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

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HIGHLIGHTS

- We conducted a central blinded revision according to a standardized protocol of all imaging studies performed in the OVHIPEC trial.
- Central revision of recurrence-free survival confirms the benefit of HIPEC as an addition to interval cytoreductive surgery.
- HIPEC specifically prevents peritoneal recurrences but has no effect on extraperitoneal disease.

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 an open-label design affected the results of the trial by central blinded assessment of recurrence-free survival, and tested whether 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 (100 mg/m^2). Patients received three additional cycles of chemotherapy after surgery. Computed tomography (CT) scans and serum cancer antigen 125 (CA125) 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 Response Evaluation Criteria in Solid Tumors (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 neoadjuvant 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 (HR for disease recurrence or death 0.72, 95% CI 0.55 to 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 extraperitoneal recurrences.

Conclusion Centrally-assessed recurrence-free survival analysis confirms the benefit of adding HIPEC to interval cytoreductive surgery in patients with stage III ovarian cancer, with fewer 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 present with advanced disease that has spread to the peritoneal surface and beyond (International Federation of Gynecological 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 2 years, and 10 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 with 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 in patients with advanced stage ovarian cancer.[9–12] Adoption of

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intraperitoneal/intravenous 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 intraperitoneal 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] The 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 neoadjuvant 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 stage III ovarian cancer who had undergone neoadjuvant chemotherapy were randomized (1:1) to receive interval cytoreductive surgery with or without HIPEC using cisplatin 100 mg/m^2. These patients were not candidates for primary surgery due to the extent of disease, and they had at least stable disease after three cycles of neoadjuvant chemotherapy with carboplatin (area under the curve 5–6 mg) and paclitaxel 175 mg/m^2. Randomization was performed intraoperatively 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 (CA125) level were repeated every 3 months for 2 years, and every 6 months thereafter until at least 5 years after the completion of chemotherapy or until recurrence occurred. Computed tomography (CT) scans were performed at 1, 6, 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 CA125 level, as recommended by the Gynecologic Cancer InterGroup (GCIG).[15] The 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 cut-off was set at March 31, 2017.

Data Collection

We collected CT scans at diagnosis, during neoadjuvant chemotherapy, and during follow-up from all patients who 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] extraperitoneal 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 five target lesions, were measured in at least one dimension.

The FIGO substage was determined on the baseline CT scan before the start of neoadjuvant chemotherapy.[17] Response during neoadjuvant 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, CA125 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 CA125 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 the start of treatment, mean preoperative peritoneal cancer index on CT scan, and radiological response during neoadjuvant treatment were listed for both treatment arms. Median recurrence-free survival based on central revision was calculated using Kaplan-Meier estimates and compared using the log-rank test. Hazard ratios (HR) and the corresponding 95% confidence intervals (95% 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 preoperative peritoneal cancer index scores and radiological response during neoadjuvant chemotherapy. HR and corresponding 99% CI were estimated using Cox proportional hazard models, with associated p values for interaction. Time-dependent receiver operating curves 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 chemotherapy, 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 (Online supplemental figure 1 and 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).

