

Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer

First Report of the HYPER-O Registry

Cyril William Helm, MB, BChir,* Scott D. Richard, MD,† Jianmin Pan, MD,‡
David Bartlett, MD,§ Martin D. Goodman, MD,|| Rick Hoefler, DO, FACS,¶ Sam S. Lentz, MD,**
Edward A. Levine, MD,†† Brian W. Loggie, MD,‡‡ Daniel S. Metzinger, MD,* Brigitte Miller, MD,**
Lynn Parker, MD,* James E. Spellman, MD,§§ Paul H. Sugarbaker, MD, FACS, FRCS,||||
Robert P. Edwards, MD,¶¶ and Shesh N. Rai, MD***†††

Introduction: An analysis of experience of surgical and gynecologic oncologists in the United States with the use of hyperthermic intraperitoneal chemotherapy for women with invasive epithelial ovarian cancer (EOC).

Methods: An Internet-based registry (HYPER-O) collected data from collaborating institutions. Eligibility included women with EOC treated with hyperthermic intraperitoneal chemotherapy. Borderline and nonepithelial cancers were excluded.

Results: As of July 1, 2008, 141 women were eligible for analysis treated at the following time points: frontline (n = 26), interval debulking (n = 19), consolidation (n = 12), and recurrence (n = 83). The mean perfusion temperatures were 38.5 to 43.6°C (median, 41.9°C) for inflow and 36.9 to 42.9°C (median, 41°C) for outflow for 30 to 120 minutes. Treatment was with a platinum agent (n = 72), mitomycin (n = 53), or a combination (n = 14). Median follow-up was 18 months (range, 0.3–140.5 months) and median overall survival 30.3 months (95% confidence interval, 23.0–37.6) with 2-, 5-, and 10-year overall survival probabilities of 49.1%, 25.4%, and 14.3%, respectively. Of the 141 patients, 110 (78%) experienced recurrence of ovarian cancer and 87 died, 3 (0.5%) dying within 30 days of surgery. In the multivariable analysis, the factors significant for increased survival were sensitivity to platinum response ($P = 0.048$), completeness of cytoreduction scores of 1 or 0 ($P = 0.025$), carboplatin alone or a combination of 2 or more chemotherapy agents used ($P = 0.011$), and duration of hospital stays of 10 days or less ($P = 0.021$).

Conclusions: Hyperthermic intraperitoneal chemotherapy is a viable additional treatment option for patients with invasive EOC and may extend life in selected groups. It warrants further study in randomized controlled trials.

Key Words: Hyperthermic intraperitoneal chemotherapy (HIPEC), Ovarian neoplasms, Intraperitoneal chemotherapy, Hyperthermia, Cytoreductive surgery

*Division of Gynecologic Oncology, James Graham Brown Cancer Center, University of Louisville, Louisville, KY; †University of Pittsburgh Physicians, Department of Obstetrics, Gynecology and Women's Health, Magee-Women's Hospital, Pittsburgh, PA; ‡Biostatistics Shared Facility, James Graham Brown Cancer Center, University of Louisville, Louisville, KY; §Division of Surgical Oncology, University of Pittsburgh Medical Center, Pittsburgh, PA; ||Tufts Medical Center, Boston, MA; ¶Surgical Oncology Newport News, VA; Divisions of **Gynecologic Oncology, and ††Surgical Oncology, Wake Forest University, Winston-Salem, NC; ‡‡Division of Surgical Oncology, Creighton University Medical Center, Omaha, NE; §§Oncologic Surgery, Beebe Medical Center, Rehoboth Beach, DE; ||||Washington Hospital Center, Washington, DC; Copyright © 2010 by IGCS and ESGO
ISSN: 1048-891X
DOI: 10.1111/IGC.0b013e3181c50cde

¶¶Magee Hospital for Women, Pittsburgh, PA; and ***Biostatistics Shared Facility, James Graham Brown Cancer Center, and †††Department of Bioinformatics and Biostatistics, University of Louisville, Louisville, KY.

Address correspondence and reprint requests to
C. William Helm, MB, BChir, Division of Gynecologic Oncology, James Graham Brown Cancer Center,
Third Floor, 529 S Jackson St, Louisville, KY 40202.
E-mail: cwilliamhelm@gmail.com.

Dr Helm has received 3 honoraria for lectures on hyperthermic intraperitoneal chemotherapy in ovarian cancer from ThermaSolutions, Inc (White Bear Lake, Minn).

