest influence on the ICER were the utility for RFS, the number of hospitalization days, and the utility for recurrent disease with grade 3-4 toxicity. Even with a broad variation in range for each parameter, the ICER remained below €33,000 per QALY.

Table 6.3. Base case results for initial treatment with interval CRS and HIPEC, and scenario analyses calculated for different treatment strategies for relapsed ovarian cancer

Treatment strategy for recurrent disease		Total treatment costs (95% CrI)			Effectiveness	
	mean cost estimation	interval CRS	interval CRS+HIPEC	Incremental costs	Incremental QALY	ICER (€/QALY)
Standard chemotherapy	€39,000.00	€70,046 (€64,016-€76,661)	€85,791 (€78,766-€93,935)	€15,745 (€5,829-€25,927)	0.56	€28,299
Bevacizumab for platinum sensitive recurrent disease	€60,000.00	€85,797 (€76,654-€96,479)	€101,277 (€91,442-€111,553)	€15,479 (€878.55-€29,151)	0.56	€27,882
Maintenance PARP inhibitor for high-grade serous recurrent disease	€100,000.00	€116,435 (€101,604-€132,347)	€131,202 (€116,790-€147,831)	€14,766 (€-8,090-€37,208)	0.55	€26,896

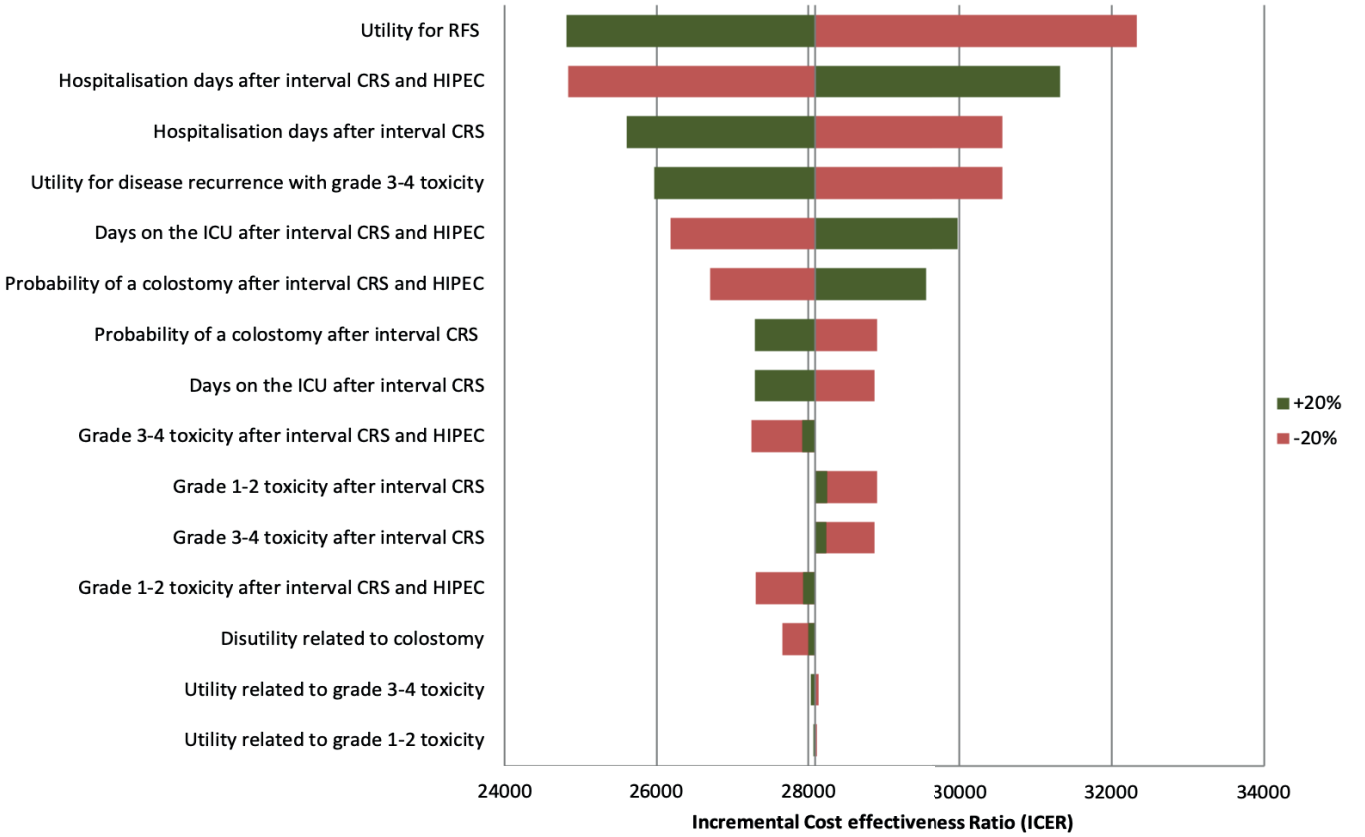

Figure 6.4. Tornado diagram showing one-way sensitivity analysis results. Bars indicate the effect of a ± 20% variance of a variable on the incremental cost-effectiveness ratio. Costs are expressed in 2017 euros (€). Abbreviations: CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; ICU, intensive care unit; QALY, quality-adjusted life-year; RFS, recurrence-free survival.

Discussion

We performed a CEA of treatment with interval CRS and HIPEC in patients with stage III ovarian cancer, who were ineligible for primary cytoreductive surgery. Treatment with interval CRS and HIPEC resulted in a high incremental QALY benefit. In the randomized OVHIPEC-1 trial, adding HIPEC to interval CRS prolonged OS by 11.8 months, and increased costs by €15,745. For all scenarios tested in the univariable sensitivity analyses, the ICER remained below €33,000 per QALY. The PSA revealed that the probability of interval CRS and HIPEC being cost effective was 83% for the Dutch WTP-threshold of €80,000 per QALY. Based on these data, treatment with interval CRS and HIPEC falls within the accepted values for cost-effective incremental costs of care in the Netherlands.

The WTP-thresholds vary across countries, and generally are based on the market value of goods and services of a country, expressed in per-capita Gross Domestic Product (GDP) or the Commission on Macroeconomics and Health's corresponding estimate of the economic value of a QALY.[15] Interventions that cost less than three times GDP per-capita are generally considered cost effective.[16] The National Institute for Health and Care Excellence (NICE) in England and Wales uses a range of £20,000-£30,000 per QALY (€22,000–€33,000 in 2014 euros).[17] In the United States, ranges have been recommended but have not been officially adopted and remain subject of ongoing debate; both a range of $20,000- $100,000 (€15,000–€75,000), and a threshold of $50,000 (€36,000) are discussed.[18, 19] This CEA could support implementation and coverage decisions in countries with similar health care systems and expenditure ranges. Depending on the difference in treatment strategies and associated costs, the substantial gain in QALYs and the incremental costs demonstrated here might not translate into similar results in all countries.

Few observational and retrospective studies report the cost-effectiveness of the HIPEC procedure.[20-25] Study populations in these reports vary considerably precluding their comparison. Our results provide the first evidence of HIPEC being cost-effective, based on data from a randomized controlled trial. The additional costs associated with HIPEC mainly result from the increased duration of surgery, the capacity of the operation room, and prolonged hospitalization including an additional day on the ICU (table 6.1). These costs were estimated based on internal costs and open sources in the Netherlands, but may vary across hospitals, countries, and over time. Treatment might deviate from the standardized protocols used to design the model. In the OVHIPEC-1 trial, HIPEC was performed in hospitals with expertise in performing HIPEC for patients with gastro-intestinal malignancies. Volumes and experience of the surgical team could influence the complication rate. The various cost elements related to the HIPEC procedure might vary between countries, although the procedure is well described and can be executed with a high degree of uniformity. Treatment with interval CRS and HIPEC results in fewer disease recurrences, resulting in a decline of the ICER when additional costs after disease recurrences rise (table 6.3).[4] Given this, treatment with interval CRS and HIPEC will be cost-effective when combined with other costlier treatment strategies in the relapsed setting.[26]

Our study has some limitations. First, surgery costs, the number of diagnostic tests, the administered regimens and associated costs, and costs for toxicities and recurrences used

in our analyses were based on assumptions. Second, the questionnaires used for the HRQoL analyses are not directly translatable to health-state utilities. Mapping algorithms might be used to derive utility values from QLQ-C30 results, but existing mapping algorithms have been tested and validated in different cancer populations, without sufficient overlap with patients with ovarian cancer.[27-29] In the absence of disease-specific validation, the mapping technique may lead to a bias of unknown magnitude and direction. Thus, we used previously reported utilities for each health state, and for subsequent toxicities in both treatment arms. These utilities were based on a small sample, resulting in a relatively large degree of uncertainty in the PSA and a relatively low median cost-effectiveness probability (figures 6.2 and 6.3). The univariable sensitivity analysis, however, shows that the ICER remains below €33,000 per QALY with a potential variance in utilities of 20%. A more adequate estimation of the health-state utilities, preferably based on prospective use of the EuroQoL-5-dimension (EQ-5D) questionnaire, would have resulted in less uncertainty, and thereby a higher cost-effectiveness probability.[30] Currently, an implementation study of OVHIPEC in the Netherlands is being conducted in which patient-specific utilities are being obtained prospectively. To validate these results additional trials are warranted, collecting data on patient-specific utilities, costs, and outcomes, so that the level of uncertainty decreases. Nevertheless, the OVHIPEC-1 trial provides unbiased estimates of the RFS and OS probabilities, the incidence of toxicities, and important treatment characteristics, such as hospital stay, and duration of the surgical procedure.

In conclusion, this CEA demonstrated that, based on the trial data, the addition of HIPEC to interval CRS results in a substantial gain in QALYs in patients with stage III ovarian cancer. The ICER compares favorably to the current WTP-threshold in the Netherlands. This finding lends further support for reimbursing treatment with interval CRS and HIPEC for these patients in countries with similar health care systems.

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Supplementary files chapter 6

Table S6.1. Fitting of parametric survival models for overall survival

	AIC Interval CRS	AIC Interval CRS + HIPEC	Beta Interval CRS	Beta Interval CRS + HIPEC	Model parameter Interval CRS	Model parameter interval CRS + HIPEC
Gompertz	293,216	248,1844	-4,29985	-4,80545	0,018328	0,019949
Exponential	297,6367	252,2469	3,888232	4,31215		
LogLogistic	**292,5543**	**243,1616**	**3,520574**	**3,869327**	**0,580489**	**0,562621**
LogNormal	305,7255	246,3521	3,524731	3,898928	1,154619	1,04583
Weibull	290,8582	244,2029	3,821719	4,130042	1,359991	1,479369

Table S6.2. Fitting of parametric survival models for recurrence-free survival

	AIC Interval CRS	AIC Interval CRS + HIPEC	Beta Interval CRS	Beta Interval CRS + HIPEC	Model parameter Interval CRS	Model parameter interval CRS + HIPEC
Gompertz	310,7972	318,349	-2,84833	-3,1921	0,004352	0,001881
Exponential	309,0982	316,4098	2,795496	3,163921		
LogLogistic	**258,9284**	**292,9522**	**2,44863**	**2,74987**	**0,399296**	**0,509325**
LogNormal	264,1469	293,119	2,491676	2,780159	0,722282	0,883841
Weibull	296,2527	311,3206	2,848694	3,177862	1,344761	1,250792

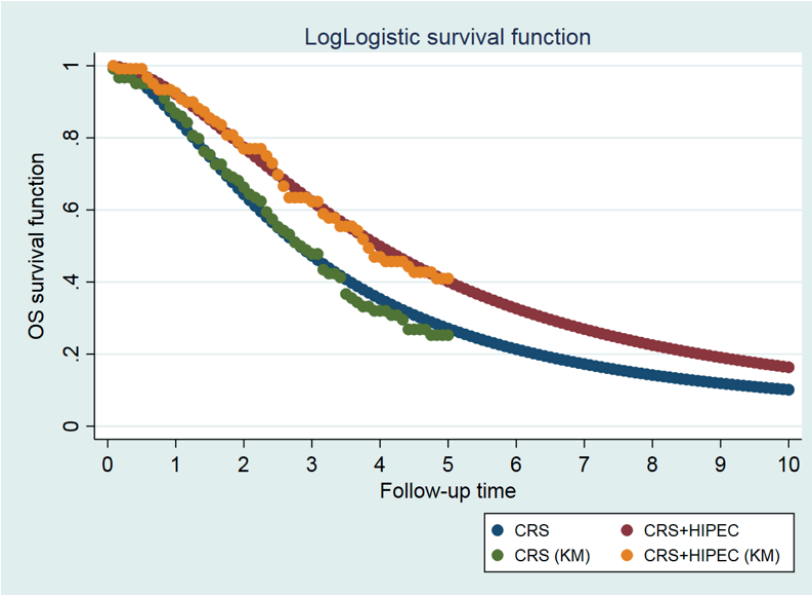

Figure S6.1. Log-logistic overall survival functions with cumulative overall survival curves for both treatment arms

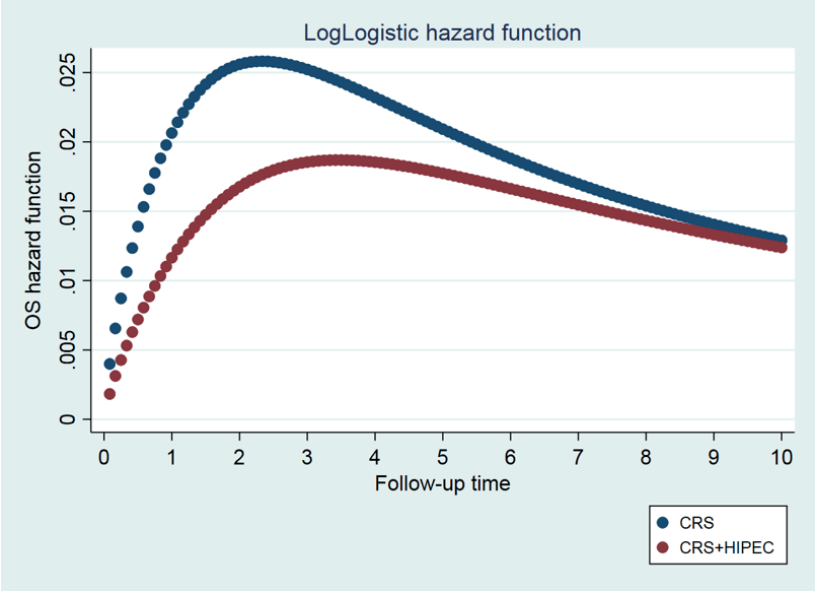

Figure S6.2. Log-logistic overall survival hazard functions for both treatment arms

CHAPTER 7

Validation of an algorithm-based *BRCA1*-like classifier for ovarian cancer patients

Parts of this chapter appear in the following manuscript:
S.N. Koole, P.J. Schouten* & J. Hauke*, R. Kluin, L.K. Richters, G. Krebsbach, K. Sikorska, M. Alkemade, M. Opdam, J.H. Schagen van Leeuwen, H.W.R. Schreuder, R.H.M. Hermans, I.H.T.J. de Hingh, J. van der Velden, H.J.G. Arts, M. van Ham, P. van Dam, P. Vuylsteke, J. Sanders, H. Horlings, K.K. Van de Vijver, E. Hahnen, W.J. van Driel † & R. Schmutzler †, G.S. Sonke‡, S. Linn‡

Effect of HIPEC according to HRD/BRCAwt genomic profile in stage III ovarian cancer - results from the phase III OVHIPEC-1 trial.
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Abstract

Background About 50% of high-grade serous ovarian tumors are depending on error-prone DNA-repair mechanisms due to germline or somatically acquired mutations in the homologous recombination pathway. Identifying homologous repair deficiency (HRD) tumors is increasingly relevant for treatment selection. An algorithm-based *BRCA1*-like ovarian cancer classifier was developed to assess HRD. We validated this classifier within the OVHIPEC-1 cohort.

Methods Two-hundred samples derived from patients in the OVHIPEC-1 trial were analyzed using next-generation sequencing to generate copy-number variation (CNV) profiles and panel sequencing for HRD-related pathogenic mutations, including *BRCA1/2*. *BRCA1* promotor hypermethylation was assessed using multiplex PCR. The CNV profiles were categorized according to the previously developed algorithm-based classifier as HRD or non-HRD.

Results Ninety-one samples were identified as *BRCA1*-like (45.5%). Over 50% of the *BRCA1*-like tumors carried mutations in *BRCA1, BRCA2*, or other HRD-related genes, or had *BRCA1* promotor hypermethylation. Of the 17 *BRCA1* mutated tumors, 17 were classified as *BRCA1*-like (sensitivity 100%).

Conclusion The *BRCA1*-like ovarian cancer classifier is able to identify tumors harboring HRD related mutations, including *BRCA1/2* mutations with high sensitivity, and can be an effective tool for selection of HRD tumors.