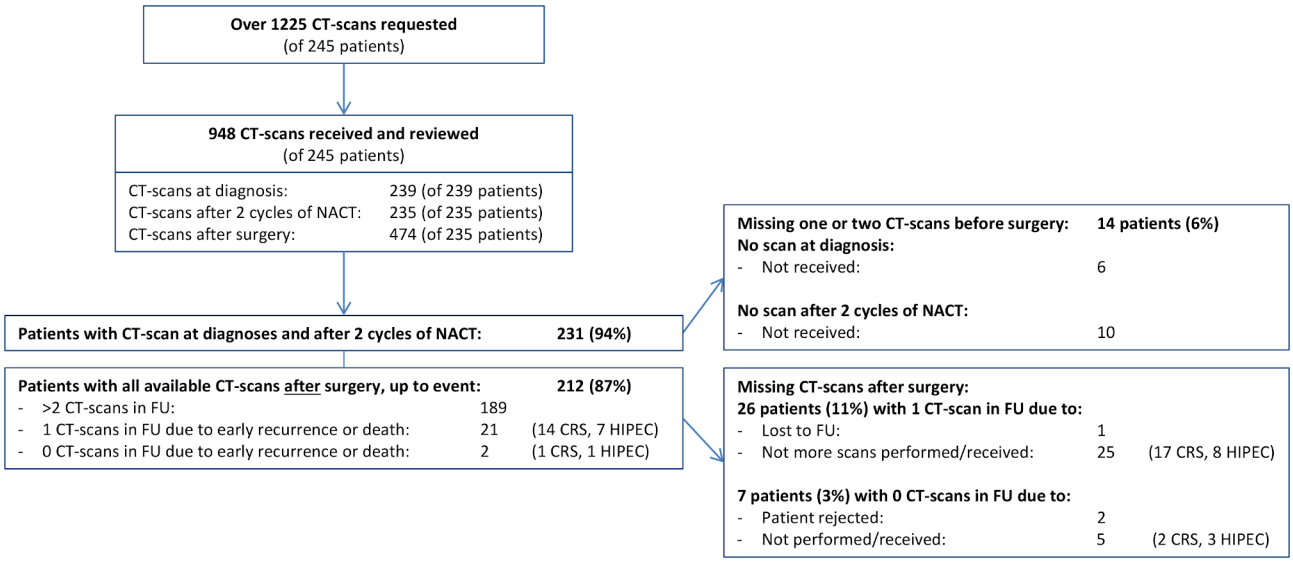

Figure 1 CONSORT diagram for availability of CT scans and missing CT scans. CRS, cytoreductive surgery; CT, computed tomography; FU, follow-up; HIPEC, hyperthermic intraperitoneal chemotherapy; NACT, neoadjuvant chemotherapy.

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 1). Two hundred and thirty-one patients (94%) had CT scans available before and after neoadjuvant chemotherapy. For 212 patients (87%) all CT scans were available during neoadjuvant 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 1 and online supplemental table 2B).

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

Death, or centrally reviewed events of recurrence, occurred in 112/123 (91%) patients in the surgery alone group, and in 102/122 (84%) patients in the surgery plus HIPEC group (Table 2). Centrally assessed median recurrence-free survival was 9.9 months in the surgery group and 13.2 months in the surgery plus HIPEC group (HR for disease recurrence or death 0.72, 95% CI 0.55 to 0.94; p=0.015) (Figure 2). In exploratory subgroup analyses, the benefit of HIPEC on centrally assessed recurrence-free survival and overall survival 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 3A,B).

The location of recurrence per treatment arm is listed in Online supplemental table 3. The cumulative incidence of peritoneal or extraperitoneal recurrences was centrally reviewed. These analyses show significantly fewer peritoneal recurrences over time after treatment with interval cytoreductive surgery plus HIPEC (HR 0.72, 95% CI 0.52 to 0.99; Gray's test p=0.046; Online supplemental figure 1A). There was no difference in the incidence of

Table 1 Baseline characteristics

	CRS		CRS+HPEC	
	n=123		n=122	
FIGO, N (%)				
IIA	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	

CRS, cytoreductive surgey; CT, computed tomography; FIGO, International Federation of Gynecologic Oncology; HIPEC, hyperthermic intraperitoneal chemotherapy; NACT, neoadjuvant chemotherapy; PCI, peritoneal cancer index; RECIST, Response Evaluation Criteria in Solid Tumors.

Table 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 with previous CT†	21	17%	28	23%
Recurrence based on clinical symptoms/CA125 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/CA125 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.
‡Without availability of CT scan within 4 weeks.
CA125, cancer antigen 125; CRS, cytoreductive surgery; CT, computed tomography; HIPEC, hyperthermic intraperitoneal chemotherapy.

extraperitoneal recurrences over time (HR 0.85, 95% CI 0.55 to 1.30; Gray's test p=0.45; Online supplemental figure 1C). The most common location of extraperitoneal disease was in enlarged lymph nodes on CT scan (Online supplemental table 4). Sensitivity analyses in which recurrences based on CA125, symptoms or recurrences without availability of CT scan were considered either peritoneal or extraperitoneal, and did not affect these results (Online supplemental figure 1B,D).