Dr Helm has received grant support from ThermaSolutions, Inc for the HYPER-O registry and from Sanofi-Aventis (Bridgewater, NJ) for a clinical research study investigating hyperthermic intraperitoneal chemotherapy.

Received August 5, 2009, and in revised form September 11, 2009.

Accepted for publication October 7, 2009.

(*Int J Gynecol Cancer* 2010;20: 61–69)

Epithelial ovarian cancer (EOC) is a significant cause of cancer death globally.¹ It causes few symptoms in early stages, and most women present with widespread metastases when cure is difficult. Although great strides have been made in treatment, there remains urgent need for improvement because 5-year overall survival (OS) remains just more than 50%.

Epithelial ovarian cancer remains confined to the peritoneal cavity for much of its natural history, and being relatively sensitive to chemotherapy should be a good target for intraperitoneal (IP) treatment.² For drugs most active in EOC, the ratio of IP to plasma concentration varies from 18 to 20 times for carboplatin and cisplatin to 120 to more than 1000 times for the taxanes, docetaxel, and paclitaxel.³ Three large, randomized cooperative group studies showed survival benefit for women receiving IP chemotherapy,^{4–6} and a Cochrane meta-analysis of all randomized studies confirmed this.⁷ The most recent study⁵ reported that patients receiving IP chemotherapy had a median survival of 16 months greater than those receiving intravenous (IV) only (65.6 vs 49.7 months), and in consequence, the National Cancer Institute issued a clinical announcement recommending that all women with optimal EOC after frontline (FL) surgery should be offered IP chemotherapy.⁸ Despite the extension of survival, median progression-free survival (PFS) increased by only 5 months, and the recurrence rate was 65% in the investigational arm. Clearly, improved treatment methods are still needed, and 1 possibility is the incorporation of hyperthermia together with IP chemotherapy (hyperthermic IP chemotherapy [HIPEC]).

Hyperthermia alone is tumoricidal,⁹ and it increases the cytotoxicity of many chemotherapeutic agents in human cell culture and animal models.^{10–23} It increases DNA cross-linking and DNA adduct formation in combination with cisplatin^{24,25} and deepens penetration into peritoneal tumor implants.²⁵

After the pioneering work of Spratt,^{26,27} there have been reports of HIPEC treatment of gastric,²⁸ mesothelioma,²⁹ appendiceal,³⁰ endometrial,³¹ and colorectal cancer.^{32,33} Reports of HIPEC in EOC have been summarized previously,³⁴ but the evidence is all level 4.³⁵ There have been no completed randomized controlled trials (RCTs) to date. In the absence of large RCTs both now and likely for many years to come, HYPER-O aimed to combine the experience of surgical and gynecologic oncologists performing HIPEC for EOC, much of which has never been analyzed or published. The data would be entered in a uniform format that would allow systematic analysis of a large group of patients not obtainable within a single institution.

METHODS

HYPER-O (www.hyperoregistry.com) based at the James Graham Brown Cancer Center, Louisville, Ky, is an

TABLE 1. Patient characteristics in HYPER-O registry study: categorical variables (n = 141)

Characteristic	n	%
Race		
White (not Hispanic)	133	94.3
Black	5	3.6
Other	3	2.1
Primary site		
Ovary	114	80.9
Peritoneal	26	18.4
Fallopian tube	1	0.7
Histologic grade of primary cancer		
1	14	10.7
2	12	9.2
3	105	80.1
Initial FIGO stage		
II	10	7.3
III	113	82.5
IV	14	10.2
Time point HIPEC used		
Frontline	26	18.5
Interval debulking	19	13.6
Consolidation	12	8.56
Recurrence	83	59.3
Frontline platinum response		
Resistant	48	38.7
Sensitive	76	61.3
Macroscopic residual disease immediately before HIPEC		
No	81	58.3
Yes	58	41.7
CC score		
0	81	58.3
1	21	15.1
2	30	21.6
3	7	5.0
Largest residual lesion size immediately before HIPEC		
0	81	59.1
0–0.5 cm	33	24.1
>0.5 cm	23	16.8
Duration of HIPEC chemotherapy perfusion		
≤90 min	64	45.4
90–120 min	77	54.6

FIGO, International Federation of Gynecology and Obstetrics.