Introduction

Double-strand DNA breaks (DSB) are strongly associated with cancer susceptibility because they are prone to base-pair mismatch.[1] One of the mechanisms for reparation of DSB is homologous recombination. During homologous recombination, resection of the DNA ends generates single-stranded DNA. The single-stranded ends are bound by replication protein A (RPA), *BRCA1*, *BRCA2*, *RAD51* and its homologs.[2, 3] Hereditary or somatic mutations in BRCA1, BRCA2 or related genes in the homologous recombination pathway cause homologous recombination deficiency (HRD). HRD results in activation of error-prone DSB repair mechanisms such as nonhomologous end joining, leading to genomic instability.[3, 4] Up to 50% of patients with high-grade serous ovarian cancer are HRD due to germline or somatically acquired *BRCA1* or *BRCA2* mutations, epigenetic inactivation of *BRCA1*/*BRCA2* or other independent defects in the homologous recombination pathway.[5, 6]

Selecting the HRD tumors is increasingly relevant for treatment selection. A DNA copy number variation (CNV) profile generated by comparative genomic hybridization (CGH) can display gains and losses over the genome. A computer-based algorithm was developed to recognize those tumors that carry a *BRCA1*-like genomic scar. This classifier was used to classify tumors into being *BRCA1*-like or non-*BRCA1*-like, based on the CNV profile derived data.(14-18) Recently, this ovarian cancer classifier was validated on a large dataset.[7] Here, we present the results of the validation of the *BRCA1*-like ovarian cancer classification within the OVHIPEC-1 trial.

Methods

We analyzed available tissue samples from patients in the OVHIPEC-trial.[8] All patients included in this analysis gave written informed consent for biomarker research.

DNA isolation

Formalin-fixed paraffin-embedded (FFPE) tissue was collected at three time points: 1) before neo-adjuvant chemotherapy; 2) during interval CRS before the administration of HIPEC; and 3) at disease recurrence. After central review by two specialized pathologists (KVV, JS), DNA was isolated from FFPE tumor samples containing more than 30% tumor cells, using Qiagen AllPrep DNA/RNA kit. One sample per patient was selected for each patient.

Low coverage next generation sequencing

All available DNA samples were sequenced low coverage, to distinguish amplifications or deletions on a minimal resolution of 20kb. The amount of double-stranded DNA was quantified using the Invitrogen™ Qubit™ dsDNA HS Assay Kit (Fisher Scientific Ltd, Leicestershire, UK) and fragmented to lengths of about 160 base pairs using a Covaris, then purified using 2x AMPure XP beads (Beckman Coulter, cat no A63881). The DNA library was adapted for sequencing using the KAPA HTP library prepartation kit (KAPA Biosystems, KK8504). Samples were sequenced single-read 65 base pair, 13-14 samples per lane, on an Illumina HiSeq2500. Reads where aligned against the GRCh38 reference genome using BWA 0.7.17, mem algorithm. Reads, per 20kb on the genome, were counted and compared against reference-based, predicted mappability, gc correction took place and this yielded the 2log ratios for analyses.

BRCA1-like classification
CNV profiles were classified as BRCA1-like (HRD) or non-BRCA1-like (non-HRD), using a previously trained, shrunken-centroids classifier specific for ovarian cancer patients. (unpublished) Briefly, the 20kb resolution copy number profiles were mapped to the 1 MB resolution input for the classifier. The 2log ratios were averaged per 1MB, centered and scaled to conform the next-generation sequencing data to the oligonucleotide array CGH data, the classifier was trained on. This correction is similar to quantile normalization, and was performed by fitting a linear regression model with gaussian distribution and the identity link function using the glm R function to the sorted location-wise average of the training set and to this dataset. The centering of the current dataset is then corrected by subtracting the alpha coefficient of the model. Subsequently the scaling is corrected by multiplying by the beta coefficient. The 1 MB mapped, platform-corrected samples are subsequently segmented using the uniseg function from the cghseg R package, and are classified with the pamr R package.[9, 10] These methods were implemented in a pipeline package, which can be run in a created docker image. The classifier assigns a discriminative score, between 0 (non-BRCA1-like) and 1 (BRCA-like), to any new DNAcopy number profile. The previously validated cutoff value of 0.5 was used for these analyses.

Panel mutational sequencing
All DNA samples were centrally analyzed in an accredited laboratory (Center for Familial Breast and Ovarian Cancer, Cologne, Germany) using targeted next generation sequencing (NGS) covering the entire coding regions and exon-flanking sequences (±15nt) of BRCA1 (NM_007294.4), BRCA2 (NM_000059.3), and 25 non-BRCA1/2 cancer predisposition genes (ATM, NM_000051.3; BARD1, NM_000465.4; BRIP1, NM_032043.3; CDH1, NM_004360.5; CHEK2, NM_007194.4; FAM175A, NM_139076.3; FANCM, NM_020937.4; MLH1, NM_000249.3; MRE11A, NM_005591.3; MSH2, NM_000251.2; MSH6, NM_000179.2; MUTYH, NM_001128425.1; NBN, NM_002485.4; NF1, NM_001042492.2; PALB2, NM_024675.4; PMS2, NM_000535.6; PTEN, NM_000314.8; RAD50, NM_005732.4; RAD51C, NM_058216.3; RAD51D, NM_002878.3; RECQL, NM_002907.3; SMARCA4, NM_001128849.1; STK11, NM_000455.5; TP53, NM_000546.5; XRCC2, NM_005431.2). (20, 21) For NGS, we employed a customer-tailored SureSelect gene panel (Agilent, Santa Clara, U.S.). Sample preparation was performed using the SureSelect XT Low Input Reagent Kit (Agilent) and SureSelect XT HS and XT Low Input Enzymatic Fragmentation Kit (Agilent) with 70 ng of input DNA. Sequencing was performed on a NextSeq500 platform (Illumina, San Diego, U.S.) using the NextSeq500/550 Mid Output Kit v2.5 (Illumina).

Bioinformatic analyses were carried out using the SeqNext module of the SeqPilot Software Package, Version 5.1.0 Build 503 (JSI medical systems GmbH, Ettenheim, Germany). The filters were selected in such a way that only variants at positions which were covered by at least 50 total reads and a variant fraction of at least 5% of the Fwd and Rev reads were recorded. Variant classification was performed in accordance with the regulations of the international ENIGMA consortium (https://enigmaconsortium.org) as previously described in detail.(22) All genetic variants were classified using a 5-tier variant classification system as proposed by the International Agency for Research on Cancer (IARC) Unclassified Genetic Variants Working Group, namely, deleterious=class 5, likely deleterious=class 4, variant of

uncertain significance (VUS)=class 3, likely benign=class 2, and benign=class 1. Class 4/5 germline variants were subsequently defined as “mutations”.

BRCA1 promotor hypermethylation Multiplex ligation-dependent probe amplification (MLPA)
The BRCA1 promotor methylation status was determined using the ME001 kit (Version D3, MRC Holland, the Netherlands) using manufacturers protocol. The optimal input was 80ng dsDNA (Qubit based), minimum input was 25ng dsDNA. All samples were diluted in a Tris-EDTA buffer (10:0,1).

Germline mutational status
Germline mutational status (g*BRCA1* mutation, g*BRCA2* mutation, no pathogenic g*BRCA* mutation or status unknown) was derived from the clinical patient files. In addition, we crosslinked the OVHIPEC patient-set with the national hereditary breast and ovarian cancer (HEBON) database to obtain additional hereditary information and germline BRCA status. For patients with a sequenced tumor *BRCA* mutation and a reported germline mutation, the sequenced variant was assigned to the germline status. Sequenced tumor *BRCA* mutations in the absence of a known germline mutation were labelled as somatic mutations, irrespective of the mutation/variant allele frequency.

Statistics
All randomized patients from the OVHIPEC-1 trial are included in these analyses if a *BRCA1*-like profile could be determined. Baseline and treatment characteristics are presented and compared for the *BRCA1*-like and non-*BRCA1*-like groups. The mutational background and BRCA1 promotor hypermethylation status of the *BRCA1*-like and the non-*BRCA1*-like profiles are graphically displayed. All analyses were performed using R-statistics (R 3.6.3 GUI 1.70).

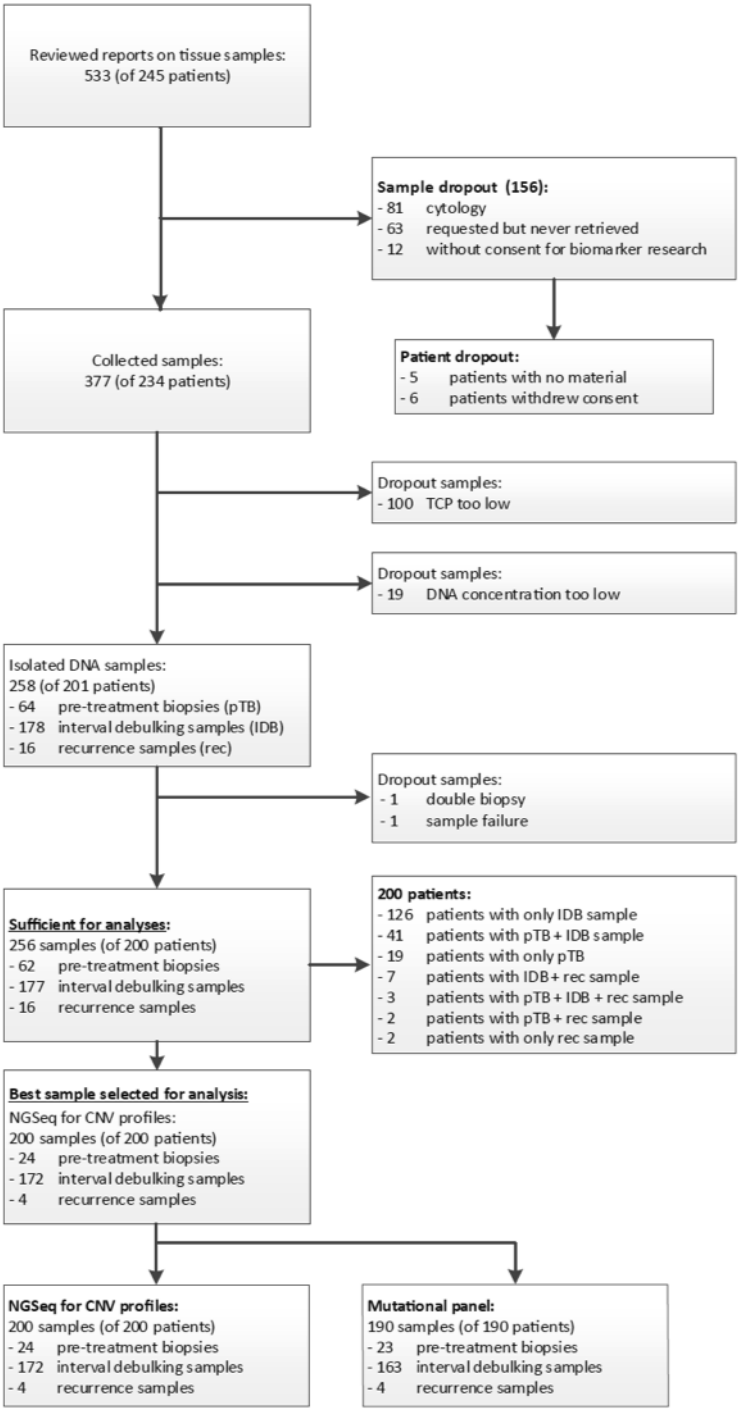

Figure 7.1. CONSORT of tissue-derived DNA availability

Table 7.1. Baseline characteristics of *BRCA1*-like vs. non-*BRCA1*-like tumors

	Non-BRCA1-like N=109		BRCA1-like N=91		p-value‡
Histological type (%)					0.094
- high-grade serous	92	(84%)	86	(95%)	
- low-grade serous	5	(5%)	1	(1%)	
- carcinosarcoma	5	(5%)	0		
- clear-cell	3	(3%)	1	(1%)	
- high-grade endometrioid	1	(1%)	1	(1%)	
- high-grade mucinous	1	(1%)	1	(1%)	
- low-grade endometrioid	2	(2%)	0		
- metastasis gastro-intestinal tumor	0		1	(1%)	
Pathologic response (%)					0.464
- complete/ near complete	5	(5%)	2	(2%)	
- partial to no response	91	(83%)	75	(82%)	
- no panel mutation or germline information available*	13	(12%)	14	(15%)	
TP53 mutation (%)					0.003
- yes	82	(75%)	81	(89%)	
- no	22	(20%)	5	(5%)	
- unknown*	5	(5%)	5	(5%)	
BRCAmut (%)					<0.001
- g*BRCA1*†	1	(1%)	12	(13%)	
- tumor *BRCA1*	0		7	(8%)	
- g*BRCA2*	5	(5%)	5	(5%)	
- tumor *BRCA2*	2	(12%)	2	(2%)	
- *BRCA*wt	97	(89%)	62	(68%)	
- not measurable (pre-treatment sample sequenced)*	4	(4%)	3	(3%)	
Other mutations (%)					0.018
- *NF1*	1	(1%)	1	(1%)	
- *ATM*	1	(1%)	1	(1%)	
- *MUTYH*	0		1	(1%)	
- *PMS2*	0		2	(2%)	
- *FANCC*	0		2	(2%)	

- *MSH6*	0		1	(1%)	
- *NBN*	0		1	(1%)	
- *CDH1*	0		1	(1%)	
- *RECQL*	0		1	(1%)	
- *RAD51C*	0		1	(1%)	
- *SMARCA4*	1	(1%)	0		
***BRCA1* hypermethylation (%)**					0.065
- *BRCA1* hypermethylated	4	(4%)	13	(14%)	
- not *BRCA1* hypermethylated	93	(85%)	69	(76%)	
- unknown	12	(11%)	8	(9%)	
No mutations or hypermethylation found	96	(88%)	44	(48%)	
Treatment					0.777
- interval CRS	59	(54%)	47	(52%	
- interval CRS + HIPEC	50	(46%)	44	(48%)	

* not included for test

† For 3/13 gBRCA1 mutation carriers, no tumor material for sequencing was available for panel mutational testing. For all other germline BRCA1/2 mutation carriers the pathologic variant was confirmed with tumor panel sequencing

‡ exact test p-value

Results

Tissue samples with sufficient amounts of DNA for CNV-sequencing were available for 200/245 (82%) patients included in the OVHIPEC-1 trial (figure 1). Reasons for missing samples were no informed consent for biomarker analyses, insufficient tumor following response to neo-adjuvant chemotherapy, low quality of the retrieved DNA, and missing samples (figure 1). Data on germline mutational testing was retrieved from clinical files and the HEBON database for 108/200 (54%) patients. Panel sequencing results were available for 190/200 (95%) of the samples, because DNA was insufficient in the remaining ten patients. Baseline and treatment characteristics were well balanced across *BRCA1*-like and non-*BRCA1*-like groups, except for *BRCA1/2* mutations and other HRD related mutations, which were more frequent in the *BRCA1*-like group (table 1).

Validation of the BRCA1-like classifier

The *BRCA1*-like classifier identified 91 samples as *BRCA1*-like and 109 as non-*BRCA1*-like (figure 1). Thirty-eight (42%) of the 91 *BRCA1*-like samples are explained by mutations in *BRCA1/2* (29%) and other genes (13%) (table 1, figure 2). Nine (10%) of *BRCA1*-like cases were based on *BRCA1* promotor hypermethylation (table 1). All of the sequenced tumor *BRCA1* mutations (17/17) were classified as *BRCA1*-like (sensitivity 100%). One tumor from a patient with a g*BRCA1* carrier status (known from the patient-file) was classified as non-*BRCA1*-like. For this patient we were not able to perform panel sequencing.

Table 2 shows the mutational prevalence of TP53, BRCA1/2 and all the other non-BRCA1/2 genes within the 190 other tumor samples. In this cohort, no mutations were identified in *BARD1, BRIP1, FAM175A, MSH2, MUTYH, PALB2, RAD50, RAD51D, STK11, XRCC2*.

Table 7.2. Mutation prevalence of *TP53*, *BRCA1/2* and 24 further non-*BRCA1/2* genes.

