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Cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy in patients with advanced ovarian cancer (OVHIPEC-1): final survival analysis of a randomised, controlled, phase 3 trial

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Summary

Background The OVHIPEC-1 trial previously showed that the addition of hyperthermic intraperitoneal chemotherapy (HIPEC) to interval cytoreductive surgery resulted in improved progression-free and overall survival compared with cytoreductive surgery alone at 4·7 years of follow-up in patients with stage III epithelial ovarian cancer who were ineligible for primary cytoreduction. We report the final survival outcomes after 10 years of follow-up.

Methods In this open-label, randomised, controlled, phase 3 trial, patients with primary epithelial stage III ovarian cancer were recruited at eight HIPEC centres in the Netherlands and Belgium. Patients were eligible if they were aged 18–76 years, had not progressed during at least three cycles of neoadjuvant carboplatin plus paclitaxel, had a WHO performance status score of 0–2, normal blood counts, and adequate renal function. Patients were randomly assigned (1:1) to undergo interval cytoreductive surgery without HIPEC (surgery group) or with HIPEC (100 mg/m² cisplatin; surgery-plus-HIPEC group). Randomisation was done centrally by minimisation with a masked web-based allocation procedure at the time of surgery when residual disease smaller than 10 mm diameter was anticipated, and was stratified by institution, previous suboptimal cytoreductive surgery, and number of abdominal regions involved. The primary endpoint was progression-free survival and a secondary endpoint was overall survival, analysed in the intention-to-treat population (ie, all randomly assigned patients). This study is registered with ClinicalTrials.gov, NCT00426257, and is closed.

Findings Between April 1, 2007, and April 30, 2016, 245 patients were enrolled and followed up for a median of 10·1 years (95% CI 8·4–12·9) in the surgery group (n=123) and 10·4 years (95% CI 9·5–13·3) in the surgery-plus-HIPEC group (n=122). Recurrence, progression, or death occurred in 114 (93%) patients in the surgery group (median progression-free survival 10·7 months [95% CI 9·6–12·0]) and 109 (89%) patients in the surgery-plus-HIPEC group (14·3 months [12·0–18·5]; hazard ratio [HR] 0·63 [95% CI 0·48–0·83], stratified log-rank p=0·0008). Death occurred in 108 (88%) patients in the surgery group (median overall survival 33·3 months [95% CI 29·0–39·1]) and 100 (82%) patients in the surgery-plus-HIPEC group (44·9 months [95% CI 38·6–55·1]; HR 0·70 [95% CI 0·53–0·92], stratified log-rank p=0·011).

Interpretation These updated survival results confirm the long-term survival benefit of HIPEC in patients with primary stage III epithelial ovarian cancer undergoing interval cytoreductive surgery.

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Introduction

Hyperthermic intraperitoneal chemotherapy (HIPEC) has emerged as a potential treatment strategy in epithelial ovarian cancer, given the high rate of peritoneal recurrences despite maximal cytoreductive surgery and adjuvant or neoadjuvant systemic therapy. The delivery of chemotherapeutic agents directly into the peritoneal cavity increases local exposure at the site of peritoneal disease. Furthermore, adding hyperthermia has direct cytotoxic effects, enhances the penetration of chemotherapeutic agents into the tissue, and increases sensitivity to platinum compounds by inducing a transient state of homologous recombination deficiency (HRD).[1,2]

Although the 5-year overall survival of patients with advanced ovarian cancer as has improved over the past few decades as a result of improved surgical and systemic management, overall survival at 10 years remains poor, at approximately 13%.[3] Long-term follow-up of clinical trials in ovarian cancer, including data on treatment for recurrent disease, is therefore essential to establish patient benefit. Unfortunately, there is a paucity of long-term survival data because few clinical trials extend follow-up beyond 5 years.

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Research in context

Evidence before this study

We searched PubMed from database inception up to March 31, 2022, for randomised controlled trials that assessed the efficacy of hyperthermic intraperitoneal chemotherapy (HIPEC) in ovarian cancer using the search terms "ovarian cancer", "hyperthermic intraperitoneal chemotherapy", and "cytoreductive surgery". The search identified three phase 3 trials in primary advanced ovarian cancer and two phase 2–3 trials in patients with recurrent ovarian cancer. A meta-analysis, which included these five trials and one randomised controlled trial that presented preliminary results in a conference abstract, analysed pooled data from 737 patients (519 patients with primary advanced ovarian cancer and 218 with recurrent ovarian cancer). The addition of HIPEC to interval cytoreduction after neoadjuvant chemotherapy significantly improved the progression-free survival and 5-year overall survival compared with standard treatment. In patients who underwent primary cytoreductive surgery, the addition of HIPEC was not associated with a survival benefit, although it is noteworthy that this sample size was smaller (126 patients). In the recurrent setting, there was no significant improvement in survival with the use of HIPEC. The rate of adverse events of grade 3 or higher in patients receiving HIPEC was similar to that in patients receiving cytoreductive surgery alone. Overall, there is an absence of long-term survival data for HIPEC in treating ovarian cancer.

Added value of this study

To our knowledge, this study reports the first long-term survival analysis of HIPEC in patients with ovarian cancer. The results confirm the significant improvement in progression-free and overall survival with the addition of HIPEC to interval cytoreductive surgery in patients with extensive disease for whom primary cytoreduction is not considered feasible. Neither the number of lines nor the type of subsequent treatment for recurrence differed between the treatment groups. Therefore, the observed improvement in overall survival is unlikely to be attributable to the use of subsequent therapies.

Implications of all the available evidence

The addition of HIPEC to interval cytoreduction following neoadjuvant chemotherapy in the front-line setting has been shown to provide a survival benefit for patients with stage III ovarian cancer who are ineligible for primary surgery. The updated survival analysis presented in this study further supports this finding. International guidelines on the use of HIPEC in primary ovarian cancer vary and reflect the ongoing controversy surrounding this treatment method. Some guidelines recommend its use in selected cases, while others do not, or have not reached a consensus on its use. Available data provide supportive evidence to combine HIPEC with interval cytoreduction for patients with advanced ovarian carcinoma who were ineligible for primary cytoreduction. Ongoing studies are evaluating the role of HIPEC combined with either primary cytoreductive surgery or in the recurrent setting. Future research should focus on refining patient selection for HIPEC and exploring its combination with other treatment modalities.