TABLE 2. Patient characteristics in HYPER-O registry study: continuous variables (n = 141)

Characteristic	n	Mean	Median	SE	Minimum	Maximum
Age at HIPEC, yr	141	58.1	58.4	10.5	18.6	81.4
Duration HIPEC surgery, h	134	7.9	7.5	2.4	3.5	16.0
Largest lesion found at HIPEC surgery, cm	123	5.0	4.0	4.8	0.0	20.0
Duration of hospital stay, d	138	15.6	10.0	15.0	4.0	102.0
Maximum inflow temperature, °C	121	42.1	42.3	1.1	39.0	44.5
Minimum outflow temperature, °C	116	40.0	40.2	1.7	33.5	43.0
Mean inflow temperature, °C	116	41.6	41.9	1.1	38.5	43.6
Mean outflow temperature, °C	114	40.8	41.0	1.3	36.9	42.9
Blood loss at HIPEC surgery, mL	134	963.8	500.0	1221.0	0.0	8400.0

institutional review board–approved, Health Insurance Portability and Accountability Act–compliant, Internet database (Lee Hagendoorn, www.advertex.net). After registration, collaborators are given secure access for data entry. Each patient has an identifying number, and a secure register with patient details and identifiers is kept at each collaborating center.

Eligibility criteria included women with epithelial ovarian, fallopian tube, and primary peritoneal carcinomas treated with HIPEC at some point in the natural history of the disease. Women with borderline (low malignant potential) tumors and those with non-EOCs were excluded. Each institution reported data from its own individual methodology for HIPEC administration. Central review of histologic slides was not performed. The extent of resection was evaluated using the greatest dimension of the largest residual lesion (centimeter) before HIPEC and the completeness of cytoreduction (CC) score,³⁶ which is widely used by surgical oncologists as a measure of the largest size of residual tumor after cytoreductive surgery: CC-0, no visible disease; CC-1, visible tumor of less than 2.5 mm; CC-2, 2.5 mm to less than 2.5 cm; and CC-3, more than 2.5 cm or confluence of tumor nodules. HYPER-O opened on August 29, 2005, and temporarily closed on July 1, 2008, for data check by the principal investigator. Final data were transferred to an Excel spreadsheet for statistical analysis by the study statisticians (J.P. and S.N.R.).

Statistical Analysis

The Kaplan-Meier method³⁷ was used to estimate OS and PFS. Survival probabilities are presented as percentage with SE in parentheses. Survival differences were compared using the unweighted log-rank test³⁸ with the OS time determined as the time from HIPEC surgery until death or last follow-up evaluation. The PFS time was the time from HIPEC surgery until the first adverse event (ie, disease progression, second malignancy, or death from any cause). Independent prognostic significance was assessed by multivariable analysis using the Cox regression method.³⁹ Results from HYPER-O are compared with published results using a 95% confidence interval (CI) because of lack of survival times in published studies. All calculations were performed with the SAS statistical software (SAS Institute Inc, Cary, NC).

RESULTS

On July 1, 2008, of 166 patients registered in HYPER-O, 25 were ineligible for inclusion in this report (non-EOC [n = 12], borderline [low malignant potential; n = 4], double primary cancer [n = 1], and insufficient data [n = 8]), leaving 141 for analysis from the following institutions: Beebe Medical Center (MC), Rehoboth Beach, DE (24); Creighton University MC, Omaha, NE (7); Mills Peninsula MC, Burlingame, CA (4); Surgical Oncology Associates, Newport News, VA (4); James Graham Brown Cancer Center, University of Louisville, Louisville, KY (22); University of Pittsburgh MC, Pittsburgh, PA (33); Wake Forest University, Winston-Salem, NC (30); and Washington Hospital Center, Washington, DC (17). Apart from 5 patients treated with HIPEC at one of the participating institutions not included in this analysis because they were identified after the deadline for registry data entry, all patients with EOC treated with HIPEC at the participating centers up to the registration deadline are included in this report. The median age at HIPEC surgery was 58.4 years (range, 18.6–81.4 years). For detail of patient characteristics and treatment variables, see Table 1 for categorical and Table 2 for continuous. Most patients, 132 (93.6%) of the 141, received FL platinum-containing chemotherapy, whereas those treated with HIPEC for recurrence, 78 (94%) of 83, received FL platinum-containing chemotherapy with 70 (84.3%) receiving a

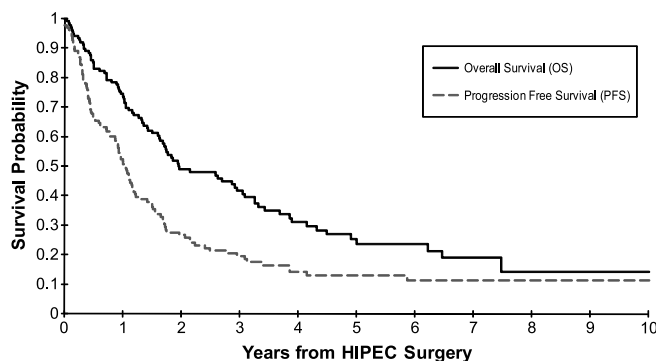


FIGURE 1. Kaplan-Meier curve OS and PFS probabilities.