***TP53*-positive samples**	**164/190 (86.3%)**
***BRCA1/2*-positive samples**	**31/190 (16.3%)**
BRCA1 only	14 (7.4%)
BRCA1 and *CHEK2* and *PTEN*	1 (0.5%)
BRCA1 and *MUTYH*	1 (0.5%)
BRCA1 and *NF1*	1 (0.5%)
BRCA2 only	12 (6.3%)
BRCA2 and *MUTYH*	1 (0.5%)
BRCA2 and *PMS2*	1 (0.5%)
BRCA1/2*-negative samples with mutations in non-*BRCA1/2* genes, excluding *TP53	**15/159 (9.4%)**
NF1 only	2 (1.3%)
ATM only	2 (1.3%)
FANCC only	2 (1.3%)
MUTYH only	1 (0.6%)
PMS2 only	2 (1.3%)
CDH1 only	1 (0.6%)
MSH6 only	1 (0.6%)
NBN only	1 (0.6%)
RAD51C only	1 (0.6%)
RECQL only	1 (0.6%)
SMARCA4 only	1 (0.6%)

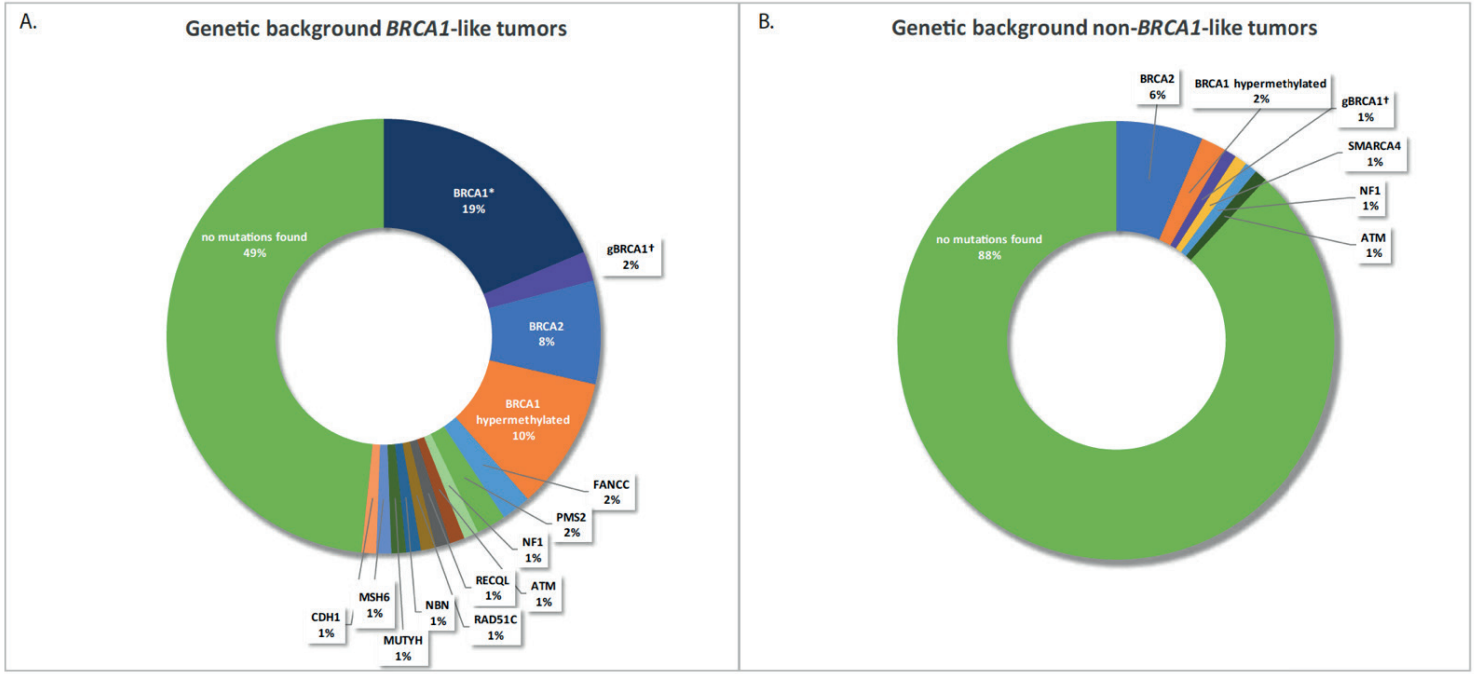

Figure 7.2. Graphical overview of genetic background of BRCA1-like and non-BRCA1-like tumors

* a BRCA1 mutation was detected in the tumor, in 12 cases this was because of an underlying germline BRCA1-mutation (see also table 1)

† germline BRCA1-carriers without confirmation with mutational testing in tumor (N=3)

Discussion

The *BRCA1*-like classifier had a sensitivity of 100% in recognizing *BRCA1* mutations. Among samples that were labeled as *BRCA1*-like, 29% had a *BRCA1* or *BRCA2* mutation, 13% had another HRD gene mutation, and 10% showed *BRCA1* promotor hypermethylation. The remaining 48% *BRCA1*-like samples possibly represent tumors with other aberrations resembling *BRCA1* mutations in the HRD pathway. These results are similar to the performance of a *BRCA1*-like classifier in breast cancer, and the results of the classifier in an earlier ovarian cancer dataset (unpublished).[11-13] As with other HRD-tests, it is unsure how well this classifier distinguishes the functional HRD tumors from the non-HRD tumors. Probably there is a gradient shift from tumors that are completely deficient in homologous recombination to those that are partially deficient and those who are fully HR proficient. The currently available HRD-tests act within a grey area, since there is no gold standard for these tests.[14-18] In this validation study we were able to partly present the mutational background of these tumors with *BRCA1*-like aberrations, but largely the cause of the HRD-phenotype remains unknown. The HRD phenotype might be explained by other mechanisms than *BRCA1* dysfunction alone, and the somatic HRD-related mutations that were tested do not necessarily lead to a *BRCA1*-like phenotype.

In conclusion, the algorithm-based classifier was able to identify HRD tumors *and* has an estimated sensitivity of 100% in recognizing *BRCA1* mutations. How well the classifier performs in comparison to other HRD-tests, whether is able to predict treatment benefit of platinum and PARP inhibitors should be further explored. In chapter 8, we report the results of a study that evaluates the value of the classifier to predict the effect of HIPEC.

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CHAPTER 8

Effect of HIPEC according to HRD/ *BRCA*wt genomic profile in stage III ovarian cancer

Parts of this chapter appear in the following manuscript:

S.N. Koole, P.J. Schouten* & J. Hauke*, R. Kluin, L.K. Richters, G. Krebsbach, K. Sikorska, M. Alkemade, M. Opdam, J.H. Schagen van Leeuwen, H.W.R. Schreuder, R.H.M. Hermans, I.H.T.J. de Hingh, J. van der Velden, H.J.G. Arts, M. van Ham, P. van Dam, P. Vuylsteke, J. Sanders, H. Horlings, K.K. Van de Vijver, E. Hahnen, W.J. van Driel † & R. Schmutzler †, G.S. Sonke‡, S. Linn‡

Effect of HIPEC according to HRD/BRCAwt genomic profile in stage III ovarian cancer - results from the phase III OVHIPEC-1 trial.
Manuscript in preparation 2020

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Abstract

Background The addition of hyperthermic intraperitoneal chemotherapy (HIPEC) with cisplatin to interval cytoreductive surgery (CRS) improves recurrence-free (RFS) and overall survival (OS) in patients with stage III ovarian cancer. Ovarian cancer cells with homologous recombination deficiency (HRD) may be particularly sensitive to HIPEC as these cells switch to error-prone mechanisms to repair the DNA double-strand breaks induced by cisplatin. We hypothesized that the benefit of HIPEC is largest in patients with HRD tumors. In addition, hyperthermia may impair *BRCA1/2* protein function, thereby inducing transient HRD in BRCA wildtype tumors.

Methods Clinical data and tissue samples were collected from patients included in the randomized, phase III OVHIPEC-1 trial. We determined DNA copy number variation (CNV) profiles using next generation sequencing, HRD-related pathogenic mutations, including BRCA1/2 using panel sequencing, and *BRCA1* promotor hypermethylation using multiplex PCR. The CNV profiles were categorized as HRD or non-HRD, based on a previously validated algorithm-based *BRCA1*-like classifier validated for ovarian cancer. Hazard ratios (HR) and corresponding 99% confidence intervals (CI) for the effect of HIPEC in the *BRCAm*, the HRD/BRCAwt and the non-HRD group were estimated using Cox proportional hazard models, with p-values for interaction.

Results DNA was available from 200/245 (82%) randomized patients. Seventeen (9%) tumors carried a pathogenic mutation in *BRCA1* and 14 (7%) in *BRCA2*. Ninety-one (46%) tumors classified as *BRCA1*-like and were associated with BRCA1/2 mutations in 26 (28%), other HRD-related mutations in 12 (13%) and BRCA1 promotor hypermethylation in 9 (10%). The effect of HIPEC varied according to BRCA and HRD status: *BRCA*m (HR 1.25; 99%CI 0.48-3.29), HRD/*BRCA*wt (HR 0.44; 99%CI 0.21-0.91), non-HRD/*BRCA*wt (HR 0.82; 99%CI 0.48-1.42), p-value for interaction: 0.024.

Conclusion Patients with HRD tumors without pathogenic *BRCA1/2* mutation appear to benefit most from treatment with HIPEC, while benefit in patients with *BRCA1/2* pathogenic mutations and patients without HRD seems less evident.

Introduction

Epithelial ovarian cancer has the highest mortality of all gynecologic tumors in the western world. The majority of patients are diagnosed with International Federation for Gynecology and Obstetrics (FIGO) stage III disease.[1-3] Standard treatment consists of maximal cytoreductive surgery (CRS) in combination with platinum-based chemotherapy. The ten-year survival of women with advanced stage ovarian cancer is 10-15% and did not improve in the past 20 years, despite extensive cytoreductive surgery and (neo-) adjuvant intravenous chemotherapy.[4, 5] The peritoneal surface is the primary site of disease recurrence in the majority of patients and therapeutic approaches that specifically target the peritoneal surface are therefore required.[6, 7] Delivering chemotherapy intraperitoneally (IP) maximizes drug exposure at the peritoneal surface. Hyperthermic intraperitoneal chemotherapy (HIPEC) is a single approach in which heated chemotherapy is administered directly into the abdominal cavity at the end of complete or near-complete surgery. The multicenter randomized phase III OVHIPEC trial showed improved recurrence-free survival (RFS) and overall survival (OS) after interval CRS with HIPEC using cisplatin, in patients with stage III ovarian cancer.[8]

Up to 50% of high-grade serous ovarian cancers are supposedly homologous recombination deficient (HRD) due to germline or somatically acquired breast cancer susceptibility gene-1 (*BRCA1*) or *BRCA2* mutations, epigenetic inactivation of *BRCA1*, or other *BRCA*-independent defects in the HR pathway.[9, 10] In the absence of homologous recombination, these tumors rely on error-prone DNA repair mechanisms such as non-homologous end-joining to repair DNA double-strand breaks (DSB) that are induced by platinum-containing chemotherapy.[11] As these mechanisms cause genomic instability and increased cell death, HRD tumors are sensitive to platinum-containing chemotherapy, including HIPEC.[12] Hyperthermia may act synergistically with platinum-based chemotherapy as heat causes depletion of the BRCA1 and BRCA2 proteins and impairs *BRCA1/2* protein function, thereby transiently inducing HRD.[13, 14] Ovarian cancers may constitute a spectrum varying from completely homologous recombination deficiency to completely homologous recombination proficient with intermediate phenotypes.

Homologous recombination deficient cancers frequently harbor the same characteristic genomic scars as *gBRCA1m*-associated cancers. These scar patterns consist of specific gains and losses in DNA copy number variation (CNV), which can be measured by comparative genomic hybridization (CGH).[15-20] We used a previously established and validated *BRCA1*-like algorithm to classify CNV profiles as HRD or non-HRD.[15-20]

We hypothesize that patients with HRD tumors might experience most benefit of treatment with HIPEC. Especially those tumors that have an intermediate phenotype between HRD and HR proficient, may derive most benefit from HIPEC, since hyperthermia will further impair *BRCA1* and *BRCA2*, conferring a more profound HRD phenotype. To test this hypothesis, we estimated the effect of HIPEC in patients who participated in the phase III OVHIPEC trial and stratified the results by HRD status and *BRCAm* status.

Methods

Patients

The multicenter, randomized, open-label, phase III OVHIPEC-1 trial included 245 patients with FIGO stage III ovarian, fallopian tube, or peritoneal cancer. Because of the extent of disease at diagnosis, patients were ineligible for primary CRS and received three cycles of neo-adjuvant carboplatin-paclitaxel chemotherapy followed by interval CRS. Full eligibility criteria have been published elsewhere.[8] During surgery, patients were randomly assigned (1:1) to interval CRS with or without HIPEC. All patients received three additional cycles of carboplatin-paclitaxel after surgery. Institutional review board approval was obtained from all participating hospitals and all patients gave written informed consent before enrolment. For this ancillary pathology study, we analyzed available tissue samples from patients in the OVHIPEC-trial. All patients included in this analysis gave written informed consent for biomarker research. One sample per patient was selected for each patient, preferably the sample derived from interval CRS. Tissue preparation, DNA isolation, low-coverage sequencing, BRCA1-like classification, and panel mutational sequencing are all conducted in the exact same manner as described in Chapter 7.

Germline mutational status

Germline mutational status (gBRCA1 mutation, gBRCA2 mutation, no pathogenic gBRCA mutation or status unknown) was derived from the clinical patient files. In addition, we crosslinked the OVHIPEC patient-set with the national hereditary breast and ovarian cancer (HEBON) database to obtain additional hereditary information and germline BRCA status. For patients with a sequenced tumor BRCA mutation and a reported germline mutation, the sequenced variant was assigned to the germline status. Sequenced tumor BRCA mutation in the absence of a known germline mutation were labelled as tumor mutations, irrespective of the mutation/variant allele frequency.

Clinical endpoints

Recurrence-free survival (RFS) was defined as the time from randomization to disease recurrence or progression, on the basis of the Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1, a rise in CA-125 level according to the Gynecologic Cancer InterGroup criteria (GCIG), or death from any cause, whichever occurred first.(21) Overall survival (OS) was defined as the time from randomization to death from any cause. Patients alive at last follow-up were censored at that time.

Statistics

All randomized patients from the OVHIPEC trial are included in these analyses if sufficient DNA samples for CNV sequencing was available. Baseline and treatment characteristics are presented per treatment arm using the exact test for categorical variables. Baseline characteristics of the included patients, and patients who dropped out of this analysis because of insufficient tumor material were compared.

The effect of HIPEC was evaluated in three mutually exclusive subgroups defined by BRCA and HRD status: *BRCA1/2mut* vs. HRD*/BRCAwt* vs. non-HRD*/BRCAwt.* Treatment effects per subgroup together with 99%-confidence intervals (CI) are displayed in a forest plot.

Hazard ratios for the effect of treatment arm (HIPEC vs. no HIPEC), and BRCA-subgroup (*BRCA1/2mut* vs. HRD*/BRCAwt* vs. non-HRD */BRCAwt*) or RFS and OS were explored in univariate and multivariate Cox proportional hazard models. Results of the model are reported with corresponding CI fitted for RFS and OS, and interaction p-values (alpha 0.05). Kaplan-Meier estimates are compared using log-rank tests. All analyses were performed using R-statistics (R 3.6.3 GUI 1.70).

Results

Tissue samples with sufficient DNA-samples for CNV-sequencing were available for 200/245 (82%) patients included in the OVHIPEC trial (figure 7.1). Reasons for missing samples included no informed consent for biomarker analyses, complete pathologic response after neo-adjuvant chemotherapy, low quality of the retrieved DNA, and non-response from referral hospitals (figure 7.1). Baseline characteristics of these 200 patients were largely similar to the 45 patients for whom no DNA sample was available, except for lower likelihood of (near-)complete pathologic response (supplementary table s8.1). Baseline and treatment characteristics among patients included in this ancillary side study were well balanced across the arms of the study (table 8.1).

Data on germline mutational testing was retrieved for 108/200 (54%) patients. Panel sequencing results were available for 190/200 (95%) of the samples, because DNA was insufficient in the remaining ten patients. The prevalence of a tumor mutation in *BRCA1* was 17/190 (9%) and in *BRCA2* 14/190 (7%). Deleterious tumor mutation variants in other predisposition genes were found in 15/190 patients (*NF1, ATM, MUTYH, PMS2. FANCC, MSH6, NBN, CDH1, RECQL, RAD51C, SMARCA4*). All gene variants found are listed in table 8.1 and table 7.2. Three of the ten patients in whom panel sequencing results were unavailable were known carriers of a germline pathogenic *BRCA1* mutation.