The OVHIPEC-1 trial is the first randomised, controlled, phase 3 trial to evaluate the addition of HIPEC to interval cytoreductive surgery in patients with International Federation of Gynecology and Obstetrics (FIGO) stage III epithelial ovarian cancer. Included patients were those deemed ineligible for primary cytoreductive surgery as decided by a multidisciplinary team meeting, or who had previously undergone suboptimal primary cytoreductive surgery.[4] The initial analysis of the trial, with a data cutoff of March 31, 2017, and a median follow-up period of 4·7 years, showed significantly improved time to recurrence, disease progression, or death due to any cause (ie, progression-free survival, reported as recurrence-free survival, hazard ratio [HR] 0·66 [95% CI 0·50–0·87], stratified p=0·0031) and overall survival (HR 0·67 [95% CI 0·48–0·94], stratified p=0·019) with the addition of cisplatin-based HIPEC to cytoreductive surgery (surgery-plus-HIPEC group) when compared with surgery alone (surgery group). The proportion of patients who had severe adverse events did not differ significantly between the surgery group (25%) and the surgery-plus-HIPEC group (27%; p=0·76), and abdominal pain, infection, and ileus were the most frequently reported events. Mortality within 30 days of surgery was low, with one (<1%) death among all study participants (n=245), which occurred in the surgery group.

Following the initial publication of OVHIPEC-1, guidelines have been adjusted variably, ranging from advocating for the use of HIPEC in a select group of patients, to no inclusion or consensus on the use of HIPEC for the treatment of primary ovarian cancer.[5–9] These variations reflect the current controversy on this treatment. Long-term survival outcomes are therefore crucial to the ongoing debate and, together with the results of many international randomised trials that are evaluating the efficacy of HIPEC, will contribute to a consensus being reached on the acceptability of this treatment. In this Article, we provide an update on the survival outcomes of the intention-to-treat population in the OVHIPEC-1 trial after 10 years of follow-up from randomisation to data cutoff. In addition, we report new data on the subsequent anticancer treatments given after disease progression.

Methods

Study design

OVHIPEC-1 was a multicentre, open-label, randomised, controlled, phase 3, trial. Patients were recruited at eight experienced HIPEC centres in the Netherlands and Belgium (at which at least 20 cytoreductive procedures for ovarian cancer were done per year and which had experience with HIPEC for colorectal cancer before the start of enrolment). The study design, full eligibility criteria, and procedures have been described in detail previously.[4] The trial was designed by an executive committee that included lead investigators and statisticians and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol (appendix pp 11–266) was approved by the ethics committee at each participating site. Due to slower than expected accrual, the total number of events (n=192) was reached before enrolment of the total number of patients (n=280) specified in the previous version of the protocol. Protocol version 4 (May 25, 2012) specified that the primary analysis would be done when 192 events had occurred, and that a total enrolment of 240 patients was anticipated to be required. The current survival update was added to statistical analysis plan version 5 in January, 2022 (appendix pp 271–273). Data were collected by the Netherlands Comprehensive Cancer Organisation and updated by the first author (SLA). Final data revisions and analyses were done at the Department of Biometrics of the Netherlands Cancer Institute (ML-Y).

Participants

Patients aged 18–76 years were eligible for the study if they had histologically confirmed FIGO stage III epithelial ovarian, fallopian tube, or peritoneal cancer that had not progressed during treatment with at least three cycles of neoadjuvant carboplatin and paclitaxel. Other key inclusion criteria included a WHO performance status score of 0–2, normal blood counts, and adequate renal function (glomerular filtration rate >60 mL/min per 1·73 m²). Patients with previous malignancies within 5 years before inclusion were ineligible. All patients provided written informed consent before enrolment, and registration occurred before interval cytoreductive surgery.

Randomisation and masking

Patients were randomly assigned (1:1) to undergo interval cytoreductive surgery either without HIPEC (surgery group) or with HIPEC (surgery-plus-HIPEC group); randomisation was done at the time of surgery when either complete cytoreduction (no visible disease) or optimal cytoreduction (residual tumour diameter <10 mm) was anticipated. Randomisation was done centrally by the method of minimisation with the use of a web-based randomisation system (ALEA software version 18.1) and with stratification according to previous suboptimal cytoreductive surgery (yes *vs* no), the institute at which the surgery was being done, and the number of involved regions in the abdominal cavity (0–5 *vs* 6–8; regions are described in the trial protocol; appendix p 32).[4] The trial was open label, with no masking of patients, physicians, or data analysts to group allocation.

Procedures

Before surgery, patients were treated with at least three cycles of intravenous carboplatin (area under the curve 5–6 mg/mL per min) and intravenous paclitaxel (175 mg per m² body-surface area), with one cycle given every 3 weeks. Response to neoadjuvant chemotherapy was assessed by physical examination, measurement of serum CA125 concentration, and CT scans of the pelvis and abdomen. If patients did not progress during neoadjuvant chemotherapy, they were considered eligible for interval cytoreductive surgery with or without HIPEC. Randomisation took place during surgery, usually 13–15 weeks after the start of neoadjuvant therapy. HIPEC was done at the end of cytoreduction using the open abdomen technique, as previously described.[4] Briefly, heated saline (40–42°C) was circulated through the abdominal cavity for 90 min. Cisplatin was added at a dose of 100 mg/m² in three stages: 50% of the dose at the start, 25% at 30 min, and 25% at 60 min. To prevent nephrotoxicity, sodium thiosulfate was administered during and after the HIPEC procedure. Patients received an additional three cycles of carboplatin (area under the curve 5–6 mg/mL per min) and paclitaxel (175 mg per m² body-surface area), given once every 3 weeks, after surgery.

See Online for appendix

The protocol for follow-up of patients involved repeated physical examinations and measurement of serum CA125 concentration every 3 months for 2 years and then every 6 months until 5 years after completion of chemotherapy. CT scans were done at 1, 6, 12, and 24 months after the final cycle of chemotherapy and were assessed according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. Once the structured follow-up period of 5 years had been completed, patients were still encouraged to present in case of signs or symptoms suggestive of recurrence, and were then evaluated through physical examination, measurement of CA125 concentration, and imaging. Recurrence status (by investigator assessment) and data on further treatment after progression were obtained from patient records at participating sites and general practitioners' records. Survival status was obtained from patient records and the National Death Registry. Platinum-resistance was defined as a recurrence occurring within 6 months of the patient's last dose of platinum-based chemotherapy.[9] Reasons for withdrawal of patients from the study were withdrawal of consent or investigator's decision. If patients consented, they continued to be followed up.

