ORIGINAL ARTICLE

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. (Funded by the Dutch Cancer Society; ClinicalTrials.gov number, NCT00426257; EudraCT number, 2006-003466-34.)

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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 cytoreductive 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.[12,13]

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, which is available with the full text of this article at NEJM.org, 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 (detailed information regarding the procedure can be found in the protocol). 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) — within 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)[14] (see the Supplementary Appendix, available at NEJM.org). 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.

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 1. Demographic and baseline disease characteristics and surgical and treatment information for the two trial groups are shown in Table 1.

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. 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. 3) and overall survival (Fig. S2 in the Supplementary Appendix) 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. 2B). The median overall survival was 33.9 months in the surgery group and 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 random-

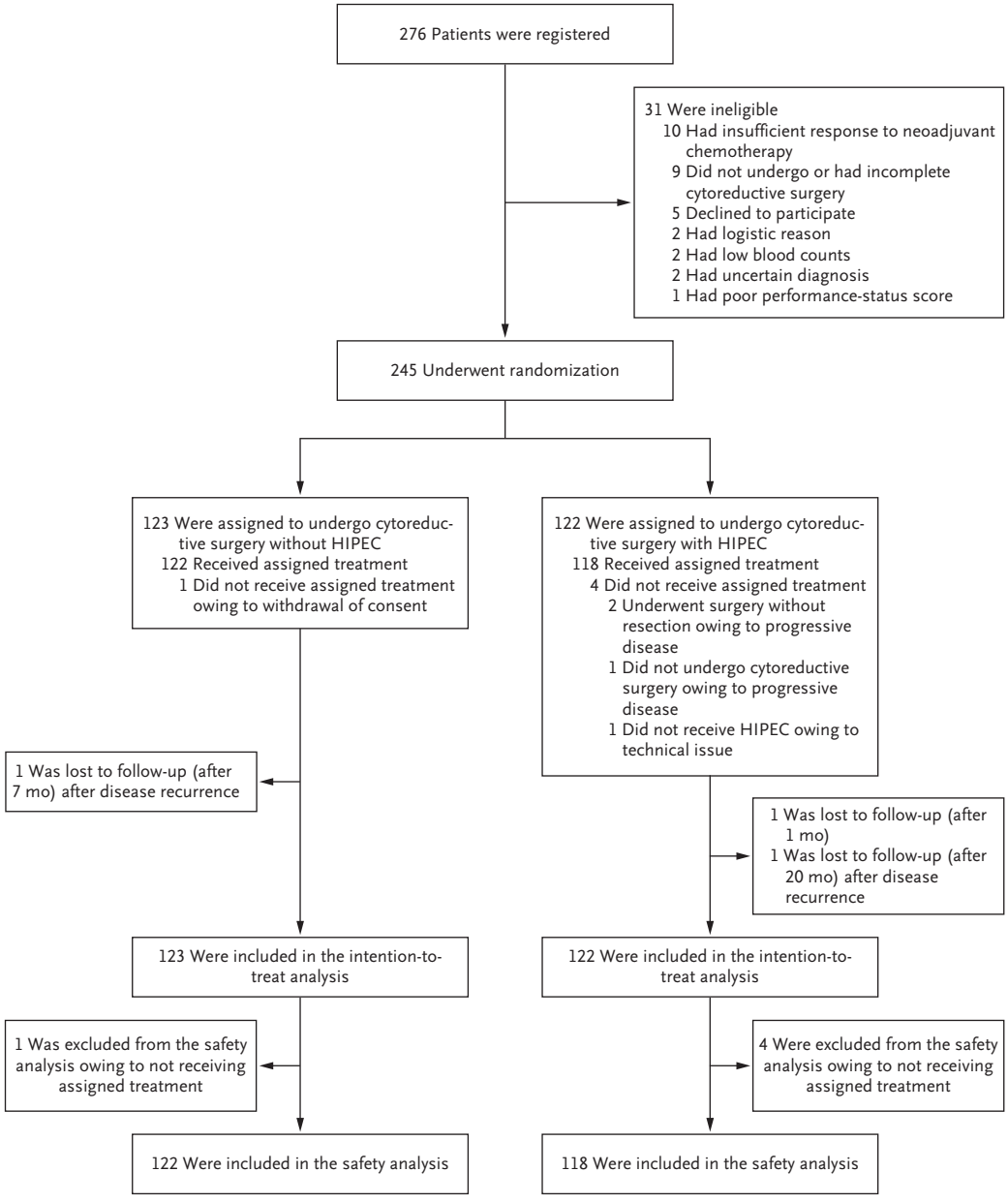


Figure 1. Enrollment, Randomization, and Follow-up.