Table 8.1. Baseline characteristics per treatment arm

	Surgery		Surgery plus HIPEC		p-value§
	n=106		n=94		
Histological type (%)					0.199
- high-grade serous	93	(88%)	85	(90%)	
- low-grade serous	2	(2%)	4	(4%)	
- carcinosarcoma	4	(4%)	1	(1%)	
- clear-cell	4	(4%)	0		
- high-grade endometrioid	1	(1%)	1	(1%)	
- low-grade endometrioid	0		2	(2%)	
- high-grade mucinous	1	(1%)	1	(1%)	
- metastasis gastro-intestinal tumor	1	(1%)	0		
Pathologic response (%)					0.267
- complete/ near complete	2	(2%)	5	(5%)	
- partial to no response	87	(82%)	79	(84%)	
- unknown*	17	(16%)	10	(11%)	
***TP53* mutation (%)**					0.097
- yes	90	(85%)	73	(78%)	
- no	10	(9%)	17	(18%)	
- unknown*	6	(6%)	4	(4%)	
***BRCA* mutation (%)†**					0.958
- g*BRCA*1†	7	(7%)	6	(6%)	
- tumor *BRCA1*	3	(3%)	4	(4%)	
- *gBRCA2*†	5	(5%)	5	(5%)	
- tumor *BRCA2*	3	(3%)1	1	(1%)	
- *BRCA*wt	84	(77%)	75	(80%)	
- no panel mutation or germline information available	4	(4%)	3	(3%)	
***BRCA1* hypermethylation (%)**					0.258
- *BRCA1* hypermethylated	7	(7%)	10	(11%)	
- not *BRCA1* hypermethylated	87	(82%)	75	(80%)	
- unknown	12	(11%)	9	(10%)	
Other mutation variants (%)					0.168
- *NF1*	0		2	(2%)	
- *FANCC*	0		2	(2%)	
- *PMS2*	2	(2%)	0		

- *ATM*	2	(2%)	0		
- *MUTYH*	1	(1%)	0		
- *MSH6*	1	(1%)	0		
- *NBN*	1	(1%)	0		
- *CDH1*	1	(1%)	0		
- *RECQL*	1	(1%)	0		
- *RAD51C*	0		1	(1%)	
- *SMARCA4*	0		1	(1%)	
No mutation or BRCA1 hypermethylation found	70	(66%)	63	(67%)	
No tumor material available, no clinical information on mutation status	4	(4%)	3	(3%)	
***BRCA1* profile (%)**					0.835
- *BRCA1*-like profile	47	(44%)	44	(47%)	
- non-*BRCA1*-like profile	59	(56%)	50	(53%)	
Median time to recurrence, months (IQR)	10.7	(9.2-12.5)	13.8	(10.8-17.0)	0.03‡
Median time to death, months (IQR)	33.9	(28.2-41.9)	45.7	(37.0-65.1)	0.037‡

* only pre-treatment biopsies or recurrence-samples were available for these patients, not included for test

† For 3/13 gBRCA1 mutation carriers, no tumor material for sequencing was available for panel testing. For all other germline BRCA1/2 mutation carriers the pathologic variant was confirmed with tumor panel sequencing

‡ Kaplan-Meier based survival estimates, p-value from log-rank test

§ exact test p-value

Subgroup analysis was performed to analyze the predictive effect of *BRCAm and/or* HRD tumor on the effect of HIPEC. For patients with tumor or germline pathogenic *BRCA1/2* mutations, the HR for the effect of HIPEC was 1.25 (99%CI 0.48-3.29) for RFS and 1.94 (99%CI 0.42-9.16) for OS. For the HRD*/BRCAwt* group hazard ratios for RFS and OS are 0.44 (99%CI 0.21-0.91) and 0.55 (99%CI 0.23-1.30) respectively. HR for the non-HRD*/BRCAwt* group was 0.82 (99%CI 0.48-1.42) for RFS and 0.63 (99%CI 0.32-1.22) for OS (figure 8.1). P-values for interaction derived from the Cox models were 0.024 for RFS and 0.099 for OS (figure 8.1). Kaplan-Meier curves for RFS and OS are presented for all tested subgroups in figure 8.2, and supplementary figure s8.1.

Subgroup	Surgery	Surgery-plus-HIPEC	Hazard Ratio (99% CI)	
Recurrence-free survival	*no. of events/total no.*			
HRD/HRP			Interaction p= 0.024	
gBRCA1/2 and/or tumorBRCA1/2	14/18	16/16	1.251	(0.476-3.289)
BRCA1-like/BRCAwt	33/35	24/30	0.437	(0.209-0.914)
non-BRCA1like/BRCAwt	50/53	41/48	0.822	(0.477-1.415)
Overall survival				
HRD/HRP			Interaction p= 0.099	
gBRCA1/2 and/or tumorBRCA1/2	4/18	9/16	1.941	(0.412-9.155)
BRCA1-like/BRCAwt	24/35	15/30	0.550	(0.233-1.299)
non-BRCA1like/BRCAwt	39/53	25/48	0.630	(0.325-1.220)

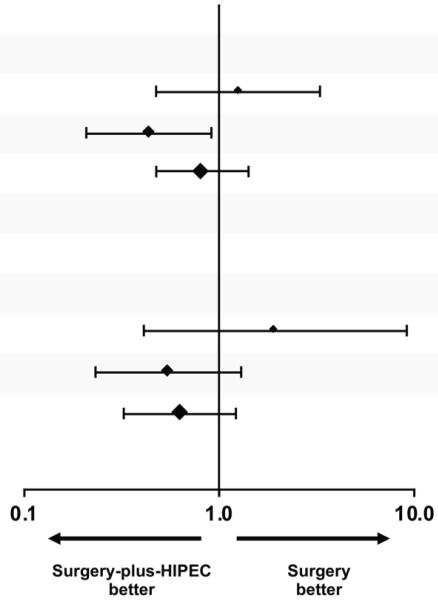

Figure 8.1. Exploratory subgroup analysis for recurrence-free survival and overall survival. Reported p-values for interaction resulted from the multivariable cox model from table 2.

Table 8.2. Univariable and multivariable analysis for recurrence-free survival and overall survival

Recurrence-free survival	**Univariable**			**Multivariable***		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
CRS + HIPEC	0.719	0.534-0.968	0.030	0.709	0.525-0.957	0.025
germline and/or tumor *BRCA1/2*m	0.753	0.483-1.173	0.210	0.710	0.454-1.110	0.133
***BRCA1*-like/*BRCA*wt**	1.160	0.831-1.621	0.383	1.111	0.794-1.554	0.540
Overall survival						
CRS + HIPEC	0.675	0.467-0.977	0.037	0.676	0.467-0.979	0.038
germline and/or tumor *BRCA1/2*m	0.519	0.277-0.972	0.041	0.513	0.274-0.961	0.037
***BRCA1*-like/*BRCA*wt**	1.216	0.815-1.813	0.338	1.201	0.806-1.790	0.369

* Variables included in the model are treatment arm (HIPEC vs. no HIPEC) and *BRCA*-subgroup (*BRCA1/2*m vs. *BRCA1*-like/*BRCA*wt vs. non-*BRCA1*-like)

A significant independent beneficial effect remained for treatment with HIPEC (HR 0.676 [95% CI 0.467-0.979], p =0.038, and having a *BRCA1/2* mutation in multivariable analysis for OS (HR 0.513 [95%CI 0.274-0.961], p=0.037). Having a *BRCA1*-like/*BRCA*wt tumor did not appear a prognostic factor in both univariate and multivariable analyses for RFS and OS; see table 8.2.

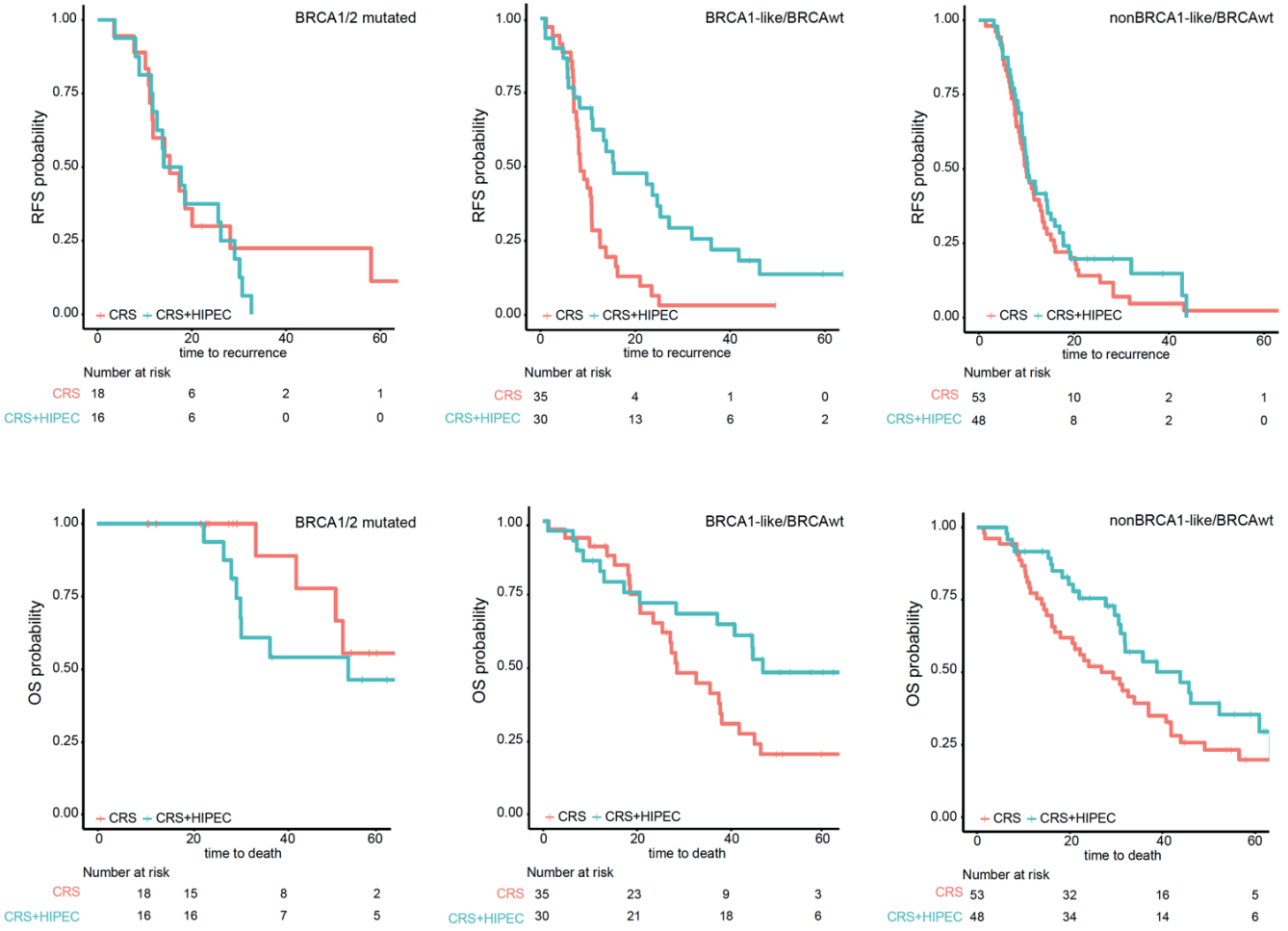

Figure 8.2. Kaplan-Meier curves for BRCAmut, BRCA1-like/BRCAwt, and non-BRCA1-like patients for RFS and OS by treatment arm

Discussion

Patients with stage III ovarian cancer whose tumor harbor a *BRCA1*-like HRD genomic profile without pathogenic *BRCA1/2* tumor mutations, benefit most from the addition of HIPEC to interval cytoreductive surgery. These analyses provide evidence that HRD assessed with the ovarian cancer *BRCA1*-like classifier is a potential tool for selection of patients who may benefit from HIPEC.

We hypothesized that patients with HRD tumors were most likely to benefit from treatment with HIPEC. We here show that HIPEC may not add additional benefit over intravenously administered platinum for patients with *BRCA1/2*m tumors. Patients with *BRCA1/2*m tumors are particularly sensitive to the platinum chemotherapy, and HIPEC might not improve effects over intravenously administered chemotherapy. This might be enhanced by the neoadjuvant administration of the chemotherapy, possibly inducing resistance. The *BRCA1/2*m subgroup was particularly small (n=34), and more data is required to study the effect of intraperitoneal chemotherapy and HIPEC in this specific subgroup.

The HRD/*BRCA*wt tumors derive significant benefit of HIPEC. The HRD phenotype in these patients is explained by other mechanisms than *BRCA1* dysfunction alone and may result in intermediate *BRCA1* or *BRCA2* protein function. Possibly, an intermediate intrinsic ability to repair DS DNA breaks can be further hampered with hyperthermia leading to significant tumor cell kill and the observed recurrence free and overall survival benefit. Hyperthermia has shown to deplete *BRCA1* and *BRCA2* protein function, and upregulate mammalian heat-shock proteins (HSP).[13, 21] *HSP90* inhibition disrupts DNA damage repair pathways, induces further *BRCA1* protein degradation, and thereby sensitizes cells to the DNA damage caused by platinum or poly(adenosine diphosphate [ADP]–ribose) polymerase (PARP)-inhibition.[22, 23] *HSP* inhibition further causes cellular sensitivity to hyperthermia, by degradation of *BRCA2*, resulting in suppressing homologous recombination.[14] These results strengthen the hypothesis that hyperthermia degrades *BRCA1* and *BRCA2* function, sensitizing HRD/*BRCAwt* tumors with the presumable intermediate sensitivity to platinum.

For patients with non-HRD signature, the trends for effect of HIPEC for both RFS and OS were less convincing. Probably, these tumors are HR proficient and thus well capable of DS DNA damage repair, despite hyperthermia. The exploratory nature of our analyses prohibit firm conclusions and these patients might actually benefit from HIPEC, given the HR <1 and broad confidence intervals (HR 0.82 and 0.63 for RFS and OS, respectively). Trends for the effect of HIPEC in the different subgroups are hypothesis generating and the results should be confirmed in independent datasets. Additional hypothesis regarding the optimal temperature, chemotherapy agent and concentration and the duration of HIPEC need to be evaluated in further studies.

The population included in this ancillary pathology study, comprised 82% of the total OVHIPEC-1 study population. Within this group, deleterious germline/tumor *BRCA1* or *BRCA2* mutations were identified in 34 (17%) patients (table 8.1). Both the total prevalence of pathogenic *BRCA1* and *BRCA2* mutations, and the proportion of germline mutants is likely higher in the total OVHIPEC-1 intention-to-treat population than we observed in this

dataset for two reasons. First, we were able to analyze 190 tumor samples of the 245 total patients. Second, standard hereditary testing was not performed for all patients at the onset of this trial (2006). Patients included early in the trial were less likely to be tested for germline mutations. We were not able to determine (blood-derived) germline mutational status. We relied on germline mutational status obtained from the patient file or the HEBON database for 54% of the individuals. In previously published ovarian cancer cohorts, germline and somatic mutations in *BRCA1/2* have been observed in 22-27% of tumors.[10, 24] The developed *BRCA1*-like HRD classifier had a sensitivity of 100% in recognition of pathogenic tumor *BRCA1* mutations. Of the patients with a HRD tumor, 29% had *BRCA1* or *BRCA2* mutations, 13% had other HRD related gene mutations and 10% had *BRCA1* promotor hypermethylation. The remaining 52% of HRD tumors, possibly represent tumors with other aberrations in the HRD pathway (see figure 7.2). This resembles the adequacy of the *BRCA1*-like classifier in breast cancer, and the results of the classifier in an earlier ovarian cancer dataset.[16, 20, 25]

This analysis has some limitations. First, although material was available for the vast majority of the trial population (82%), tumors that were most sensitive to neo-adjuvant chemotherapy were underrepresented due to missing tumor tissue. A relatively large proportion of these patients carried a germline BRCA mutation. Second, the OVHIPEC-1 trial did not include blood-sample collection. As a result, we were unable to collect blood-derived reference DNA to determine germline mutational status. Germline mutational status was derived from the patient file or the HEBON database in 54% of the individuals. For early inclusions, the germline mutation status was more often not determined.

We show that the developed HRD classifier is a potential tool for selection of ovarian cancer patients who benefit from treatment with HIPEC. The algorithm-based classifier was able to identify HRD tumors based on a *BRCA1*-like profile, with a sensitivity of 100% in recognizing tumor *BRCA1* mutations. Whether this HRD classifier is also predictive for platinum sensitivity, PARP-inhibitor resistance or PARP-inhibitor sensitivity, should be further explored.[26]

Conclusions

Our results show that an HRD*/BRCAwt* status obtained with the *BRCA1*-like ovarian cancer classifier may predict benefit for the addition of HIPEC to interval CRS in patients with stage III ovarian cancer. Benefit of HIPEC in patients with pathogenic *BRCA1/2* mutations and in those without HRD is less obvious. As this HRD classifier is a potential tool for selection of ovarian cancer patients who benefit from treatment with HIPEC, it may also predict the effect of other treatment modalities relying on HRD in ovarian cancer.