Germline *BRCA1/2* mutational status was derived from clinical patient files and the Dutch Hereditary Breast and Ovarian Cancer Research Group (HEBON) database. To assess tumour *BRCA1/2* mutations and copy-number variation profiles, tumour DNA was isolated from tissue

For more on **HEBON** see https://www.hebon.nl/

samples and analysed with low coverage and targeted next-generation sequencing. On the basis of copy-number variation profiles, tumours were classified as *BRCA1*-like (homologous recombination deficient) or non-*BRCA1*-like (homologous recombination proficient), using a previously trained and validated classifier specific for patients with ovarian cancer.[10] These methods have been described in detail elsewhere.[11]

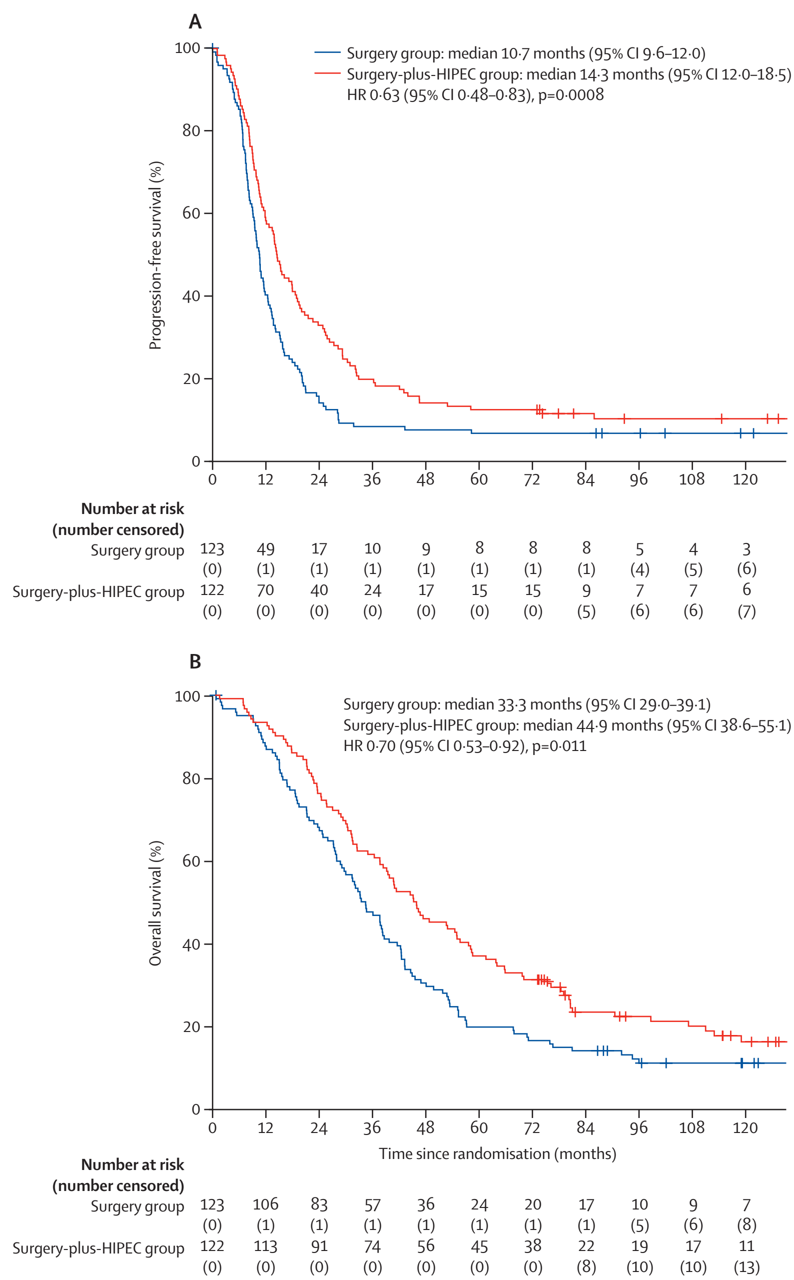


***Figure 1:* Kaplan-Meier curves of survival in the intention-to-treat population**

(A) Progression-free survival. (B) Overall survival. HRs are from stratified Cox proportional hazards models and p values from stratified log-rank tests (stratification factors were those used at randomisation). HIPEC=hyperthermic intraperitoneal chemotherapy. HR=hazard ratio.

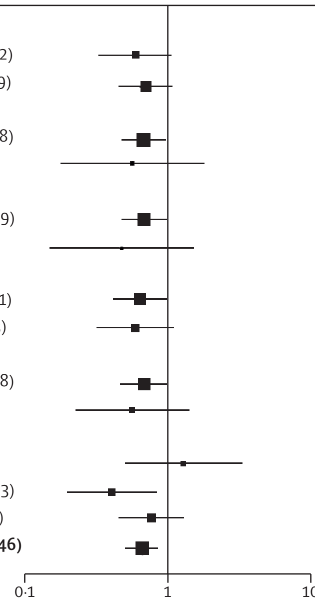
Outcomes

We updated the analysis of the primary endpoint, progression-free survival (referred to in previous publications as recurrence-free survival),[4] defined as the time from randomisation to disease recurrence, progression, or death from any cause, whichever occurred first. Disease recurrence or progression was confirmed by imaging (according to RECIST version 1.1) or elevated CA125 concentrations, according to the Gynecologic Cancer InterGroup criteria.[12] Here we also report an updated analysis of the secondary endpoint of overall survival, which was defined as the time from randomisation to death from any cause. Survival data were censored at the date of last contact for patients who had no evidence of disease or remained alive, with a cutoff date of March 31, 2022. All other secondary endpoints have been reported previously,[4,13,14] including a cost-effectiveness analysis.[15] The proportion of patients who received subsequent therapies was a predefined exploratory endpoint.

Statistical analysis

In the OVHIPEC-1 trial, 245 patients were enrolled and 192 events were observed, to reach 80% power to detect a HR of 0·67 for the surgery-plus-HIPEC group versus the surgery group in the primary analysis. A prespecified interim analysis for efficacy, according to O'Brien-Fleming boundaries, was done after 50% of the patients had been recruited. This long-term survival update was described in version 5 (January, 2022) of the statistical analysis plan and was planned to be done 5 years after the primary survival analysis, with a data cutoff of March 31, 2022. For time-to-event endpoints, analyses comparing the surgery with the surgery-plus-HIPEC group were based on the intention-to-treat population and done with log-rank tests stratified according to the same factors used to stratify patients at randomisation. The intention-to-treat population was defined as all randomly allocated patients according to the group they were allocated to. The Kaplan-Meier method was used to generate time-to-event curves, from which medians, 95% CIs, and survival probabilities were calculated. HRs and their corresponding 95% CIs were estimated with use of Cox proportional hazards models stratified by factors used at randomisation. The assumption of proportionality of hazards was assessed using tests for independence between scaled Schoenfeld residuals and time, as well as by visual inspection of scaled Schoenfeld residuals versus time with a smoothed curve and 95% CI. Exploratory subgroup analyses were prespecified for subgroups based on previous suboptimal cytoreductive surgery (yes *vs* no) and the number of involved regions of the abdominal cavity (0–5 *vs* 6–8), and were done post hoc for subgroups based on patient age (<65 *vs* ≥65 years), tumour histological type (high-grade serous *vs* other), previous laparoscopy (yes *vs* no), and *BRCA1/2* status (*BRCA1/2* mutated *vs* homologous recombination deficient *vs* homologous recombination proficient). Subgroup analyses evaluating time-to-event