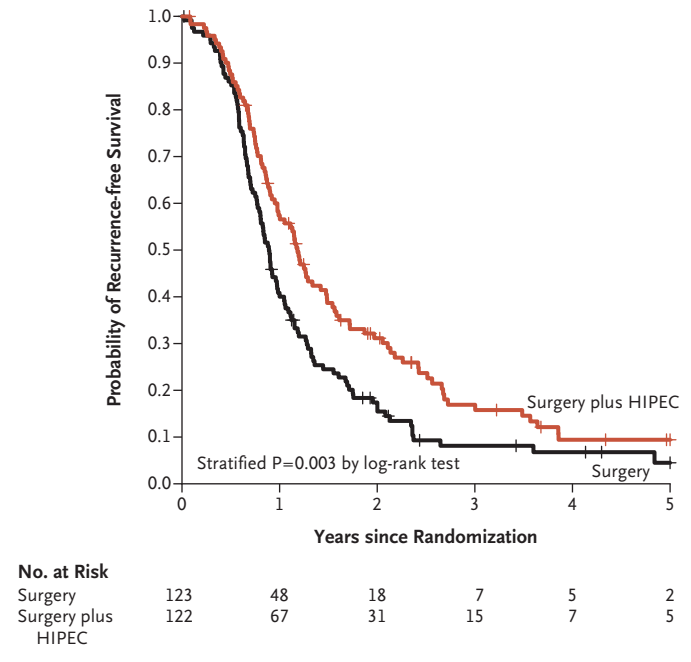
The patient who was randomly assigned to the surgery group but did not undergo cytoreductive surgery owing to withdrawal of consent allowed the use of all her registered data before the time of withdrawal. Incomplete cytoreductive surgery was defined as surgery that resulted in the presence of one or 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.

ization 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

Table 1. Demographic and Baseline Disease Characteristics and Surgery Information.*

Variable	Surgery (N=123)	Surgery plus HIPEC (N=122)
Baseline characteristics		
Median age (IQR) — yr	63 (56–66)	61 (55–66)
Tumor histologic type — 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
Low-grade serous	2 (2)	4 (3)
Low-grade endometrioid	0	2 (2)
Metastasis of gastrointestinal tumor	1 (1)	0
Unknown	1 (1)	1 (1)
Previous 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)
Treatment characteristics		
Residual disease after surgery — no. (%)		
R-1, no visible tumor, complete cytoreduction	82 (67)	84 (69)
R-2a, tumor nodules ≤2.5 mm	24 (20)	22 (18)
R-2b, tumor nodules >2.5 mm and ≤10 mm	14 (11)	13 (11)
Tumor nodules >10 mm, incomplete cytoreduction	1 (1)	0
No resection§	1 (1)	2 (2)
No surgery performed	1 (1)	1 (1)
Bowel resection — no. (%)		
No bowel resection performed	93 (76)	93 (76)
Bowel resection with ileostomy or colostomy	13 (11)	21 (17)
Bowel resection without ileostomy or colostomy	17 (14)	8 (7)
Median duration of surgery (IQR) — min	192 (153–251)	338 (299–426)
Median duration of hospitalization (IQR) — days¶	8 (7–10)	10 (8–12)
Median time between surgery and start of first cycle of adjuvant chemotherapy (IQR) — days	30 (25–41)	33 (28–41)
Number of completed cycles of adjuvant chemotherapy after surgery — no. (%)		
0	7 (6)	5 (4)
1	2 (2)	0
2	3 (2)	2 (2)
3	111 (90)	115 (94)

* 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 (P=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 involved with 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.