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Supplementary files chapter 8

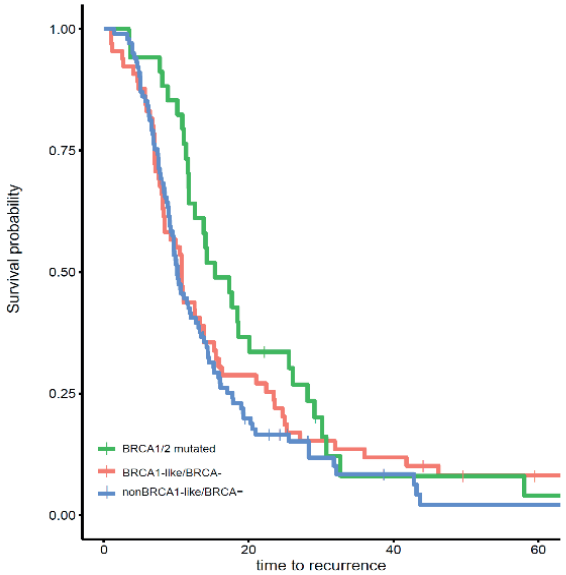
Table s8.1. Baseline characteristics of included patients vs. dropouts

	Patients included in pathology substudy N=200		Dropout for HRD analysis N=45		p-value†
Histological type (%)					0.403
- high-grade serous	178	(89%)	41	(91%)	
- low-grade serous	6	(3%)	0		
- carcinosarcoma	5	(3%)	0		
- clear-cell	4	(2%)	1	(2%)	
- high-grade endometrioid	2	(1%)	0		
- high-grade mucinous	2	(1%)	1	(2%)	
- low-grade endometrioid	2	(1%)	0		
- gastro-intestinal tumor	1	(1%)	0		
- unknown*	0		2	(4%)	
***TP53* mutation (%)**					
- yes	163	(82%)	unknown		
- no	27	(14%)	unknown		
- unknown	10	(5%)	45	(100%)	
Pathologic response (%)					<0.001
- complete/near complete	7	(4%)	27	(60%)	
- partial/no response	166	(83%)	9	(20%)	
- unknown*	27	(14%)	9	(20%)	
***BRCA*mut (%)**					<0.001
- *gBRCA1m*	13	(7%)	3	(7%)	
- *sBRCA1m*	7	(4%)	unknown		
- *gBRCA2m*	10	(5%)	3	(7%)	
- *sBRCA2m*	4	(2%)	unknown		
- *BRCA1/2wt*	159	(80%)	1	(2%)	
- no panel mutation or germline information available*	7	(5%)	38	(84%)	
Treatment					0.071
- interval CRS	106	(53%)	17	(38%)	
- interval CRS + HIPEC	94	(47%)	28	(62%)	

* not included for test

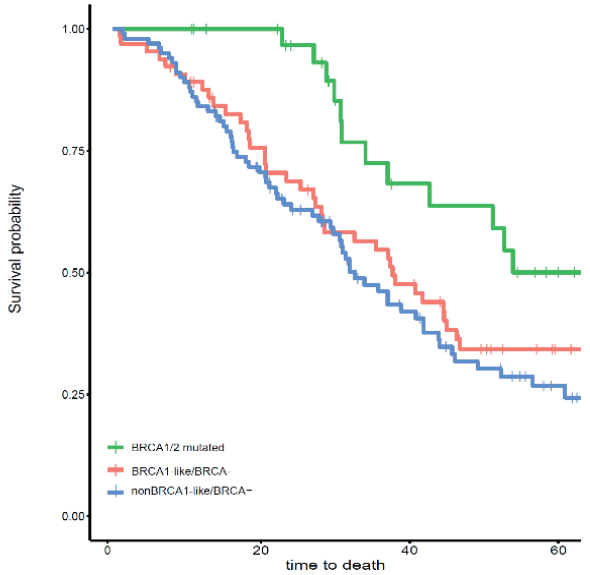
† exact test p-value

Abbreviations: CRS, cytoreductive surgery; HIPEC, Hyperthermic Intraperitoneal Chemotherapy



Number at risk table

BRCA1-like/BRCA-	65	17	7	2
BRCA1/2 mutated	34	12	2	1
nonBRCA1-like/BRCA-	101	18	4	1



Number at risk table

BRCA1-like/BRCA-	65	44	27	9
BRCA1/2 mutated	34	31	15	7
nonBRCA1-like/BRCA-	101	66	30	11

Supplementary table s8.1. Kaplan meier curves for RFS and OS, stratified by the BRCApos, BRCA1-like/BRCAwt, and nonBRCA1-like group

CHAPTER 9
General discussion

Parts of this chapter appear in the following articles:
S.N. Koole, W.J. van Driel, and G.S. Sonke
Hyperthermic intraperitoneal chemotherapy for ovarian cancer: the heat is on.
*Cance*r 2019; Supplement 24: 4587-93

S.N. Koole, R. van Stein, K. Sikorska, D. Barton, L. Perrin, D. Brennan, O. Zivanovic, B. J. Mosgaard, A. Fagotti, P. E. Colombo, G.S. Sonke, and W.J. van Driel
Primary cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy (HIPEC) for FIGO Stage III epithelial ovarian cancer: OVHIPEC-2, a phase III randomized clinical trial.
International Journal of Gynecological Cancer 2020;30(6):888-92

There is a great unmet medical need to improve the treatment for women with advanced ovarian cancer. The publication of the OVHIPEC-1 results elicited a fierce debate in the field of gynecologic oncology. While the randomized evidence of improved recurrence-free and overall survival following HIPEC was welcomed by many professionals and patients alike, criticism regarding the design and outcome of the study was also ventilated by several experts in the field. Various national and international treatment guidelines currently advice HIPEC as addition to interval cytoreductive surgery in advanced ovarian cancer, but others conclude that confirmatory evidence is required before HIPEC can be considered standard of care.[1] This chapter discusses the opposing views on the OVHIPEC-1 data and highlights directions for future research. We furthermore discuss the mechanism of action, selection of patients with ovarian cancer for treatment with HIPEC, and provide insight in current developments in treatment for patients with advanced stage ovarian cancer.

OVHIPEC-1 opposing views

OVHIPEC-1 randomized patients with FIGO stage III ovarian cancer to interval cytoreductive surgery with or without HIPEC. After a median follow-up of 4.7 years, we observed significant improvement in recurrence-free (HR, 0.66; 95% CI, 0.50-0.87), and overall survival (HR, 0.67; 95% CI, 0.48-0.94) (**chapter 2**).[2] Various issues were raised and will be discussed, regarding the surgical quality, random imbalances in prognostic variables between the treatment groups, the trial endpoint, the open-label design of the study, safety of HIPEC, and evidence from other clinical trials.

Surgical quality

There was no evidence to suggest any difference in surgical quality between both treatment arms: in nearly all patients, a complete or nearly complete (residual disease <2.5mm) cytoreductive surgery was reached (106 patients in the interval CRS arm [86%], and 106 patients in the interval CRS and HIPEC arm [87%]). The number of patients receiving bowel resection was also similar: 30 (24%) in the interval CRS group and 29 (24%) in the interval CRS and HIPEC group.[2] The study was carried out in eight hospitals with experience in performing HIPEC in patients with peritoneal disease from colon cancer or pseudomyxoma peritonei. There were no specific HIPEC teams in the participating centers; all surgical teams had experience in performing HIPEC and were devoted to obtain complete cytoreduction in all patients, regardless of the allocated treatment arm. Time between surgery and start of adjuvant chemotherapy did not differ between arms, nor did the number of patients completing six cycles of chemotherapy. The number of patients receiving treatment for recurrent disease was also similar (26/123 patients [25%] in the interval CRS group vs. 23/122 patients [24%] in the interval CRS and HIPEC group). These finding all indicate that the treatment patients received after surgery are unlikely to explain the results of the trial.[2]

Random imbalances

Questions have been raised regarding bias that might have been introduced in the OVHIPEC-1 trial by imbalances in prognostically important variables. Clearly, however, the peroperative randomization process in OVHIPEC-1 precluded systematic bias at baseline of all measured and non-measured prognostic variables.[3] OVHIPEC-1 was well balanced for age, FIGO substage, response to neo-adjuvant chemotherapy, hospital size, histological subtype

BRCA-status, and the extent of disease at start and at the end of the surgical procedure (**chapter 2, chapter 3, chapter 8**). The number of patients with non-high-grade serous histology in our study was nine in the HIPEC arm, versus 15 in the control arm, an imbalance compared to a perfect 1:1 randomization of only three patients. The imbalance in non-high-grade serous subtypes is therefore very unlikely to explain the outcome of the trial. The proportionality of the survival curves over time also point to the fact that a small imbalance, in for instance low grade tumors, cannot explain the benefit that was observed in the CRS plus HIPEC group. Nevertheless, given the relatively small sample size, the OVHIPEC-1 trial is somewhat more prone to be affected by random imbalances compared with other phase 3 trials in ovarian cancer. Most importantly, however, highlighting a random imbalance, in for example histologic subtype, ignores the general principle that randomization ensures equality of prognosis based on all known and unknown prognosticators combined.

The primary endpoint

As advocated by the 3rd consensus statements on the management of ovarian cancer the primary outcome of the trial was recurrence-free survival, to prevent bias from treatment for recurrent disease.[4] Sample size calculation indicated that 192 events were needed to detect a 50% increase in median recurrence-free survival (from 18 to 27 months, HR 0.667) by the addition of HIPEC to interval cytoreductive surgery, with 80% power and an overall two-sided type I error of 0.05. The median RFS in the control arm was assumed based on the data available at the time of trial design.[5] OVHIPEC-1 was an investigator-initiated trial with funding from the Dutch Cancer Society for data management only. Hospitals had to pay for the HIPEC procedures they performed without reimbursement from health insurance companies or industry, and accrual per year was therefore maximized in most hospitals. As a result, the accrual time was longer than anticipated, and the required 192 events of disease recurrence were reached before the initially anticipated number of patients were included. Due to a relatively long follow-up, but with the sufficient number of RFS events to perform primary analysis, a relatively small number of accrued patients were needed compared to other phase 3 trials in ovarian cancer. The hazard ratios for RFS and OS reported from the OVHIPEC-1 trial are almost identical, alluding to the fact that RFS is a valid surrogate endpoint for OS in this setting.[5, 6] Given the similar HRs and the lower rate of OS events than RFS events, the absolute improvement in median OS (12 months) is larger than in median RFS (3.5 months). HIPEC adds about a third of RFS time and about a third of OS time compared to the control group. This pattern of similar relative and differing absolute RFS and OS benefit is also seen with adjuvant intraperitoneal chemotherapy, or interval vs. primary surgery.[5, 7, 8] When comparing the median RFS and OS estimates in the OVHIPEC-1 trial to those reported in other ovarian cancer trials, it is important to account for the timing of randomization. While many studies randomized patients shortly after diagnosis [7-11], the OVHIPEC-1 trial randomized during interval surgery, approximately 14 weeks (3.2 months) after diagnosis.

Open-label design

As a double blinded study design with the HIPEC procedure was considered unfeasible, the open-label design of the OVHIPEC-1 trial may have introduced bias. First, there is a potential surgical bias that can work in both directions: knowing the outcome of randomization during

surgery could theoretically either result in "better" or "worse" surgery for those randomized to HIPEC. However, as previously discussed, there was no indication of more radical surgery in either of the groups, with similar rates of minimal residual disease and a same number of bowel resections. Second, there is a potential bias in investigators' assessment of recurrences. Regularly planned serum CA-125 measurements and CT-scans during follow-up were strictly defined in the protocol and adhered to, to overcome differences between the study arms. In order to ensure the open-label design did not affect results of the primary outcome (recurrence-free survival), we performed blinded centrally-assessed recurrence-free survival analysis in **chapter 3**. This central blinded review of all imaging studies confirmed the earlier reported investigator-assessed recurrence-free survival benefit, and shows the open-label design did not affect the assessment of recurrence-free survival. The median recurrence-free survival was slightly shorter compared with the investigator-assessed recurrence-free survival, potentially because the trained radiologist was more prone to find evidence for recurrent disease during retrospective reviewing.

As discussed above, the various suggested biases are all very unlikely to explain the statistically significant survival benefit observed in patients randomly allocated to receive HIPEC in addition to interval cytoreductive surgery. Nevertheless, the level of evidence for HIPEC in this setting will improve if the results of OVHIPEC-1 can be confirmed in another randomized trial. While acknowledging the importance of critical review of trial results and trial designs before implementation, the agonizing discussions about intraperitoneal chemotherapy and HIPEC lead to confusion and distraction from the evidence. The mind of the critical researcher is trained to identify every possible circumstance that may introduce bias in a clinical trial. The general philosophical rules of science advise on testing hypotheses by trying to refute them. Instead, people in general quite often seek data that are likely to be compatible with the beliefs they currently hold. This confirmation bias is a result of the unconscious associative mind which might lead to exaggeration of the likelihood of extreme and improbable events.[12]

The similarity of the discussions about the OVHIPEC-1 trial and the earlier adjuvant intraperitoneal chemotherapy trials is striking, as is the reluctance to adopt either method of intraperitoneal treatment despite randomized phase 3 data. Meanwhile, other interventions, like surgery in the recurrent setting, are easily adopted in international guidelines despite the lack of mature comparative data. Confirmation bias may play a role in the methodological issues raised regarding studies on intraperitoneal chemotherapy in general and the OVHIPEC-1 trial in particular.

Safety and quality of life

The HIPEC procedure prolonged surgical time with 146 minutes. The median duration of hospitalization was two days longer after HIPEC, including admission to the intensive care unit for one day, according to protocol. While the number of patients with a complete resection and the number of patients requiring bowel surgery were similar in both treatment arms, numerically more patients in the HIPEC arm received a colostomy or ileostomy, although this difference was not statistically significant (13/123 [11%] after interval CRS vs. 21/122 [17%], p=0.19 after interval CRS+HIPEC). Treatment with HIPEC was thought to cause more

anastomotic leakage, although literature remains contradictory. In the OVHIPEC-1 trials, we did not observe more anastomotic leakage after HIPEC. The numeric difference observed in the OVHIPEC-1 trial probably reflects some precaution of the involved surgeons and should be discussed with patients during counseling. There is no evidence to suggest that HIPEC increases the rate of anastomotic leakage, and this issue deserves further study.

The incidence of investigator reported adverse events of any grade did not significantly differ between both arms of the trial (115/122 [94%] in the interval CRS group, and 113/118 [96%] of patients in the interval CRS and HIPEC group, **chapter 2**). The distribution of observed adverse events was similar (p-value: 0.67 [exact Fisher test for testing independence between arm and grade distribution]), although a bias in reporting toxicity cannot entirely be ruled out in open label trials like OVHIPEC-1. For data collection on safety and adverse events after surgery with HIPEC, the NCI-CTCAE classification is an accurate measurement tool. Comparison with for example the Clavien-Dindo method, shows that the latter may underestimate post-operative morbidity compared to the NCI-CTCAE classification after treatment with surgery and HIPEC.[13]

During the trial, quality of life was scored using the EORTC QLQ-C30 questionnaire, which is a validated and widely used measure of the quality of life of cancer patients.[14] The quality of life data, with pre-specified focus on the QLQ-C30 summary score, and symptom scales for fatigue, neuropathy and gastro-intestinal symptoms was analyzed using linear and non-linear mixed effect models (**Chapter 5**). Analysis of the patient-reported outcomes indicate comparable health-related quality of life and symptom burden between patients treated with interval CRS and HIPEC and those treated with interval CRS without HIPEC.[15] These analysis are hampered by trial not being powered for patient reported outcome measure analysis, and the undesirable compliance of questionnaires during the trial.

Clinical evidence for HIPEC for ovarian cancer besides OVHIPEC-1
Two case-control studies concluded that HIPEC was feasible and safe in the management of primary ovarian cancer, but were not able to conclude about the effect of HIPEC on survival.[16, 17] Other case-control studies showed effects in terms of promising 1-year survival numbers, which is confirmed by a review of a selection of comparative studies.[18] A recent meta-analyses including randomized controlled trials and case control studies, showed better outcome after treatment with surgery and HIPEC, in patients with primary advanced ovarian cancer (pooled HR for OS 0.54 [95% CI 0.45-0.66], for PFS 0.45 [95% CI 0.32-0.62]).[19] This meta-analysis also confirms the finding in the OVHIPEC-1 trial that the addition of HIPEC to surgery does not increase toxicity.[2, 16, 20] A Korean study group presented preliminary results of a randomized trial at the 2017 ASCO annual meeting.[21]

These interim findings were hampered by a low number of events and were based on a combination of patients treated with upfront surgery and patients receiving neo-adjuvant chemotherapy. The study also pooled patients with stage III and IV disease, and used a sub-optimal dose of cisplatin (75 mg/m^2). Nevertheless, a preliminary subgroup analysis of patients treated with neo-adjuvant chemotherapy revealed promising results; the two-year PFS was 37.2% in the HIPEC group and 29.5% in control group (HR for PFS 0.288 [CI 0.083-

0.996]), the five-year OS was 47.9% in HIPEC group and 27.7% in control group. We await the publication of the full results of this trial before drawing further conclusions.

The OVHIPEC-1 trial population and sarcopenia
Previous studies reported worse outcome in patients with ovarian cancer and a reduction in muscle mass during neo-adjuvant treatment.[22-24] To validate these findings, we analyzed whether a decrease in skeletal muscle mass (or sarcopenia) during neo-adjuvant chemotherapy was associated with worse outcome in the OVHIPEC-1 patients.[22, 25] Although a loss of skeletal muscle mass was detected in 65% of the present cohort, we did not confirm the earlier findings as sarcopenia during two cycles of neo-adjuvant chemotherapy was not associated with poor outcome (**chapter 4**). A possible reason for the lack of an association between decrease of skeletal muscle mass and outcome is the fact that our study population is relatively fit and does not fully represent the real-world ovarian cancer population. We did observe a significant association of sarcopenia with reported toxicities This finding might indicate that skeletal muscle depletion is a measure of clinical fitness that impacts the patients' ability to receive maximum treatment and thereby affects survival, rather than being an independent prognostic variable on its own.