A	Events/patients, n/N		Median progression-free survival, months (95% CI)		Hazard ratio (99% CI)	$P_{interaction}$
	Surgery group	Surgery-plus-HIPEC group	Surgery group	Surgery-plus-HIPEC group		
Age, years						0·68
≥65	44/45	38/43	10·84 (9·63–16·26)	14·95 (10·25–26·12)	0·60 (0·33–1·08)	
<65	70/78	71/79	10·12 (7·92–14·32)	14·03 (11·37–23·59)	0·71 (0·46–1·10)	
Histological type*						0·61
High-grade serous	100/107	100/112	10·71 (9·20–13·80)	14·34 (11·01–19·88)	0·69 (0·48–0·99)	
Other	14/15	8/9	10·51 (6·97–NR)	13·77 (6·21–NR)	0·57 (0·18–1·84)	
Previous suboptimal cytoreductive surgery†						0·58
No	103/111	99/110	10·58 (8·97–13·04)	14·09 (10·81–19·29)	0·69 (0·49–1·00)	
Yes	11/12	10/12	12·29 (7·56–NR)	28·91 (11·99–NR)	0·48 (0·15–1·55)	
Number of involved regions†						0·88
0–5	75/83	70/83	11·50 (9·95–16·10)	17·68 (13·77–29·01)	0·65 (0·42–1·00)	
6–8	39/40	39/39	8·15 (6·57–13·44)	9·89 (6·80–18·73)	0·60 (0·32–1·12)	
Laparoscopy before surgery						0·52
No	98/105	92/103	10·78 (9·13–13·80)	14·49 (11·37–19·88)	0·69 (0·47–1·00)	
Yes	16/18	17/19	9·46 (7·56–NR)	13·54 (10·74–NR)	0·57 (0·23–1·44)	
***BRCA1/2* mutational status‡**						0·015
Germline or somatic mutation	15/18	16/16	14·70 (10·84–NR)	15·54 (11·70–NR)	1·31 (0·51–3·39)	
Wildtype, HRD	34/35	25/30	8·38 (6·97–13·80)	17·66 (10·81–46·23)	0·41 (0·20–0·85)	
Wildtype, HRP	52/53	47/48	9·66 (7·79–13·80)	10·28 (8·97–17·77)	0·78 (0·46–1·32)	
Overall	**109/122**	**114/123**	**10·68 (9·59–11·96)**	**14·34 (11·99–18·46)**	**0·67 (95% CI 0·51–0·87)§**	..



B	Events/patients, n/N		Median overall survival, months (95% CI)		Hazard ratio (99% CI)	$P_{interaction}$
	Surgery group	Surgery-plus-HIPEC group	Surgery group	Surgery-plus-HIPEC group		
Age, years						0·47
≥65	42/45	33/43	33·91 (26·87–46·26)	40·74 (28·29–79·84)	0·62 (0·34–1·14)	
<65	66/78	67/79	32·85 (26·58–47·44)	45·27 (34·33–69·03)	0·77 (0·49–1·21)	
Histological type*						0·23
High-grade serous	94/107	91/112	33·91 (28·48–44·29)	44·19 (34·33–57·89)	0·75 (0·51–1·09)	
Other	14/15	8/9	27·30 (4·86–NR)	69·03 (18·37–NR)	0·44 (0·13–1·47)	
Previous suboptimal cytoreductive surgery†						0·72
No	97/111	91/110	32·33 (27·07–41·82)	44·19 (35·78–57·89)	0·72 (0·49–1·05)	
Yes	11/12	9/12	44·12 (22·21–NR)	63·00 (30·72–NR)	0·59 (0·18–1·91)	
Number of involved regions†						0·33
0–5	7/83	61/83	37·03 (30·78–51·15)	56·97 (40·31–80·33)	0·65 (0·41–1·02)	
6–8	38/40	39/39	27·30 (14·98–43·96)	30·98 (22·01–52·24)	0·82 (0·45–1·48)	
Laparoscopy before surgery						0·66
No	92/105	85/103	33·84 (27·33–42·61)	45·34 (34·33–60·88)	0·72 (0·49–1·07)	
Yes	16/18	15/19	32·56 (18·86–NR)	40·31 (25·00–NR)	0·63 (0·24–1·60)	
***BRCA1/2* mutational status‡**						0·016
Germline or somatic mutation	12/18	15/16	51·91 (37·59–NR)	46·52 (30·72–NR)	1·73 (0·64–4·72)	
Wildtype, HRD	34/35	23/30	28·48 (23·43–44·94)	55·64 (37·06–NR)	0·43 (0·21–0·89)	
Wildtype, HRP	49/53	43/48	29·37 (16·79–43·96)	38·70 (27·76–63·34)	0·72 (0·42–1·23)	
Overall	**100/122**	**108/123**	**33·35 (29·01–39·13)**	**44·94 (38·57–55·06)**	**0·70 (95% CI 0·53–0·92)§**	..