TABLE 3. Overall survival probabilities (in percentage) and median OS time (n = 141)

Time Point HIPEC Used	n	OS, mo		2-yr		5-yr		10-yr	
		Median	95% CI	OS	SE	OS	SE	OS	SE
Overall	141	30.3	23.0–37.6	49.1	4.9	25.4	5.3	14.3	7.6
Frontline	26	41.7	18.1–65.2	57.0	10.8	33.3	11.1	17.8	11.4
Interval debulking*	19	68.6	0–157.7	80.4	13.5	50.2	25.1		
Consolidation*	12	53.7	1.8–105.7	63.6	13.6	42.4	16.1		
Recurrence	83	23.5	16.4–30.6	40.9	5.9	18.0	5.8	9.0	6.1

*Unreliable because of the small number of events.

platinum-taxane combination. In those treated for recurrence, the median number of prior regimens received overall between completion of FL therapy and HIPEC was 1 (range, 0–6), but in those who had received any prior chemotherapy for recurrence, the median was 2 (range, 1–6).

Nongynecologic procedures performed with HIPEC included resection of diaphragmatic disease (n = 24; 17%), resection of disease on or in the liver (n = 18; 12.7%), partial gastrectomy (n = 4; 2.8%), splenectomy with or without partial pancreatectomy (n = 35; 24.8%), large- (n = 62; 44%) and small-bowel resections (n = 23; 16.3%), colostomy/ileostomy (n = 29; 20.6%), and repair/reimplantation of the ureter (n = 3; 2.1%). Hyperthermic IP chemotherapy perfusion was closed (n = 124; 87.9%) and open (n = 17; 12.1%) with equipment from ThermaSolutions, Inc (White Bear Lake, Minn; n = 94; 66.7%) and other (n = 47; 33.3%). A single HIPEC treatment was given to 134 patients (95%), whereas 2 treatments were given to 7 (5%). Data reported here are from the first HIPEC treatment only. Median durations of perfusion were 100 minutes (range, 30–120 minutes), 30 minutes (n = 1), 60 minutes (n = 3), 90 minutes (n = 60), 100 minutes (n = 36), and 120 minutes (n = 41). Chemotherapy agents delivered by HIPEC were carboplatin alone (n = 20; 14.4%), cisplatin alone (n = 51; 36.7%), cisplatin with doxorubicin (n = 10; 7.2%) including 1 with ifosfamide in addition, oxaliplatin (n = 1; 0.8%), mitomycin with carboplatin (n = 3; 2.1%), and mitomycin alone (n = 54; 38.8%), including 1 with early postoperative IP normothermic 5-fluorouracil. Analysis of toxicity is ongoing and will be reported separately.

The median durations of follow-up after HIPEC surgery were 18 months (range, 0.3–140.5 months) for all patients and 23.3 months (range, 0.3–140.5 months) for patients alive at last follow-up, with 96% of patients having at least 6 months of follow-up. Overall survival and PFS are detailed in Figure 1 with OS probabilities at 2, 5, and 10 years together with median OS by the time point HIPEC was delivered in Tables 3 and 4 and Figure 4. Eighty-seven patients died, and 110 experienced recurrence of EOC. Three patients (0.5%) died within 30 days of surgery (myocardial infarction, pulmonary embolus, and sepsis). To explore the independent prognostic significance of perioperative factors, a multivariable analysis using the Cox regression method³⁹ was made (Table 5). Factors not significant in the univariable analysis included ethnicity, primary site, histologic grade, number of HIPEC treatments, macroscopic residual disease before HIPEC, largest lesion found at time of HIPEC (≤ 4 cm and >4 cm), and age at HIPEC (<50, 50–60, 60–70, and >70 years).

In the multivariable analysis, the factors significant for increased survival in the Cox proportional hazards regression model were sensitivity to platinum response ($P = 0.048$), CC scores of 1 or 0 ($P = 0.025$), carboplatin alone or combination of 2 or more chemotherapy agents used ($P = 0.011$), and duration of hospital stay of 10 days or less ($P = 0.021$).