Mechanism of action of HIPEC
Various issues regarding the use of HIPEC in ovarian cancer remain. One subject of debate deals with HIPEC's mechanism of action and in particular the contribution of hyperthermia. In addition, the optimal technique, timing, regimen, dose and concentration are not yet fully known.

In vitro and in vivo research shows that hyperthermia to 41-43 °C has a direct cytotoxic effect on tumor cells and induces heat-shock proteins that serve as receptors for natural killer-cells, leading to apoptosis and inhibiting angiogenesis.[26-28] Hyperthermia also causes depletion of *BRCA1* and *BRCA2* protein and thus impairs *BRCA1/2* protein function. As a result, tumor cells are disabled to repair double-strand breaks and become more homologous recombination deficient (HRD), thereby sensitizing these tumors to the platinum containing or alkylating chemotherapy that is introduced during HIPEC.[29-32] Hyperthermia thus increases the cytotoxicity of platinum compounds and alkylating agents by enhancing the creation of DNA adducts leading to cell death.[33, 34]

In vitro research showed that intraperitoneal administration of cisplatin results in therapeutic intracellular drug concentrations, with a penetration depth of 1-3 mm.[35, 36] Multiple cytotoxic agents are used for administration of HIPEC. Platinum containing chemotherapy such as carboplatin, cisplatin, oxaliplatin, but also mitomycin C, paclitaxel and 5-fluorouracil are used. The intrinsic activity of a chemotherapeutic agent is leading for the agent of choice. Ovarian cancer is in general sensitive to platinum agents, and cisplatin was the agent of choice. Cisplatin has the ability to reach relatively high intracellular concentrations, with a penetration depth of 1-3mm. Dosing of chemotherapy is usually based on a patient's body surface area (BSA). The chemotherapeutic agent is dissolved in heated saline, and the total volume that is used to fill the abdomen depends on the size of a patient's intraperitoneal cavity. BSA, however, is not an accurate surrogate for the

peritoneal surface or abdominal capacity. As a result, there is a variation in the delivered concentration of chemotherapy.[37] Concentration based intraperitoneal chemotherapy dose methods might therefore be implemented to optimize dose delivery.

HIPEC can be performed using an open or closed (also called "coliseum") technique.[38] With the open technique, the surgeon pulls the surrounding laparotomy skin towards a retractor ring that is suspended above the abdominal surface. An elevated rim is formed, providing access to the abdominal cavity during the procedure. With the closed technique, the laparotomy skin edges are (temporarily) sutured during the procedure. In both methods, inflow and outflow catheters and temperature sensors are placed inside the abdominal cavity in a similar way. The open technique is mostly preferred, as temperature regulation is more consistent and fluid distribution is easier controlled. Moreover, manual manipulation or "stirring" of the fluid is more effective with the open technique. The role of manual manipulation is uncertain, but because of the circulation that is created using inflow and outflow catheters, logically this results in more stable concentrations and a larger area of contact of the chemotherapeutic solution with the peritoneal surface. Sugarbaker et al. showed that contact with the peritoneum was quite variable, when infusing blue dye into the peritoneal cavity.[39] To overcome this, the closed system is used with a single inflow catheter and often multiple outflow catheters.[40, 41] Currently available evidence suggests both HIPEC techniques are effective, and safe with regard to exposure of chemotherapy to health care personnel.[42] A comparative, randomized study could distinguish efficacy and toxicity of both techniques, but until today, these studies do not exist.

Intraperitoneal administration of chemotherapy specifically targets remaining microscopic disease after complete cytoreduction. In vitro research showed that intraperitoneal administration of chemotherapy results in higher intracellular concentrations, compared to intravenous administration of chemotherapy, with limited systemic exposure.[35, 36, 43] Up to 50% of patients with high-grade serous ovarian cancer are homologous recombination deficient (HRD) due to germline or somatically acquired *BRCA1* or *BRCA2* mutations, epigenetic inactivation of *BRCA1*, or other *BRCA*-independent defects in the HR pathway.[44, 45] Platinum containing agents are specifically effective in the absence of homologous recombination, since chemotherapy-induced double-strand breaks now will lead to activation of error-prone double-strand repair mechanisms such as nonhomologous end joining, leading to genomic instability and cell-death.[31]

Presumably, tumors with an intermediate phenotype between HRD and HR proficiency, may derive most benefit from HIPEC, since hyperthermia will further impair *BRCA1* and *BRCA2*, conferring a more profound HRD phenotype [30, 46] Possibly, the hyperthermia of the HIPEC procedure further sensitizes these HRD-prone tumor cells to the platinum-component. In **chapter 8** we show that HIPEC appeared to provide little benefit in patients with germline or somatic pathogenic mutations in *BRCA1/2*. As these tumors are very platinum sensitive, HIPEC may not add benefit over intravenously administered platinum. As it seems, the *BRCA1*-like/*BRCA*wt tumors are additionally impeded in repairing double strand breaks by HIPEC, sensitizing them for the cisplatin compound in HIPEC and further chemotherapy treatment. The *BRCA1*-like status might be explained by other mechanisms

than *BRCA1* dysfunction and thus there might be residual *BRCA1* or *BRCA2* function, explaining the possible effect of HIPEC and hyperthermia in these patients. Translational studies analyzing potential biomarkers, the genetic background, and homologous repair deficiency may help selecting patients who will benefit most from HIPEC. Translational mouse models and organoïd studies could cover the separate effects of hyperthermia and chemotherapy, the optimal temperature, duration, the use of different chemotherapeutic regimen or even PARP-inhibition, and the optimal fluid concentration, as is already done in recent literature.[47-49]

To identify tumors that harbor HRD, DNA copy number variation (CNV) profiles generated by comparative genomic hybridization (CGH) can display gains and losses over the genome. Computer based algorithms can classify tumors into being *BRCA*-like or non-*BRCA*-like, based on the CNV-profile derived data.(14-18) Recently, such a classifier was developed to class ovarian tumors into a *BRCA1*-like or non-like CNV-profile, and was validated on a large dataset.[50]

Identifying the HRD tumors is increasingly relevant for treatment selection. Different HRD-tests are currently used to differentiate HRD from HR proficient ovarian and breast tumors. These tests are based on 1) scores capturing large genomic aberrations, so-called 'genomic scars', 2) analysis of mutational signatures or 3) point mutations identified in homologous recombination repair genes using DNA sequencing panels.[51-54] The accuracy of these tests, however, remains uncertain, since there is no accepted gold standard and the false negativity and false positivity can never be confirmed.[55] Ideally there would be one uniform functional test, able to for adequate treatment selection. Genome-wide copy-number aberration data can be used to visualize genomic scar signatures of defective DNA repair in tumors.[52, 56] So called copy-number variation profiles give insight in gains and losses of genomic sequences, and based on this profiles tumors can be grouped to specific mutational patterns, resembling homologue-recombination deficient tumors. We developed an algorithm-based classifier, able to classify *BRCA1/2* mutated tumors as being *BRCA*-like, with 100% sensitivity in recognizing *BRCA1* mutated tumors in the OVHIPEC-1 cohort (**chapter 7**). Of all the *BRCA1*-like tumors, over 50% was explained by mutations in *BRCA1* or *BRCA2*, other HRD-related genes, or *BRCA1* promotor hypermethylation.

Patient selection

To find predictive factors for the effect of HIPEC in patients with ovarian cancer in order to select the right patient population and prevent overtreatment, we perform several subgroup analyses for recurrence-free and overall survival throughout this thesis. Subgroup analyses for recurrence-free and overall survival showed that the effect of HIPEC was homogenous across the levels of pre-defined stratification factors (institute, previous surgery, and the number of involved abdominal regions) and post-hoc subgroup-analyses (age, histologic type, previous laparoscopy, **chapter 2**). Exploratory subgroup analyses were performed on response to neo-adjuvant chemotherapy and PCI-score, showing a similar effect of HIPEC across all subgroups (**chapter 3**). Subgroup analyses for patients with a *BRCA1/2* mutated tumor, a *BRCA1*-like/*BRCA*wt tumor, or a non-*BRCA1*-like tumor, suggested that patients with stage III ovarian cancer and a *BRCA1*-like genomic profile without pathogenic *BRCA1/2*

mutations, possibly benefit most from treatment with interval cytoreductive surgery and HIPEC (**chapter 8**). Caution is warranted when emphasizing the effects within subgroups of a randomized trial. Subgroup analyses are generally undertaken to investigate the consistency of the trial conclusions among different subpopulations defined by baseline characteristics of the patients. A statistical test for interaction is the basis for conclusion regarding the (lack of) consistency. A common mistake is to claim heterogeneity on the basis of separate tests of treatment effects, for example within inclusion centers, without formal test for interaction.[2, 57] Though the effect of HIPEC is negligible in *BRCA1/2*m tumors, preferably further powered analyses should confirm the earlier mentioned results.

Implementation of HIPEC for interval cytoreduction

Following the results of the OVHIPEC-1 trial, HIPEC added to interval cytoreductive surgery was implemented in the Netherlands in 2019 and included in various international guidelines. The treatment is offered to stage III patients undergoing interval cytoreduction in 10 Dutch hospitals. The beginning of the COVID-19 pandemic reduced numbers of HIPEC procedures performed, mostly as a result of the increased pressure on intensive care units. Although there is national willingness, HIPEC might still be seen as an additive rather than standard of care, as it shortly ebbed away in this precarious situation. For the financial coverage of HIPEC following interval cytoreduction for patients with advanced ovarian cancer, we studied the cost-effectiveness of the addition of HIPEC by constructing a Markov health-state transition model. The incremental cost-effectiveness ratio (ICER), expressed as Euro per quality-adjusted life-year (QALY) was calculated. Although treatment with interval CRS and HIPEC costs about €15.500 euro more than without HIPEC, it is accompanied by a substantial gain in mean QALYs, from 2.12 without HIPEC to 2.68 in the group treated with interval CRS an HIPEC. The ICER amounted to €28,299 per QALY, which is under the Dutch willingness-to-pay threshold of €80,000 (**Chapter 6**).[58] These results lend support for reimbursing the costs of treating these patients with interval CRS and HIPEC in countries with comparable health care systems. The analysis represents the cost-effectiveness of the trial situation, and incorporates all study measurements, also for follow-up. A budget impact analysis of HIPEC for ovarian cancer after implementation on a Nation-Wide level, could therefor result even in slightly lower costs. The results only imply to the current setting, but could alter in other treatment settings, countries, or health-care systems. Although the implementation of HIPEC requires education of staff, nurses, operation room team, involvement of a perfusionist, operation equipment, training of anesthesia experts, pharmacists, handling of toxic waste, spill management, personal protection, diuresis control, preventive measures against renal toxicity, temperature regulation and electrolyte control; these measures are all close to the standards for regular surgery and chemotherapy care. The additional costs do not come close to costs of novel treatment strategies, such as costs for niraparib (~330 euro per patient per day, ICER = 235.000 dollar per PFS life-year), or bevacizumab (~3.000 euro per cycle, per patient in the Netherlands).[59]

HIPEC and primary cytoreductive surgery

Because the OVHIPEC-1 results are only considered relevant for the patient population that resemble the included patients in the study, HIPEC is now implemented for stage III patients

that need neo-adjuvant chemotherapy. For patients with the same stage ovarian cancer but less extensive abdominal disease, who can undergo primary cytoreduction, the additive effect of HIPEC is considered not to be justified. Apart from the extend of disease, these patient-groups are very much alike the OVHIPEC-1 population, with the same nature of the disease, tumor genetic background, and the same hypothesis for working mechanism of HIPEC. For pharmaceutic treatment options, quite regularly trial results are extrapolated to broader patient groups than included in the evidence providing trials. For example, the PRIMA study showed evidence that Niraparib improves recurrence-free survival in advanced stage ovarian cancer.[60] This study, 99.6% of patients had residual disease >1cm after primary cytoreduction, for whom 67% received neo-adjuvant chemo and secondary cytoreduction. EMA registration nevertheless includes all patients with advanced stage ovarian cancer, regardless of the timing and success of surgery. This is just one example of the inconsistent judgement of extrapolation of study results within the field of oncology.

Given the reluctance to the uptake of HIPEC for ovarian cancer patients, and to prevent unjustified extrapolation of results, we designed the OVHIPEC-2 study (NCT03772028).[61] The OVHIPEC-2 trial evaluates if HIPEC is also beneficial in combination with upfront cytoreductive surgery. Patients with stage III ovarian cancer are eligible after complete or nearly complete (residual disease <2.5mm) primary cytoreductive surgery and are randomized (1:1) to receive HIPEC or no HIPEC. Patients are stratified for the institute in which they are treated, for low (0-15), intermediate (16-30), or high (31-45) ovarian PCI score at the start of surgery, and for the completeness of surgery (CC0: complete cytoreduction, or CC1: residual disease up to 2.5mm). All patients are treated with six cycles of adjuvant chemotherapy. The trial is designed as an open-label, international, multicenter randomized phase III trial, with overall survival as primary endpoint. Secondary endpoints are recurrence-free survival, time to subsequent anticancer treatment, and toxicity. Time to second subsequent anticancer treatment, quality of life analysis and economic- and cost-effectiveness are exploratory endpoints. Intra-operative randomization after cytoreduction will minimize surgical bias caused by the open-label design. The OVHIPEC-2 trial is currently recruiting in the Netherlands and France, and will be recruiting in other countries as well.

Primary cytoreductive surgery, HIPEC and adjuvant intraperitoneal chemotherapy

Since the publication by Armstrong et al. on primary cytoreduction with adjuvant intraperitoneal chemotherapy, this option is offered to our patient today in the Netherlands in a selected number of hospitals.[5] This resembles the exact target population for OVHIPEC-2, and therefore this adjuvant option is also included in the OVHIPEC-2 trial. As adjuvant intraperitoneal chemotherapy can be accompanied by nausea, renal dysfunction, pain and catheter related problems, safety of the combination of HIPEC followed by intraperitoneal chemotherapy is strictly controlled. The decision for adjuvant chemotherapy should not affected by the outcome of randomization, and therefore numbers of patients receiving intraperitoneal chemotherapy in each arm is monitored. Intraperitoneal chemotherapy is often discussed when counseling patients, but in the end only applied to the minority of patients who undergo primary cytoreductive surgery. No trial has compared HIPEC with adjuvant intraperitoneal chemotherapy and the relative or added efficacy of both interventions is thus unknown.

A changing landscape

In the last decade, novel systemic strategies as dose-dense chemotherapy, maintenance anti-angiogenic therapy, maintenance PARP inhibition have been introduced in the treatment of advanced ovarian cancer.[9, 62-67] Most striking were the results from the SOLO-1 trial, where the risk of disease progression or death was 70% lower with olaparib than with placebo after a median follow-up of 41 months.[67] Treatment with PARP-inhibitors is now standard of care following response to platinum-containing chemotherapy. Results from the PRIMA and VELIA trial emphasize the effect of PARP-inhibition in the HR-deficient and *BRCA1/2* mutated populations.[60, 68] PARP-inhibitors are probably less effective in tumors that shift more towards HR-proficiency. In the PRIMA subgroup of patients with homologous-recombination proficient tumors, the median duration of progression-free survival was 8.1 months in the niraparib group and 5.4 months in the placebo group (hazard ratio, 0.68; 95% CI, 0.49 to 0.94).[60] Although this 95%-CI for the HRP subgroup is statistically significant, this most likely reflects a lack in specificity in the HRD/HRP classification or unknown mechanisms of action of PARP-inhibitors in only a small subset. As said before, 99.6% of the stage III patients in the PRIMA trial had residual disease after primary cytoreduction, 67% received neo-adjuvant chemotherapy and interval cytoreduction. When comparing the PRIMA RFS of the niraparib group (8.1 months)[60] with the results of the control-arm of the study of Armstrong et al. (18.3 months after complete/optimal primary cytoreduction)[5], this only highlights the importance of complete surgery, and reminds us that we could question the use of PARP-inhibitors for HRP tumors, especially after complete or near complete surgery. An appropriate and uniform HRD test should distinguish the patients without HRD mutations that might benefit from treatment with PARP-inhibition. Overtreatment with PARP inhibition goes at a high price, with costs of about 100 euro per patient per day, but also with various consequences in terms of toxicity (grade 3-4 anemia in 22%), and should be avoided as much as possible.[67]

Whether HIPEC and PARP-inhibition strengthen or counteract each other's effects is yet unknown. What is the additional effect of HIPEC once all patients receive maintenance PARP-inhibitors, or vice versa? Our analysis in **chapter 8** suggests that treatment with HIPEC might be withheld for patients with *BRCA1/2* mutations; those that are most likely to benefit from treatment with PARP-inhibitors, even with curative potential.[67] Our analysis suggest that patients with HR-deficient tumors without *BRCA1/2* mutation are most likely to benefit from HIPEC. For patients with HR proficient tumors treatment with HIPEC is currently less convincing, but as symptom burden and costs of treatment with HIPEC are low, these patients could get the benefit of the doubt.