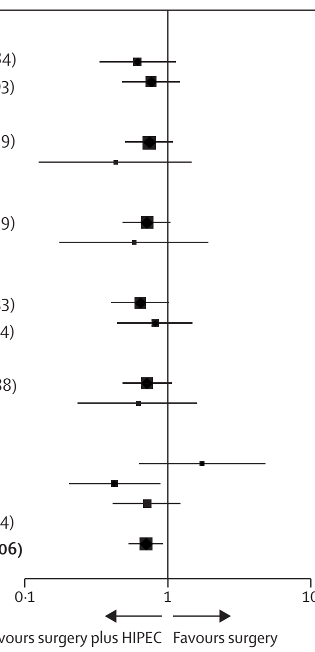


***Figure 2:* Forest plot of prespecified and post-hoc subgroup analyses**

(A) Progression-free survival. (B) Overall survival. Prespecified analyses were by previous suboptimal cytoreductive surgery and number of regions involved; all other subgroup analyses were done post hoc. The size of each diamond is proportional to the number of patients. HIPEC=hyperthermic intraperitoneal chemotherapy. HRD=homologous recombination deficient. HRP=homologous recombination proficient. NR=not reached. *Histological data were missing (ie, no tumour sample was available for review) for one patient in each group; histological type was determined by centrally reviewed pathological assessment. †Previous suboptimal cytoreduction and number of involved regions in the abdominal cavity were used as stratification factors at randomisation (prespecified). ‡Tissue samples for DNA isolation were available for 200 of 245 patients (106 patients in the surgery group; 94 patients in the surgery-plus-HIPEC group). §For the overall results, the stratified HR is shown with its 95% CI.

outcomes in the surgery-plus-HIPEC group versus the surgery group were done with a Cox regression model were reported with 99% CIs and first-order interaction p values ($\alpha=0\cdot05$), obtained using the likelihood ratio test of nested Cox regression models with and without study group-by-subgroup interaction. Data on subsequent treatment lines were compared with use of χ^2 or Fisher's exact tests as applicable. For statistical significance, a threshold of $p<0\cdot05$ was used. All statistical analyses were done with R software (version 4.2.1).

The trial is registered with ClinicalTrials.gov (NCT00426257) and EudraCT (2006-003466-34).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between April 1, 2007, and April 30, 2016, 245 patients were randomly allocated to receive either surgery alone (n=123) or surgery plus HIPEC (n=122; intention-to-treat population; appendix pp 3, 9). Baseline characteristics and treatment characteristics were previously published and are shown in the appendix (pp 5–6, 10).[4] For this updated analysis, data cutoff (March 31, 2022) took place 6 years after the last patient was randomised (April 18, 2016), with a median follow-up times for progression-free and overall survival of 10·1 years (95% CI 8·4–12·9) in the surgery group and 10·4 years (9·5–13·3) in the surgery-plus-HIPEC group. Follow-up was available for all patients except for one patient in the surgery group, who withdrew consent early after randomisation and was therefore censored at this point (appendix p 4). In 22 (9%) of 245 patients in the intention-to-treat population, no event occurred, and they were censored at their last follow-up assessment. 223 (91%) of 245 patients either had disease recurrence or progression or died, and 208 (85%) patients died by the time of data cutoff. The assumption of proportionality of hazards was met for both survival endpoints ($p=0\cdot71$ for progression-free survival and $p=0\cdot31$ for overall survival, according to tests for independence of scaled Schoenfeld residuals and time).

In the intention-to-treat analysis, 114 (93%) of 123 patients in the surgery group had an event of disease recurrence or progression (110 patients) or death (four patients), and 109 (89%) of 122 patients in the surgery-plus-HIPEC group had an event of disease recurrence or progression (105 patients) or death (four patients). Of the nine (7%) patients without an event in the surgery group, seven (6%) had a high-grade serous subtype, one (1%) had a clear cell subtype, and one (1%) had an unknown subtype of disease. In the surgery-plus-HIPEC group, of the 13 (11%) patients without an event, 12 (10%) had a high-grade serous subtype and one (1%) had a low-grade endometrioid subtype disease. Median progression-free survival was 10·7 months (95% CI 9·6–12·0) in the surgery group and 14·3 months (12·0–18·5) in the surgery-plus-HIPEC group (HR 0·63 [95% CI 0·48–0·83], stratified log-rank $p=0\cdot0008$; figure 1A). Progression-free survival at 5 years was 6·6% (95% CI 3·4–13·0) in the surgery group and 12·3% (7·7–19·7) in the surgery-plus-HIPEC group, and at 10 years was 6·6% (3·4–13·0) in the surgery group and 10·1% (5·8–17·5) in the surgery-plus-HIPEC group.

108 (88%) of 123 patients in the surgery group and 100 (82%) of 122 in the surgery-plus-HIPEC group died. Causes of death are listed in the appendix (p 8). Median overall survival was 33·3 months (95% CI 29·0–39·1) in the surgery group and 44·9 months (38·6–55·1) in the surgery-plus-HIPEC group (HR 0·70 [95% CI 0·53–0·92], stratified log-rank $p=0\cdot011$; figure 1B). Overall survival at 5 years was 19·7% (13·7–28·0) in the surgery group and 36·9% (29·2–46·5) in the surgery-plus-HIPEC group, and at 10 years was 10·9% (6·5–18·0) in the surgery group and 16·1% (10·3–25·2) in the surgery-plus-HIPEC group.

	Surgery group (n=123)	Surgery-plus-HIPEC group (n=122)
No recurrence or progression	9 (7%)	13 (11%)
Death without reported recurrence or progression	4 (3%)	4 (3%)
Recurrence or progression, no new therapy	6 (5%)	5 (4%)
Recurrence or progression, new therapy	104 (85%)	100 (82%)

HIPEC=hyperthermic intraperitoneal chemotherapy.

Table 1: **Frequency of recurrence or progression, death, and subsequent anticancer therapy for recurrent disease**

	Surgery group (n=110)	Surgery-plus-HIPEC group (n=105)	p value
Platinum-based chemotherapy	88 (80%)	88 (84%)	0·47
Non-platinum-based chemotherapy	58 (53%)	46 (44%)	0·19
Hormonal therapy	17 (15%)	19 (18%)	0·60
Secondary cytoreduction*	11 (10%)	11 (10%)	0·91
Combined with chemotherapy	5 (5%)	4 (4%)	..
Radiotherapy	16 (15%)	16 (15%)	0·89
Targeted therapy†	44 (40%)	34 (32%)	0·25
PARP inhibitor	11 (10%)	11 (10%)	..
Bevacizumab	30 (27%)	23 (22%)	..
Other‡	9 (8%)	5 (5%)	..
Immunotherapy	3 (3%)	0	0·25§
Embolisation	0	1 (1%)	0·49§
None	10 (9%)	9 (9%)	0·89
Trial participation for subsequent therapy	12 (11%)	8 (8%)	0·41

Only patients with recurrent or progressive disease are included. Patients could undergo more than one subsequent systemic anticancer therapy. p values are from χ^2 tests, unless otherwise indicated. HIPEC=hyperthermic intraperitoneal chemotherapy. PARP=poly(ADP-ribose) polymerase. *Cytoreductive surgery for recurrent disease. †Some patients received more than one targeted therapy. ‡Other targeted therapies included atezolizumab (n=1), avelumab (n=1), focal adhesion kinase inhibitor (n=2), nivolumab (n=1), pazopanib (n=1), pembrolizumab (n=2), pertuzumab (n=1), seribantumab (n=1), tocolizumab (n=1), and WEE1-inhibitor (n=6). §From Fisher's exact test.