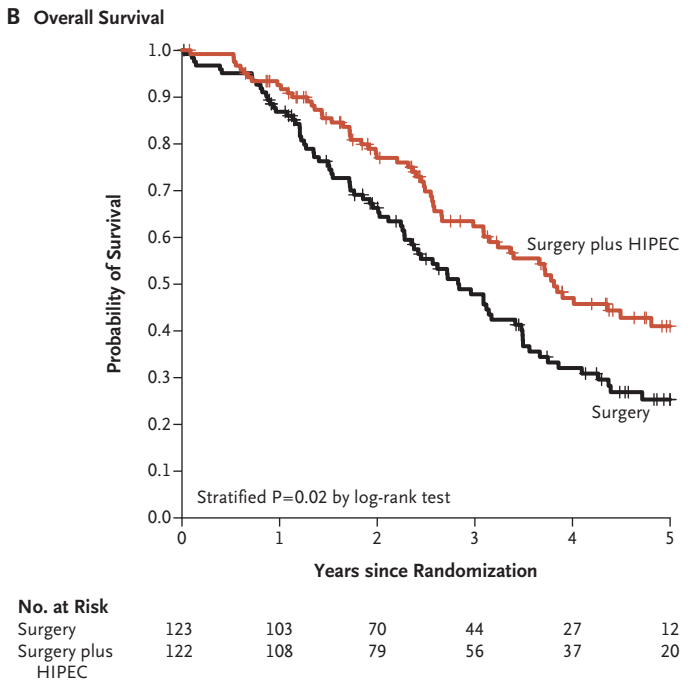


Figure 2. Kaplan–Meier Estimates of Recurrence-free Survival and Overall Survival.

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.

3 or 4 were abdominal pain, infection, and ileus (Table 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 chemotherapy 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.

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.

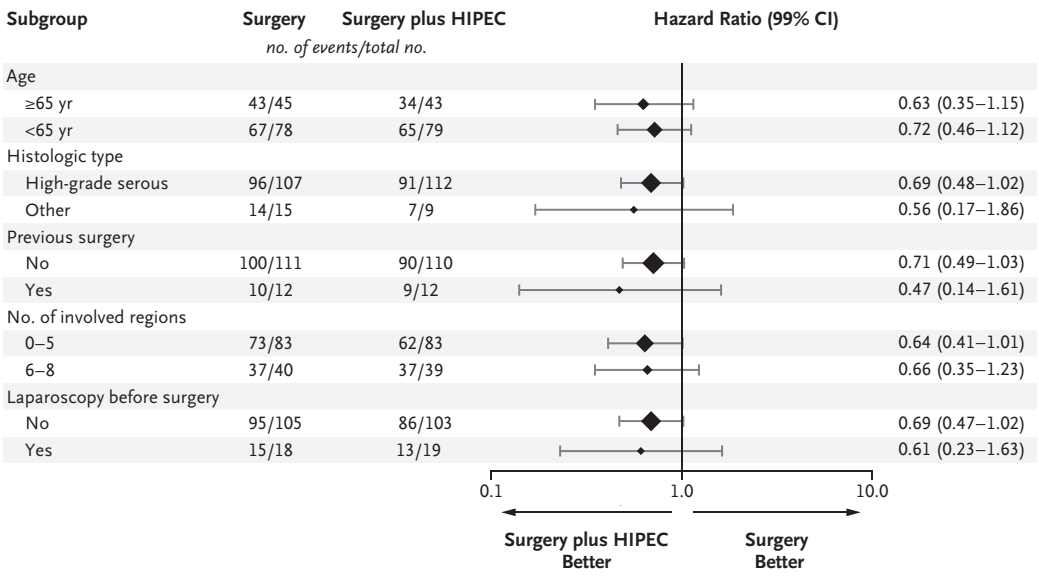


Figure 3. Prespecified Subgroup Analyses of Recurrence-free Survival.

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.

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.[12,13] 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 prespecified 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 prespecified 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 intraperitoneal 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

Table 2. Adverse Events from Randomization to 6 Weeks after Completion of Last Cycle of Chemotherapy.*

Adverse Event	Surgery (N=122)		Surgery plus HIPEC (N=118)	
	Any Grade	Grade 3 or 4†	Any Grade	Grade 3 or 4
	number of patients (percent)			
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, not otherwise specified	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)
Postoperative 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, an event of grade 5 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 included hyponatremia, hypernatremia, hypokalemia, hypercalcemia, hypomagnesemia, and hypophosphatemia.

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 in the control group of the Gynecologic 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.[5] The number of patients 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.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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