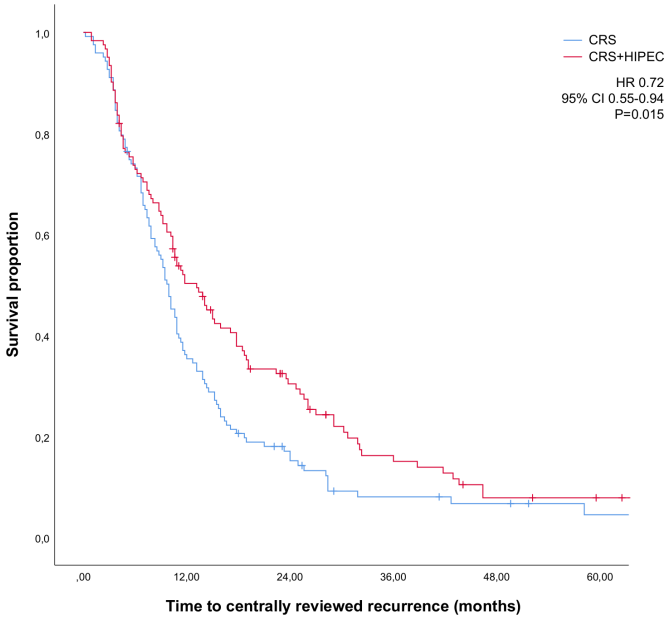

Figure 2 Recurrence-free survival curve based on centrally revised recurrences. CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy.

DISCUSSION

The multicenter, open-label phase III OVHIPEC 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 to 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 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 were 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 extraperitoneal 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, the mean peritoneal cancer index decreased during neoadjuvant chemotherapy, from a mean of 17 to a mean of 12, in both arms. The 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 neoadjuvant treatment. The effect of HIPEC was consistent across the levels of exploratory subgroups, including low and high baseline peritoneal cancer index and response to neoadjuvant 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 to 33 and from 0 to 31 after two cycles of neoadjuvant 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]

Figure 3A. Exploratory subgroup analysis for recurrence-free survival

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)	

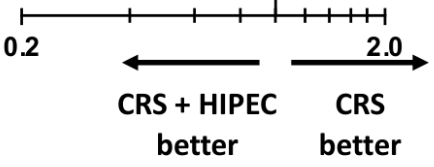

Figure 3B. Exploratory subgroup analysis for overall survival

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)	

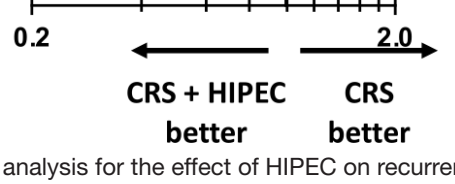

Figure 3 (A,B) Forest plot for exploratory subgroup analysis for the effect of HIPEC on recurrence-free survival and overall survival. CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; PCI, peritoneal cancer index; NACT, neoadjuvant chemotherapy; PR, partial response; SD, stable disease.

This central review has some limitations. First, CT scans were planned at 1, 6, 12, and 24 months after the last cycle of chemotherapy or in case of a CA125 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 trial randomized patients after three cycles of neoadjuvant chemotherapy, more than 3 months after the initial diagnosis. These 3 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 a 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 extraperitoneal 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 particularly effective approach to target microscopic residual peritoneal disease, as the penetrance 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 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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Contributors SK wrote the initial drafts of the manuscript and performed data curation and formal analysis. ML and CF were responsible for central CT scan review. SK and LB were responsible for central data collection. JSvL, HS, RH, JvV, HA, MvH, PvD, PV and WvD were responsible for patient acquisition and data collection. LB, KS, ME, GS, ML and WvD contributed clinical or statistical expertise to the analysis and manuscript. All authors read and commented on the manuscript and approved the final version.

Competing interests GS reports institutional research support outside the submitted work, from AstraZeneca, Merck, Novartis, and Roche, during the conduct of the study.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. In accordance with the journal's guidelines, we will provide our data for the reproducibility of this study in other centers if requested.

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