Table 2: **Subsequent anticancer treatments in patients who had recurrent or progressive disease**

The effect of HIPEC remained consistent across prespecified stratification factors (previous suboptimal cytoreductive surgery and the number of involved abdominal regions) and exploratory post-hoc subgroups (age, histological type, and laparoscopy done before surgery), as shown by subgroup analyses of progression-free survival and overall survival (figure 2; appendix p 7). However, the effect of HIPEC on progression-free and overall survival was influenced by *BRCA1/2* status, with a significant subgroup treatment effect interaction ($p_{interaction}$=0·015 for progression-free survival and $p_{interaction}$=0·016 for overall survival).

Subsequent anticancer therapies were received by 104 (85%) of 123 patients in the surgery group and 100 (82%) of 122 patients in the surgery-plus-HIPEC group (table 1). In the surgery group, 49 (40%) patients had platinum-resistant disease, in comparison with 32 (26%) patients in the surgery-plus-HIPEC group (χ^2 p=0·024). The different subsequent anticancer treatments given to patients after progression are shown in table 2. Among patients who received new treatment for recurrent or progressive disease, the median number of systemic treatment lines was 2 (IQR 1–3) in both treatment groups. The most common subsequent therapies were platinum-based chemotherapy and non-platinum-based chemotherapy. 11 (10%) of 114 patients in the surgery group and 11 (10%) of 109 in the surgery-plus-HIPEC group with recurrent or progressive disease received maintenance poly(ADP-ribose) polymerase (PARP) inhibitors (table 2). Additionally, two patients in the surgery group and one in the surgery-plus-HIPEC group received front-line maintenance therapy with olaparib in the SOLO-1 trial.[16]

Discussion

This updated 10-year survival analysis from the OVHIPEC-1 trial confirms the significant improvement in progression-free and overall survival with the addition of HIPEC to interval cytoreductive surgery in patients with FIGO stage III ovarian cancer with extensive disease for whom primary complete cytoreduction is not considered feasible.[4] With a median follow-up of 10·1 years in the overall study population, this is the first study, to our knowledge, to provide long-term survival data from a randomised trial of HIPEC in primary ovarian cancer. These survival benefits were consistent across prespecified and post-hoc patient subgroups, although in an exploratory post-hoc analysis, patients with homologous recombination-deficient tumours without pathogenic *BRCA1/2* mutation appeared to derive the greatest benefit of HIPEC as opposed to patients with *BRCA1/2*-mutated tumours. No imbalance in subsequent therapy after disease recurrence was found that would explain the improved overall survival in the study.

The addition of HIPEC to interval cytoreductive surgery in patients with unfavourable prognosis (ie, patients ineligible for primary surgery) prolonged disease control, as shown by the early divergence of the progression-free survival curves, but did not result in better cure rates, as shown by the convergence of the curves at long-term follow-up. The delay in disease recurrence is also reflected in the difference in the occurrence of platinum-resistant disease between treatment groups, which was lower in the surgery-plus-HIPEC group (40% *vs* 26%, p=0·024). Furthermore, a previously published analysis of the pattern of recurrences in this study showed significantly fewer peritoneal recurrences over time after treatment with surgery plus HIPEC compared with surgery alone after central review (HR 0·72 [95% CI 0·52–0·99], Gray's test p=0·046).[13] The combination of the delay in disease recurrence, resulting in higher platinum sensitivity, and the lower rate of peritoneal recurrence is thought to have led to the improved overall survival found in this study.

The prolonged interval without cancer and treatment-related symptoms usually translates into a better quality of life. This improvement is particularly plausible because the first-line treatment of surgery plus HIPEC and systemic chemotherapy does not result in long-term toxicity and deterioration of quality of life.[14,17] Preserving the quality of life in this patient population with a poor prognosis is essential for clinical decision making. Another advantage of the prolonged time to recurrence is that patients will qualify as having platinum-sensitive cancer based on a longer platinum-free interval, rendering them eligible for repeated platinum-based chemotherapy with maintenance PARP inhibitor therapy and secondary cytoreductive surgery according to the DESKTOP III criteria,[18] which might also provide a survival benefit.

Quality of life and overall survival are the two most relevant endpoints in oncology trials. A possible imbalance in the use of therapies received after disease progression should be considered when evaluating overall survival. Therefore, we did an exploratory analysis of subsequent anticancer therapies in this updated analysis. Subsequent therapies for patients in the OVHIPEC-1 trial were left to the treating physician's discretion and were based on Dutch and Belgian evidence-based guidelines. Neither the number of lines nor the type of subsequent therapies differed between treatment groups. Therefore, although dose intensity was not routinely collected, the observed improvement in overall survival is unlikely to be attributable to the use of subsequent therapies. The use of PARP inhibitors and bevacizumab or the use of secondary cytoreductive surgery as a subsequent treatment was relatively low because these treatments were not included in evidence-based guidelines at the time when most patients in the OVHIPEC-1 trial were treated for their recurrent disease.

An exploratory post-hoc subgroup analysis by *BRCA1/2* mutational status and HRD profile showed heterogeneity in the effect of HIPEC. These findings suggest that patients with homologous recombination deficient tumours without pathogenic *BRCA1/2* mutations might benefit more from HIPEC than patients with *BRCA1/2* tumours. A possible explanation is that the already impaired DNA-repair mechanisms in homologous recombination deficient tumours without pathogenic *BRCA1/2* mutations are further compromised by the depleting effect of hyperthermia on BRCA1 and BRCA2 protein function, making these tumours more sensitive to chemotherapy. By contrast, HIPEC might not further improve survival in *BRCA1/2* carriers, who are already particularly sensitive to systemic chemotherapy.[19,20] The results of this exploratory post-hoc subgroup analysis are not in line with our predefined hypothesis that patients with *BRCA1/2*-mutated tumours would benefit most, and these findings need further evaluation in prespecified analysis in future studies.

Following the publication of the OVHIPEC-1 trial, there have been discussions regarding the study design and the potential introduction of bias. The pros and cons of HIPEC in epithelial ovarian cancer are discussed at length in multiple publications and are not repeated here.[21,22]

A limitation of this long-term follow-up study is that no further standardised imaging or laboratory tests were done to assess recurrence after the structured 5-year follow-up period. Although the possibility of some form of bias cannot be completely disregarded, it is not plausible that the previous use of HIPEC would influence the frequency or decision for further examinations.