One might hypothesize that PARP inhibition and HIPEC act synergistically. PARP-inhibition leads to stalling of replication forks due to accumulation of unrepaired single strand DNA breaks. Stalled replication forks degrade into highly cytotoxic double strand breaks. Hyperthermia induces further *BRCA1/2* protein degradation, and thereby sensitizes cells to the DNA damage caused by platinum or PARP-inhibition.[69-71] The relation between HIPEC and PARP-inhibitors is yet unknown and should be investigated in future research.

Concluding remarks

The OVHIPEC-1 trial shows that the addition of HIPEC to interval CRS improves survival for patients with advanced ovarian cancer in whom primary cytoreductive surgery is not feasible. HIPEC adds very little toxicity, and recent national and international guidelines include the option to consider HIPEC at the time of interval cytoreductive surgery in patients with stage III disease treated with neoadjuvant chemotherapy. Importantly, HIPEC as addition to interval cytoreductive surgery is cost-effective and is now fully reimbursed by the Dutch healthcare insurance. Treatment with HIPEC seems most effective for patients with HRD-tumors without *BRCA1/2* mutations, although these findings must be further validated. If confirmed, *BRCA1/2* tumor mutations and HRD profiles should be tested before start of neo-adjuvant chemotherapy to optimize patient selection for HIPEC. PARP inhibitors have successfully made their entrance into standard treatment options in the first line, although the effect of PARP-inhibition for completely operated, HR proficient tumors is unknown, and will remain unknown because of the implementation of niraparib for this population. This might result in overtreatment and unnecessary spending, contributing to the unendurable health-care system that we currently face.

Although scientific discussion about suggested novel treatment strategies is crucial, the criticism regarding intraperitoneal treatment with HIPEC seems out of proportion when compared to the ease of approval of expensive pharmaceutics. In particular, the ease at which new drugs or new indications are increasingly approved based on limited uncontrolled data from uncontrolled studies is in sharp contrast to the level of critique that implementation of HIPEC has faced. Strong lobby from industry and pharmaceutical companies sometimes results in decision making with diverged standards. Global healthcare expenditures are rapidly rising, and while pricing of medicines should be better controlled, also extension of market authorization for new indications without sufficient evidence should be prohibited.

While the results of the OVHIPEC-1 trial are preferably confirmed in further large high-quality trials, all evidence that is currently available points to a clinically relevant effect of interval cytoreduction and HIPEC for ovarian cancer patients without adding much toxicity. The treatment is cost-effective in healthcare settings similar to the Netherlands. While others advocate that practice should not change until these results are confirmed, we believe that HIPEC in addition to interval cytoreductive surgery should be discussed as a valuable treatment option within the appropriate subset of ovarian cancer patients today.

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CHAPTER 10

Summary (English)
Samenvatting (Nederlands)

Summary

HIPEC for ovarian cancer

Ovarian cancer that has spread to the peritoneal surface is categorized as stage III. Treatment consists of cytoreductive surgery and six cycles of chemotherapy. Surgery can either be the initial treatment ("*primary cytoreductive surgery*") or can be planned after the first three cycles of chemotherapy ("*interval cytoreductive surgery"*). *Hyperthermic intraperitoneal chemotherapy,* or HIPEC in short, is an additive treatment option in which the peritoneal surface is rinsed with heated chemotherapy.

In this thesis, we described the results of the OVHIPEC-1 study. OVHIPEC-1 was the first phase III study to evaluate the effect of HIPEC in primary ovarian cancer and randomized 245 patients to receive interval cytoreductive surgery with or without HIPEC. Patients were eligible if primary cytoreductive surgery had not been feasible because of the extent of their disease and disease did not progress after two cycles of neo-adjuvant chemotherapy with carboplatin and paclitaxel. In **chapter 2**, we show that the addition of HIPEC to interval cytoreductive surgery improves recurrence-free and overall survival benefit in patients with stage III ovarian cancer. The median recurrence-free survival was 10.7 months in the surgery alone group and 14.2 months in the surgery+HIPEC group. The median overall survival was 33.9 months in the surgery alone group and 45.7 months in the surgery+HIPEC group. Treatment with HIPEC is safe as reported toxicity and adverse events were similar in both groups (25% in the surgery group and 27% in the surgery+HIPEC group).

The primary endpoint of the OVHIPEC-1 trial was investigator-assessed recurrence-free survival. CT-scans and serum CA-125 measurements were performed at regular intervals for patients in both treatment arms. Nevertheless, any open-label study is prone to biased endpoint assessments. Therefore, we performed central blinded assessment of all available CT-scans of patients that participated in the trial. This central assessment confirmed the benefit of adding HIPEC to interval cytoreductive surgery (**chapter 3)** and indicated that open-label bias had minimal impact on the results. In addition, we analyzed the primary site of disease recurrences and found confirmed that HIPEC specifically targets the peritoneal surface: the cumulative incidence of peritoneal recurrences was lower after surgery+HIPEC, but there was no apparent difference in the cumulative incidence of extra-peritoneal recurrences.

The CT-scans were further used to measure skeletal muscle mass index during neo-adjuvant chemotherapy. In **chapter 4**, we describe that a decrease in skeletal muscle mass (sarcopenia) during neo-adjuvant chemotherapy was not associated with worse recurrence-free or overall survival. This finding is in contrast with earlier results, possibly due to the fact that our study population is relatively fit and may not fully represent the real-world ovarian cancer population. We did observe a significant association of sarcopenia with reported side-effects from neo-adjuvant chemotherapy, indicating that sarcopenia measured on CT-scans can be a surrogate measure for treatment-burden or overall fitness.

In **chapter 5**, we describe our analyses of patient-reported health-related quality of life, assessed with questionnaires specific for reporting quality of life within the OVHIPEC-1 population. Health-related quality of life was a secondary endpoint of the OVHIPEC-1 trial, and analyses focused on a general summary score for quality of life, and symptom scores for fatigue, neuropathy and gastro-intestinal symptoms. No significant differences in general quality of life were observed over time, when comparing ovarian cancer patients treated with or without HIPEC. The pattern over time of symptom scores for fatigue, neuropathy and gastro-intestinal symptoms were similar as well.

The addition of HIPEC to the treatment of patients with ovarian cancer has some additional consequences. The median duration of surgery is prolonged with about 2.5 hours (chapter 2), the rinsing equipment and a perfusionist are needed during the procedure, patients are admitted to the medium or intensive care unit for one day after HIPEC and the total duration of hospitalization is prolonged. Whether the benefits of HIPEC outweigh these additional costs, was analyzed in a cost-effectiveness analysis that we describe in **chapter 6**. We showed that treatment with HIPEC is accompanied with an increase in costs of €15.500 per patient. We also show that treatment with HIPEC results in a yield of quality-adjusted life years (QALYs). The incremental cost-effectiveness ratio (ICER) amounted to €28,299 per QALY gained, which is under the willingness-to-pay threshold of €80,000 per ICER in the Netherlands.

The improved survival, limited side-effects, maintained patient-reported quality of life, and the acceptable cost-effectiveness, all support the addition of HIPEC to interval cytoreductive surgery in patients with stage III ovarian cancer. Following these results, HIPEC is now implemented in this setting in the Netherlands and incorporated in various international guidelines. Nevertheless, some gynecologists raised various points of critique regarding design and results of OVHIPEC-1. In **chapter 9**, we discuss these issues including timing of randomization, surgical quality, open-label design, random imbalances between treatment arms, generalizability, and the value of hyperthermia as a component of HIPEC. A remaining question is whether the benefits of HIPEC are similar for stage III ovarian cancer patients treated with primary surgery. This issue is the topic of the international phase III OVHIPEC-2 trial, which is currently open for patient accrual.

One of the possible mechanisms of action of HIPEC is that hyperthermia causes depletion of *BRCA1* and *BRCA2* proteins. *BRCA1/2* proteins in a (tumor)cell are crucial for double stranded DNA-damage repair. In case tumor cells harbor *BRCA1/2* mutations (and thus protein-disfunction), these cells are homologous recombination deficient and will not be able to recover from platinum-induced DNA damage. The elevated temperature of HIPEC, is thought to push cells that are *homologous recombination proficient* towards a state of *homologous recombination deficiency*. This effect disables them to recover from the simultaneously administered chemotherapy during HIPEC, with more tumor-cell death as a result. In **chapter 7** we validated a newly developed algorithm-based classifier. Based on the copy-number variation of the tumor, this test is able to identify a BRCA-like genomic scar that is associated with *homologous recombination deficiency*. This test successfully

classifies the genetic profile of ovarian tumors in the OVHIPEC-1 trial into being *BRCA1*-like or non-*BRCA1*-like, with a sensitivity of 100% in recognizing *BRCA1*-mutations.

The analyses in **chapter 8** strengthen the hypothesis that hyperthermia creates a shift towards *homologous recombination deficiency*. We show that tumors harboring *BRCA1/2* mutations (17%) respond well to the standard chemotherapy agents and do not seem to benefit from the addition of HIPEC. On the other hand, tumors that are *BRCA1/2* negative, but are *homologous recombination deficient* (32.5%), are most likely to benefit from treatment with HIPEC. For tumors without the *BRCA1*-like scar, that lean more towards *homologous recombination proficiency* (50.5%), the addition of HIPEC is currently less convincing. These findings must be further validated.

All data available today, points towards a beneficial, safe, and cost-effective use of HIPEC for patients with stage III ovarian cancer. The scientific discussion that was raised regarding HIPEC, is in great contrast with the ease at which novel, expensive drugs are approved, sometimes after uncontrolled studies. While the results described in this thesis should preferably be confirmed by further large, high-quality trials, the current evidence shows that HIPEC in addition to interval cytoreductive surgery is a valuable treatment option within the appropriate subset of ovarian cancer patients.

Samenvatting

HIPEC voor eierstokkanker

Eierstokkanker dat is uitgezaaid naar het buikvlies, of peritoneale oppervlak, wordt gecategoriseerd als stadium III. De behandeling bestaat uit een operatie, ookwel "*cytoreductieve chirurgie*" en zes kuren chemotherapie. De behandeling kan starten met een operatie ("*primaire cyotreductieve chirurgie"*) of de operatie kan worden gepland na de eerste drie kuren chemotherapie ("*interval cytoreductieve chirurgie*"). Hypertherme intraperitoneale chemotherapie, kortweg HIPEC, is een additieve behandeling waarbij het buikvlies wordt gespoeld met verwarmde chemotherapie tijdens de operatie.

In dit proefschrift hebben we de resultaten van de OVHIPEC-1 studie beschreven. OVHIPEC-1 was de eerste fase III-studie die het effect van HIPEC bij primaire eierstokkanker evalueerde, waarbij 245 patiënten gerandomiseerd werden om interval cytoreductieve chirurgie met of zonder HIPEC te ondergaan. Patiënten kwamen in aanmerking als de primaire cytoreductieve chirurgie niet haalbaar was vanwege de omvang van hun ziekte, en de ziekte niet verergerde na twee kuren chemotherapie met carboplatine en paclitaxel. In **hoofdstuk 2** laten we zien dat de toevoeging van HIPEC aan interval cytoreductieve chirurgie de ziektevrije- en algehele overleving bij patiënten met stadium III eierstokkanker verbetert. De mediane recidiefvrije overleving was 10,7 maanden in de chirurgie-groep en 14,2 maanden in de chirurgie+HIPEC groep. De mediane totale overleving was 33,9 maanden in de chirurgie-groep en 45,7 maanden in de chirurgie+HIPEC groep. De behandeling met HIPEC is veilig, aangezien de gerapporteerde toxiciteit en bijwerkingen in beide groepen vergelijkbaar waren (25% in de chirurgiegroep en 27% in de chirurgie+HIPEC-groep).

Het primaire eindpunt van de OVHIPEC-1-studie was de tijd tot terugkeer van ziekte, door de behandelaar geëvalueerd. CT-scans en serum CA-125 metingen kunnen aanwijzing geven voor terugkeer van ziekte. Deze metingen werden daarom uitgevoerd met regelmatige tussenpozen voor patiënten in beide behandelingsarmen. Desondanks is elke open-labelstudie gevoelig voor vertekening van de eindpunten, omdat de arts en de patiënt op de hoogte zijn van de behandelgroep. Daarom voerden we een centrale geblindeerde beoordeling uit van alle beschikbare CT-scans van patiënten die deelnamen aan de studie. Deze centrale beoordeling bevestigde het voordeel van het toevoegen van HIPEC aan interval cytoreductieve chirurgie (**hoofdstuk 3**) en gaf aan dat open-label bias een minimale impact had op de resultaten. Daarnaast analyseerden we de primaire locatie van terugkeer van de zieke. We lieten zien dat HIPEC specifiek gericht is op het inwendige buikvlies: de cumulatieve incidentie van terugkeer van ziekte op het buikvlies was lager na chirurgie+HIPEC, en er was geen duidelijk verschil in de cumulatieve incidentie van terugkeer van ziekte elders dan het buikvlies.

De CT-scans werden ook gebruikt om de skeletspiermassa te meten tijdens de behandeling met chemotherapie voorafgaand aan de operatie. In **hoofdstuk 4** beschrijven we dat een afname van de skeletspiermassa (sarcopenie) tijdens de eerste twee kuren chemotherapie

niet gepaard ging met een slechtere ziektevrije- of algehele overleving. Deze bevinding staat in contrast met eerdere resultaten, mogelijk door het feit dat onze studiepopulatie relatief fit is en mogelijk niet volledig representatief is voor de gehele eierstokkankerpopulatie. We hebben een significante associatie waargenomen van sarcopenie met gerapporteerde bijwerkingen van de chemotherapie, wat aangeeft dat sarcopenie gemeten op CT-scans een surrogaat meetinstrument zou kunnen zijn voor de belasting van de behandeling of algemene fitheid.

In **hoofdstuk 5** beschrijven we de analyses van patiënt-gerapporteerde kwaliteit van leven, beoordeeld met vragenlijsten die specifiek zijn voor het rapporteren van de kwaliteit van leven binnen de OVHIPEC-1-populatie. Kwaliteit van leven was een secundair eindpunt van de OVHIPEC-1 studie, en de analyses waren gericht op een algemene samenvattende score voor levenskwaliteit en symptoomscores voor vermoeidheid, neuropathie en maag- en darmklachten. Er werden geen significante verschillen in de algehele levenskwaliteit waargenomen in de loop van de tijd, bij het vergelijken van eierstokkankerpatiënten die met of zonder HIPEC werden behandeld. De symptoomscores gedurende de tijd na de operatie voor vermoeidheid, neuropathie en maag- en darmklachten was eveneens vergelijkbaar.

De toevoeging van HIPEC aan de behandeling van patiënten met eierstokkanker heeft enkele bijkomende gevolgen. De mediane duur van de operatie wordt verlengd met ongeveer 2,5 uur (**hoofdstuk 2**), de spoelapparatuur en een perfusionist zijn nodig tijdens de ingreep, patiënten worden na HIPEC opgenomen op de medium- of intensive care afdeling voor een dag, en de totale duur van de ziekenhuisopname wordt verlengd. Of de voordelen van HIPEC opwegen tegen deze extra kosten, is geanalyseerd in een kosten-batenanalyse die we in **hoofdstuk 6** beschrijven. We toonden aan dat een behandeling met HIPEC gepaard gaat met een stijging van de kosten van ongeveer €15.500 per patiënt. We laten ook zien dat een behandeling met HIPEC resulteert in een opbrengst van levensjaren, gecorrigeerd voor kwaliteit van leven (quality-adjusted life years, of (QALY's). De incrementele kosten-batenverhouding (ICER) bedroeg €28.299 per gewonnen QALY, wat onder de betalingsnorm van €80.000 per ICER in Nederland ligt.

De verbeterde overleving, de beperkte bijwerkingen, het behoud van de door de patiënt gerapporteerde kwaliteit van leven en de aanvaardbare kosteneffectiviteit, ondersteunen de toevoeging van HIPEC aan interval cytoreductieve chirurgie bij patiënten met stadium III eierstokkanker. Naar aanleiding van deze resultaten is HIPEC nu in deze setting in Nederland geïmplementeerd en opgenomen in diverse internationale richtlijnen. Desalniettemin hebben enkele gynaecologen verschillende punten van kritiek op het ontwerp en de resultaten van OVHIPEC-1 naar voren gebracht. In **hoofdstuk 9** bespreken we deze punten, waaronder de timing van de randomisatie, de chirurgische kwaliteit, het open-label ontwerp, de willekeurige onevenwichtigheden tussen de behandelingsarmen, de generaliseerbaarheid en de waarde van hyperthermie als onderdeel van HIPEC. Een resterende vraag is of de voordelen van HIPEC vergelijkbaar zijn voor stadium III eierstokkankerpatiënten die worden behandeld met primaire chirurgie. Het antwoord op deze vraag wordt onderzocht van de internationale, fase III OVHIPEC-2-studie, die momenteel openstaat voor de inclusie van patiënten.