Since the initial publication of the OVHIPEC-1 trial, Lim and colleagues[23] have reported on a heterogeneous population of 184 patients with stage III and IV ovarian cancer from South Korea who were randomly allocated to receive primary or interval cytoreduction with or without HIPEC. Although no benefit of HIPEC was observed in the overall population, HIPEC improved progression-free survival (median 15·4 months with HIPEC *vs* 17·4 months without HIPEC; HR 0·60 [95% CI 0·37–0·99], p=0·04) and overall survival (48·2 *vs* 61·8 months; HR 0·53 [95% CI 0·29–0·96], p=0·04) in a pre-planned subgroup of patients receiving neoadjuvant chemotherapy and interval cytoreductive surgery. These results support the findings of OVHIPEC-1 in a different geographical region in patients ineligible for primary cytoreductive surgery. However, there might be a different degree of benefit in patients with stage IV disease and those receiving primary cytoreductive surgery.[24]

Another trial by Cascales Campos and colleagues[25] was prematurely terminated because of slow accrual and insufficient funding. This study, in which 71 patients with primary ovarian cancer treated with three cycles of systemic neo-adjuvant carboplatin (area under the curve 5 mg/mL per min) and paclitaxel (175 mg per m^2 body-surface area), were randomly allocated to receive interval cytoreductive surgery with or without HIPEC (cisplatin 75 mg/m^2 for 60 min), found a median progression-free survival of 12 months in the surgery group and 18 months in the surgery-plus-HIPEC group (p=0·12), but was underpowered to draw any conclusions regarding the role of HIPEC.

A meta-analysis[26] of pooled the data from these three randomised controlled trials[4,23,25] showed that the addition of HIPEC to interval cytoreduction and neoadjuvant chemotherapy significantly improved disease-free survival (393 patients; HR 0·60 [95% CI 0·41–0·87], p=0·008) and 5-year overall survival (risk ratio [RR] 0·77 [95% CI 0·67–0·90], p=0·001) compared with standard treatment in patients with primary ovarian cancer. Among those with primary ovarian cancer who underwent primary cytoreduction (ie, without neoadjuvant chemotherapy), the addition of HIPEC was not associated with a survival benefit (126 patients; 4-year overall survival RR 0·92 (0·51–1·65), p=0·768) although it is noteworthy that this sample size was smaller. Overall, the rate of adverse events of grade 3 or higher in patients with primary ovarian cancer receiving surgery-plus-HIPEC was similar to that in patients receiving cytoreductive surgery without HIPEC (RR 1·08 [95% CI 0·98–1·18], p=0·120).[26]

Following the results of the OVHIPEC-1 trial in patients undergoing interval cytoreductive surgery, we initiated the international OVHIPEC-2 trial (NCT03772028) to evaluate the effect of adding HIPEC to primary cytoreductive surgery in patients with stage III epithelial ovarian cancer. In the recurrent setting, there is no evidence yet to support the addition of HIPEC to secondary cytoreductive surgery.[27,28] The results of numerous ongoing trials are awaited.[29]

The treatment of advanced ovarian cancer has undergone substantial advancements in the past decade, with the emergence of PARP inhibitors as a new effective class of drugs. Combining HIPEC and PARP inhibitors is promising because of the potential synergistic effect. PARP inhibitors have been shown to be effective in treating *BRCA1/2*-mutated tumours.[16] Because hyperthermia induces homologous recombination deficiency, it might specifically sensitise *BRCA*-wildtype tumours to PARP inhibitors. The GOG-3068 (NCT05659381) randomised trial is currently underway to investigate the use of cisplatin-based HIPEC in combination with maintenance therapy with the PARP inhibitor niraparib for the treatment of primary FIGO stage III–IV ovarian cancer.

Furthermore, the combination of HIPEC with other treatment regimens, such as immunotherapy (phase 1 trial, NCT03959761) and adjuvant intraperitoneal chemotherapy (phase 3 trial, NCT03772028), is currently under investigation.

Other future perspectives for HIPEC include the search for biomarkers to predict a patient's response to HIPEC. Gene expression signatures, histopathological data, and immunohistochemical markers could help to select patients for HIPEC.[11,20,30] Cells in the tumour environment and their interactions with cancer cells potentially have a role here.[31] Accurate patient selection is crucial for optimising treatment efficacy and limiting health-care costs. There are also several unanswered questions regarding aspects of the administration procedure (eg, temperature, dosage, duration, and open *vs* closed technique) and the additive effect of hyperthermia. There is an opportunity to enhance the efficacy of HIPEC by optimising the HIPEC regimen, which warrants further research.

Contributors

WJvD was the coordinating principal investigator for the study and was responsible for funding acquisition. SLA, SNK, JHSvL, HWRS, RHMH, IHJTdH, MDJMvG, HJGA, MAPCvH, PAvD, PV, GSS, and WJvD were involved in patient accrual and data collection. KKvdV performed central pathology review. AGJA and NKA had clinical advisory roles. SLA, ML-Y, GSS, and WJvD have accessed and verified the data. The formal analysis was done by SLA and ML-Y. SLA, ML-Y, GSS, WJvD interpreted the data. SLA wrote the original draft of the manuscript. GSS and WJvD supervised the study. All authors were involved in critically revising the report. All authors had access to the data in the study and approved the final version of the manuscript. All authors take responsibility for decision to submit the manuscript for publication.

Declaration of interests

IHJTdH has received institutional research support from Roche and Quality in Products & Service/RanD. PV has received conference fees and travel expenses from Roche and honoraria from Roche (Genentech), Novartis, and MSD Oncology. KKVdV has served on advisory boards for Exact Sciences and AstraZeneca. GSS has received institutional research support from Merck Sharp & Dohme, Agendia, AstraZeneca, Roche, and Novartis, and consulting fees from Biovica and Seagen. All other authors declare no competing interests.

Data sharing

Data supporting this work are available upon reasonable request. Requests to access data should be made to Netherlands Cancer Institute's scientific repository at repository@nki.nl, which will contact the corresponding author (WJvD). The institutional review board of the Netherlands Cancer Institute will review all requests.

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References

1 Vos LMC, Aronson SL, van Driel WJ, et al. Translational and pharmacological principles of hyperthermic intraperitoneal chemotherapy for ovarian cancer. *Best Pract Res Clin Obstet Gynaecol* 2022; **78:** 86–102.

2 Dellinger TH, Han ES. State of the science: the role of HIPEC in the treatment of ovarian cancer. *Gynecol Oncol* 2021; **160:** 364–68.