Een van de mogelijke werkingsmechanismen van HIPEC is dat hyperthermie uitputting van *BRCA1*- en *BRCA2*-eiwitten veroorzaakt. *BRCA1/2*-eiwitten in een (tumor)cel zijn cruciaal voor het herstel van dubbelstrengs DNA-schade. In het geval van *BRCA1/2*-mutaties (en dus eiwit-disfunctie), zijn deze tumorcellen "*homologous recombinatie deficiënt*" en zullen ze niet in staat zijn om te herstellen van chemo-geïnduceerde DNA-beschadigingen. Van de verhoogde temperatuur van HIPEC, wordt verondersteld dat het in staat is tumorcellen die in staat zijn om te herstellen van de chemotherapie-schade, te veranderen naar een staat waarin ze dat niet meer kunnen (*homologous recombinatie deficiëntie)*. Dit effect voorkomt dat tumorcellen kunnen herstellen van de gelijktijdig toegediende chemotherapie tijdens HIPEC, met meer tumorceldood als gevolg. In **hoofdstuk 7** hebben we een nieuw ontwikkelde, op een algoritme-gebaseerde test gevalideerd. Op basis van het genetisch profiel van de tumor, is deze test in staat om een *BRCA1*-like genetisch profiel te herkennen dat geassocieerd wordt met *homologous recombinatie deficiëntie*. Deze test classificeert met succes het genetische profiel van eierstoktumoren in de OVHIPEC-1 studie als *BRCA1*-like of niet-*BRCA1*-like, met een sensitiviteit van 100% voor het herkennen van *BRCA1*-mutaties.

De analyses in **hoofdstuk 8** versterken de hypothese dat hyperthermie een verschuiving naar *homologous recombinatie deficiëntie* veroorzaakt. We laten zien dat tumoren met *BRCA1/2*-mutaties (17%) goed reageren op de standaard chemotherapie, en niet lijken te profiteren van de toevoeging van HIPEC. Aan de andere kant hebben tumoren die *BRCA1/2* negatief zijn, maar die wel een *homologous recombinatie deficiënt* genetisch profiel hebben (32,5%), de meeste kans om te profiteren van behandeling met HIPEC. Voor tumoren zonder het *BRCA1*-like profiel (50,5%), is de toevoeging van HIPEC momenteel minder overtuigend. Deze bevindingen moeten verder worden gevalideerd.

Alle gegevens die op dit moment beschikbaar zijn, wijzen in de richting van een gunstig, veilig en kosteneffectief gebruik van HIPEC voor patiënten met stadium III eierstokkanker. De wetenschappelijke discussie die wordt gevoerd over HIPEC staat in schril contrast met het gemak waarmee nieuwe, dure geneesmiddelen worden goedgekeurd, soms zelfs na ongecontroleerde studies. Hoewel de resultaten die in dit proefschrift worden beschreven bij voorkeur moeten worden bevestigd door grote, kwalitatief hoogwaardige studies, toont het huidige bewijs dat HIPEC in combinatie met interval cytoreductieve chirurgie een waardevolle behandelingsoptie is binnen de juiste subgroep van patiënten met eierstokkanker.

APPENDICES

PhD portfolio
Author contributions
List of publications
Dankwoord
Curriculum Vitae

PhD portfolio

PhD training

	Year	ECTS
General courses		
- Good Clinical Practice training (GCP), NKI-AvL	2017	0.25
- English scientific writing course, OOA NKI-AvL	2017	1
- Basic course in R, LUMC	2018	1.25
- Medical statistics in oncology, OOA NKI-AvL	2019	1
- Good Clinical Practice training (GCP) - repeat, NKI-AvL	2020	0.25
Specific courses		
- Basic microscopy course, OOA NKI-AvL	2017	1.25
- Introduction in health-economics, UMCU/UT	2019	1.25
- Discrete event simulation modelling in R, UT	2020	1.5
- Modelling in health-economics, DARTH-R workshop	2020	1.5
- Course indesign, OOA NKI-AvL	2020	0.25
Seminars, workshops and master classes		
- Workshop “the art of presenting science” - OOA NKI-AvL	2018	0.25
- Organizing OVHIPEC symposium	2019	1

Presentations

-	Poster presentation, ESMO congress, Madrid	2017	0.5
-	Oral presentation, ESGO congress, Vienna	2017	0.5
-	Oral presentation, ESHO congress, Berlin	2018	0.5
-	Poster, IGCS congress, Japan	2018	0.5
-	Oral presentation, PSOGI congress, Paris	2018	0.5
-	Oral presentation, Hyperthermia symposium, Amsterdam	2018	0.5
-	Oral presentation, 22nd Dutch-Belgian Doelencongress, Rotterdam	2019	0.5
-	Oral presentation, AvL symposium 2019, Amsterdam	2019	0.5
-	Poster presentation Benzon symposium, Copenhagen	2019	0.5
-	DPOG workgroup meeting, Utrecht	2018	0.5
-	Oral presentation working group gyn. tumors, NKI-AvL	2017	0.5
-	Oral presentation OVHIPEC symposium, NKI-AvL	2019	0.5
-	Oral presentation immunotoxicity meeting, NKI-AvL	2019	0.5
-	Oral presentation CGOA research meeting, NKI-AvL	2018	0.5
-	Oral presentation CGOA research meeting, NKI-AvL	2019	0.5

(Inter)national conferences

-	Oncology graduate school (OOA) retreat, Renesse	2017	0.75
-	Oncology graduate school (OOA) retreat, Renesse	2018	0.75
-	Oncology graduate school (OOA) retreat, Renesse	2019	0.75
-	ESMO congress, Madrid	2017	1.25
-	ESGO congress, Vienna	2017	1
-	ESHO congress, Berlin	2018	1
-	PSOGI congress, Paris	2018	1
-	Hyperthermia symposium, Amsterdam	2018	0.25
-	22nd Doelencongress, Rotterdam	2019	0.25
-	AvL symposium, Amsterdam	2019	0.25
-	Benzon symposium, Copenhagen	2019	1.25
-	ESMO congress, Barcelona	2019	1.25

Other

-	Attending CGOA research meeting, 4x/year	2017-19	0.5

Teaching

Supervising

Supervising master student (L. Bruijs)	2018	1

Parameters of esteem

	Year
Grants	
- OVHIPEC-2 - Dutch Cancer Society (11540/2018-1) Budget: € 1,049,561	2018
- OVHIPEC-2 - National Health Care Institute, the Netherlands (80-85200-98-20501) Budget: € 3,383,127 + € 400,000	2019
Awards and Prizes	
- Young investigator award - ESHO congress, Berlin	2018
- Presentation award, second place, OOA retreat, Renesse	2018
- Patient impact award (OVHIPEC-team), NKI-AvL	2019

Author contributions per publication

Chapter 2: Hyperthermic intraperitoneal chemotherapy in ovarian cancer
Conception and design: WJ van Driel, SN Koole, K Sikorska, GS Sonke
Provision of study materials or patients: WJ van Driel, JH Schagen van Leeuwen, HWR Schreuder, RHM Hermans, IH de Hingh, J van der Velden, HJG Arts, LFAG Massuger, AG Aalbers, VJ Verwaal, KK Van de Vijver
Collection and assembly of data: WJ van Driel, SN Koole, K Sikorska, JM Kieffer, H van Tinteren, NK Aaronson, GS Sonke
Data analysis: K Sikorska, SN Koole, JM Kieffer
Data interpretation: WJ van Driel, SN Koole, K Sikorska, H van Tinteren, NK Aaronson, GS Sonke
Manuscript writing: WJ van Driel, SN Koole, K Sikorska, H van Tinteren, NK Aaronson, GS Sonke
Final approval of manuscript: All authors

Chapter 3: Central radiology assessment of the randomized phase III open-label OVHIPEC-1 trial in ovarian cancer
Conception and design: SN Koole, L Bruijs, M Lahaye, GS Sonke, WJ van Driel
Provision of study materials or patients: WJ van Driel, JH Schagen van Leeuwen, HWR Schreuder, RHM Hermans, J van der Velden, HJG Arts, M van Ham, P Van Dam, P Vuylsteke
Collection and assembly of data: SN Koole, L Bruijs, C. Fabris, M Lahaye
Data analysis: SN Koole, L Bruijs, K Sikorska
Data interpretation: SN Koole, L Bruijs, K Sikorska, C. Fabris, M Lahaye, GS Sonke, WJ van Driel
Manuscript writing: SN Koole, L Bruijs, M Lahaye, GS Sonke, WJ van Driel
Final approval of manuscript: All authors

Chapter 4: No influence of sarcopenia on survival of ovarian cancer patients in a prospective validation study.
Conception and design: SN Koole, J Ubachs, M Lahaye, J Bastings, R Kruitwagen, S Lambrechts, SWM Olde Daminking, SS Rensen, T Van Gorp, GS Sonke, WJ van Driel
Provision of study materials or patients: WJ van Driel, JH Schagen van Leeuwen, HWR Schreuder, RHM Hermans, de Hingh IH, J van der Velden, HJG Arts, M van Ham, P Van Dam, P Vuylsteke
Collection and assembly of data: SN Koole, L Bruijs, J Ubachs, C Fabris,
Data analysis: SN Koole, J Ubachs
Data interpretation: SN Koole, J Ubachs, M Lahaye, J Bastings, R Kruitwagen, S Lambrechts, SWM Olde Daminking, SS Rensen, T Van Gorp, GS Sonke, WJ van Driel
Manuscript writing: SN Koole, J Ubachs, M Lahaye, R Kruitwagen, T Van Gorp, GS Sonke, WJ van Driel
Final approval of manuscript: All authors

Chapter 5: Health-related quality of life after interval cytoreductive surgery with or without HIPEC
Conception and design: SN Koole, JM Kieffer, GS Sonke, WJ van Driel, NK Aaronson
Provision of study materials or patients: WJ van Driel, JH Schagen van Leeuwen, HWR Schreuder, RHM Hermans, de Hingh IH, J van der Velden, HJG Arts, M van Ham, AG Aalbers, VJ Verwaal, KK Van de Vijver
Collection and assembly of data: SN Koole, JM Kieffer
Data analysis: SN Koole, JM Kieffer
Data interpretation: SN Koole, JM Kieffer, K Sikorska, GS Sonke, WJ van Driel, NK Aaronson
Manuscript writing: SN Koole, JM Kieffer, GS Sonke, WJ van Driel, NK Aaronson
Final approval of manuscript: All authors

Chapter 6: Cost effectiveness of interval cytoreductive surgery with HIPEC for ovarian cancer
Conception and design: SN Koole, C van Lieshout, WJ van Driel, RH Hermans, AG Aalbers, VJ Verwaal, NK Aaronson, H van Tinteren, GS Sonke, WH van Harten, VP Retèl
Provision of study materials or patients: WJ van Driel, JH Schagen van Leeuwen, IH de Hingh, J van der Velden, LFAG Massuger, HWR Schreuder, RH Hermans, HJG Arts, AG Aalbers, VJ Verwaal, KK van de Vijver
Collection and assembly of data: WJ van Driel, SN Koole, C van Lieshout, E van Schagen, K Sikorska, H van Tinteren, VP Retèl
Data analysis: SN Koole, C van Lieshout, VP Retèl
Data interpretation: SN Koole, C van Lieshout, WJ van Driel, GS Sonke, E van Schagen, JM Kieffer, NK Aaronson, K Sikorska, H van Tinteren, WH van Harten, VP Retèl
Manuscript writing: SN Koole, C van Lieshout, WJ van Driel, GS Sonke, WH van Harten, VP Retèl
Final approval of manuscript: All authors

Chapter 7&8: Effect of HIPEC according to HRD/BRCAwt genomic profile in stage III ovarian cancer - results from the phase III OVHIPEC-1 trial
Conception and design: SN Koole, PJ Schouten, LK Richters, R Schmutzler, WJ van Driel, GS Sonke, SC Linn
Provision of study materials or patients: WJ van Driel, JH Schagen van Leeuwen, IHTJ de Hingh, RHM Hermans, J van der Velden, M van Ham, HWR Schreuder, HJG Arts, P van Dam, P Vuylsteke
Collection and assembly of data: SN Koole, PJ Schouten, J Sanders, H Horlings, KK Van de Vijver, M Alkemade, M Opdam, R Kluin, R Rahman, G Krebsbach, E Hahnen, J Hauke, E Hahnen, L Richters
Data analysis: SN Koole, K Sikorska, PJ Schouten, R Kluin, R Rahman, J Hauke
Data interpretation: SN Koole, PJ Schouten, WJ van Driel, GS Sonke, SC Linn
Manuscript writing: SN Koole, PJ Schouten, WJ van Driel, GS Sonke, SC Linn
Final approval of manuscript: All authors

Chapter 9:

- **Hyperthermic intraperitoneal chemotherapy in ovarian cancer (letter)**
  Conception and design: SN Koole, WJ van Driel, GS Sonke
  Manuscript writing: SN Koole, WJ van Driel, GS Sonke
  Final approval of manuscript: SN Koole, WJ van Driel, GS Sonke

- **Hyperthermic intraperitoneal chemotherapy for ovarian cancer: The heat is on**
  Conception and design: SN Koole, WJ van Driel, GS Sonke
  Manuscript writing: SN Koole, WJ van Driel, GS Sonke
  Final approval of manuscript: SN Koole, WJ van Driel, GS Sonke

- **Primary cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy (HIPEC) for FIGO stage III epithelial ovarian cancer: OVHIPEC-2, a phase III randomized clinical trial**
  Study conception and design: SN Koole, K Sikorska, D Barton, L Perrin, D Brennan, O Zivanovic, BJ Mosgaard, A Fagotti, PE Colombo, GS Sonke, WJ van Driel
  Manuscript writing: SN Koole, R van Stein, K Sikorska, GS Sonke, WJ van Driel
  Final approval of manuscript: All authors

List of publications

Related to this thesis:

van Driel WJ, **Koole SN**, Sikorska K, Schagen van Leeuwen JH, Schreuder HWR, Hermans RHM, de Hingh I, van der Velden J, Arts HJ, Massuger L, Aalbers AGJ, Verwaal VJ, Kieffer JM, Van de Vijver KK, van Tinteren H, Aaronson NK, Sonke GS.
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Koole SN, van Lieshout C, van Driel WJ, van Schagen E, Sikorska K, Kieffer JM, Schagen van Leeuwen JH, Schreuder HWR, Hermans RH, de Hingh IH, van der Velden J, Arts HJ, Massuger L, Aalbers AG, Verwaal VJ, Van de Vijver KK, Aaronson NK, van Tinteren H, Sonke GS, van Harten WH, Retèl VP.
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Manuscript in preparation:

Koole SN, Schouten PJ, Hauke J, Kluin R, Richters LK, Rahman R, Krebsbach G, Sikorska K, Alkemade M, Opdam M, Schagen van Leeuwen JH, Schreuder HWR, Hermans RHM, de Hingh IHTJ, van der Velden J, Arts HJG, van Ham M, van Dam P, Vuylsteke P, Sanders J, Horlings H, Van de Vijver KK, Hahnen E, van Driel WJ & Schmutzler R, Sonke GS, Linn SC.
Effect of HIPEC according to HRD/BRCAwt genomic profile in stage III ovarian cancer - results from the phase III OVHIPEC-1 trial.

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Bogie R, Arts JJ, **Koole SN**, LW van Rhijn, Willems PC.
The use of metal sublaminar wires in modern growth-guidance scoliosis surgery: a report of 4 cases and literature review.
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Other:

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Koole SN, Boog L, van Driel WJ: Hypertherme intraperitoneale chemotherapie (HIPEC) voor patiënten met een ovariumcarcinoom.
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Koole SN, van Driel WJ, Roes EM, Witteveen PO, Boll D: Plaats HIPEC in de behandeling van patiënten met een primair stadium III epitheliaal ovariumcarcinoom.
Revisie richtlijn epitheliaal ovariumcarcinoom, module: behandeling hoog stadium 2018

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Curriculum Vitae

Simone Nienke Koole was born on January 12, 1992 in Uppsala, Sweden. After completing secondary school at the Porta Mosana College in Maastricht, she started studying Medicine in 2010, at the University of Maastricht. During her studies, she did a clinical internship in Iganga, Uganda in 2013. Her master's thesis about hypoxia in cervical cancer was supervised by prof. R. Kruitwagen at the Maastricht University Medical Center (MUMC+). In her final year, Simone did an internship in Gynecologic Oncology in the Netherlands Cancer Institute - Antoni van Leeuwenhoek, under supervision of dr. C. Lok.

Simone obtained her Medical Degree in 2017, after a senior clinical internship at the Gynecology department in the MUMC+, supervised by dr. B. Slangen. Shortly thereafter, she started as a PhD-student in the Netherlands Cancer Institute under supervision of prof. dr. G.S. Sonke and dr. W.J. van Driel, researching ovarian cancer and treatment with HIPEC. The results of her research are described in thesis. She also coordinated a clinical trial on immunotherapy for ovarian cancer, and was involved in the development of the national guidelines on HIPEC for ovarian cancer. In April 2020, Simone started a post-doctoral fellowship at the department of Health Economics in the Netherlands Cancer Institute, under supervision of prof. dr. W. van Harten. She holds a postdoctoral position within the European Fair Pricing Network, and is working on Health Technology Assessments for cancer care.