3 Timmermans M, Sonke GS, Van de Vijver KK, van der Aa MA, Kruitwagen RFPM. No improvement in long-term survival for epithelial ovarian cancer patients: a population-based study between 1989 and 2014 in the Netherlands. *Eur J Cancer* 2018; **88:** 31–37.

4 van Driel WJ, Koole SN, Sikorska K, et al. Hyperthermic intraperitoneal chemotherapy in ovarian cancer. *N Engl J Med* 2018; **378:** 230–40.

5 Auer RC, Sivajohanathan D, Biagi J, Conner J, Kennedy E, May T. Indications for hyperthermic intraperitoneal chemotherapy with cytoreductive surgery: a clinical practice guideline. *Curr Oncol* 2020; **27:** 146–54.

6 National Comprehensive Cancer Network. Ovarian cancer (version 3.2022). https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf (accessed Aug 3, 2022).

7 Hoppenot C, Schuitevoerder D, Izquierdo FJ, et al. The Chicago Consensus on peritoneal surface malignancies: management of ovarian neoplasms. *Cancer* 2020; **126:** 2553–60.

8 Lavoué V, Huchon C, Akladios C, et al. Part II drafted from the short text of the French guidelines entitled "Initial management of patients with epithelial ovarian cancer" developed by FRANCOGYN, CNGOF, SFOG, GINECO-ARCAGY and endorsed by INCa. (Systemic and intraperitoneal treatment, elderly, fertility preservation, follow-up). *Gynécol Obstét Fertil Sénol* 2019; **47:** 111–19 (in French).

9 Colombo N, Sessa C, du Bois A, et al. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease. *Ann Oncol* 2019; **30:** 672–705.

10 Schouten PC, Richters L, Vis DJ, et al. Ovarian cancer-specific *BRCA*-like copy-number aberration classifiers detect mutations associated with homologous recombination deficiency in the AGO-TR1 trial. *Clin Cancer Res* 2021; **27:** 6559–69.

11 Koole SN, Schouten PC, Hauke J, et al. Effect of HIPEC according to HRD/*BRCA*wt genomic profile in stage III ovarian cancer—results from the phase III OVHIPEC trial. *Int J Cancer* 2022; **151:** 1394–404.

12 Rustin GJ, Vergote I, Eisenhauer E, et al. Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIG). *Int J Gynecol Cancer* 2011; **21:** 419–23.

13 Koole SN, Bruijs L, Fabris C, et al. Central radiology assessment of the randomized phase III open-label OVHIPEC-1 trial in ovarian cancer. *Int J Gynecol Cancer* 2020; **30:** 1928–34.

14 Koole SN, Kieffer JM, K Sikorska, et al. Health-related quality of life after interval cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with stage III ovarian cancer. *Eur J Surg Oncol* 2021; **47:** 101–07.

15 Koole SN, van Lieshout C, van Driel WJ, et al. Cost effectiveness of interval cytoreductive surgery with hyperthermic intraperitoneal chemotherapy in stage III ovarian cancer on the basis of a randomized phase III trial. *J Clin Oncol* 2019; **37:** 2041–50.

16 Moore K, Colombo N, Scambia G, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med* 2018; **379:** 2495–505.

17 Kim JH, Lee DE, Lee Y, et al. Quality of life outcomes from the randomized trial of hyperthermic intraperitoneal chemotherapy following cytoreductive surgery for primary ovarian cancer (KOV-HIPEC-01). *J Gynecol Oncol* 2022; **33:** e54.

18 Harter P, Sehouli J, Vergote I, et al. Randomized trial of cytoreductive surgery for relapsed ovarian cancer. *N Engl J Med* 2021; **385:** 2123–31.

19 Bolton KL, Chenevix-Trench G, Goh C, et al. Association between *BRCA1* and *BRCA2* mutations and survival in women with invasive epithelial ovarian cancer. *JAMA* 2012; **307:** 382–90.

20 Ghirardi V, De Felice F, D'Indinosante M, et al. Hyperthermic intraperitoneal chemotherapy (HIPEC) after primary debulking surgery in advanced epithelial ovarian cancer: is *BRCA* mutational status making the difference? *Cancer Treat Res Commun* 2022; **31:** 100518.

21 Koole SN, van Driel WJ, Sonke GS. Hyperthermic intraperitoneal chemotherapy for ovarian cancer: the heat is on. *Cancer* 2019; **125** (suppl 24)**:** 4587–93.

22 Vergote I, Harter P, Chiva L. Hyperthermic intraperitoneal chemotherapy does not improve survival in advanced ovarian cancer. *Cancer* 2019; **125** (suppl 24)**:** 4594–97.

23 Lim MC, Chang SJ, Park B, et al. Survival after hyperthermic intraperitoneal chemotherapy and primary or interval cytoreductive surgery in ovarian cancer: a randomized clinical trial. *JAMA Surg* 2022; **157:** 374–83.

24 Koole S, van Stein R, Sikorska K, et al. 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. *Int J Gynecol Cancer* 2020; **30:** 888–92.

25 Cascales Campos PA, González Gil A, Gil Gómez E, et al. Cytoreductive surgery with or without HIPEC after neoadjuvant chemotherapy in ovarian cancer: a phase 3 clinical trial. *Ann Surg Oncol* 2022; **29:** 2617–25.

26 Filis P, Mauri D, Markozannes G, Tolia M, Filis N, Tsilidis K. Hyperthermic intraperitoneal chemotherapy (HIPEC) for the management of primary advanced and recurrent ovarian cancer: a systematic review and meta-analysis of randomized trials. *ESMO Open* 2022; **7:** 100586.

27 Zivanovic O, Chi DS, Zhou Q, et al. Secondary cytoreduction and carboplatin hyperthermic intraperitoneal chemotherapy for platinum-sensitive recurrent ovarian cancer: an MSK team ovary phase II study. *J Clin Oncol* 2021; **39:** 2594–604.

28 Spiliotis J, Halkia E, Lianos E, et al. Cytoreductive surgery and HIPEC in recurrent epithelial ovarian cancer: a prospective randomized phase III study. *Ann Surg Oncol* 2015; **22:** 1570–75.

29 Aronson SL, van Stein RM, Sonke GS, van Driel WJ. Future of HIPEC for ovarian cancer. *BJOG* 2023; **130:** 135–40.

30 Dellinger TH, Han ES, Raoof M, et al. Hyperthermic intraperitoneal chemotherapy-induced molecular changes in humans validate preclinical data in ovarian cancer. *JCO Precis Oncol* 2022; **6:** e2100239.

31 Junttila MR, de Sauvage FJ. Influence of tumour micro-environment heterogeneity on therapeutic response. *Nature* 2013; **501:** 346–54.