The effect of chemotherapy agents on survival was analyzed in relation to the time point at which they were used. For overall recurrence, carboplatin was associated with a greater survival chance than mitomycin ($P = 0.003$) or cisplatin ($P = 0.003$). Outcome for patients with platinum-sensitive recurrence was better with carboplatin versus

TABLE 4. Progression-free survival probability (percentage) and median PFS time (n = 141)

Time Point HIPEC Used	n	PFS, mo		2-yr		5-yr		10-yr	
		Median	95% CI	OS	SE	OS	SE	OS	SE
Overall	141	16.6	12.1–21.1	26.7	4.1	13.0	3.6	11.3	6.2
Frontline	26	24.8	8.7–40.9	34.5	9.9	19.7	8.8	13.1	8.7
Interval debulking	19*	16.8	5.0–28.7	28.9	12.2	9.6	6.5		
Consolidation	12*	29.6	0–63.9	36.4	13.0	24.2	12.2		
Recurrence	83	13.7	9.1–18.4	23.1	4.9	9.6	4.1	9.6	6.5

*Unreliable because of the small number of events.

TABLE 5. Overall survival probability (percentage) in HYPER-O registry study (n = 141)

Characteristic	n	Median, mo	5-yr		10-yr		Univariable	Multivariable
			OS	SE	OS	SE	P	
Overall	141	30.3	25.4	5.3	14.3	7.6		
Initial FIGO stage							0.049	
II	10	190.4†	90.0	20.1			Reference	
III	113	29.6	23.1	5.2	12.9	6.9	0.025	
IV	14	20.6					0.030	
Time point HIPEC used							0.049	
Frontline	26	41.8	33.3	11.1	17.8	11.4	Reference	
Interval debulking	19	56.3†	50.2	25.1			0.518	
Consolidation	12	53.7	42.4	16.1			0.579	
Recurrence	83	23.5	18.0	5.8	9.0	6.1	0.103	
Platinum response							0.026	0.048
Resistant	48	20.5	14.4	6.0				
Sensitive	76	33.7	32.3	8.0				
CC score							<0.001	0.025
0	81	37.0	26.7	7.6	17.8	11.4	Reference	
1	21	41.3	38.4	12.3	20.5	12.9	0.972	
2	30	19.9	15.6	8.3			0.018	
3	7	7.5	0.0	0.0	0.0	0.0	<0.001	
Largest residual lesion size immediately before HIPEC							0.027	
0	81	36.6	27.1	7.7	14.4	9.4		
0–0.5 cm	33	30.0	30.9	10.5	16.5	10.6	0.289	
>0.5 cm	23	17.9	13.0	7.0			0.007	
Chemotherapy agent							0.028	0.0114
Cisplatin alone	51	28.6	18.0	9.4	18.0	9.4	Reference	
Mitomycin alone	53	22.3	16.1	6.6			0.540	
Carboplatin alone	20	71.5	55.1	13.1			0.013	
Combination (≥2 agents)	13	44.7	38.4	15.1			0.350	
Duration of HIPEC chemotherapy perfusion							0.293	
≤90 min	64	35.6	33.8	7.6	16.1	10.4	0.047*	
90–120 min	77	26.3	16.7	6.8	16.7	10.8		
Blood loss at HIPEC surgery							0.005	
≤500 mL	68	40.9	33.6	7.9	17.4	9.1		
>500 mL	66	20.5	14.0	6.5				
Duration of hospital stay								0.021
≤10.00 d	74	37.5	31.2	7.8			0.008	
>10.00 d	64	23.2	20.1	6.8	10.7	5.9		

Reference is the baseline group for comparisons. *P* values in the Multivariable column are from the Cox proportional hazards model.

*One-sided *P* value based on year 5.

†Unreliable because of the small number of events.

cisplatin ($P = 0.012$) and mitomycin ($P = 0.011$), but there was no significant difference between agents in platinum-resistant disease. However, the numbers in the carboplatin group were small.

Survival curves in relation to platinum response and CC score before HIPEC are given in Figures 2 and 3. The mean

inflow temperature was 41.6°C (range, 38.5–43.6°C) and the mean outflow temperature 40.8°C (range, 36.9–42.9°C). With the continuous variables categorized as mean inflow 38.5 to 41°C, 41 to 43°C, and 43 to 43.6°C and mean outflow 36.9 to 41°C and 41 to 43°C, analysis (Fisher exact test) revealed no significant association between the mean temperature of

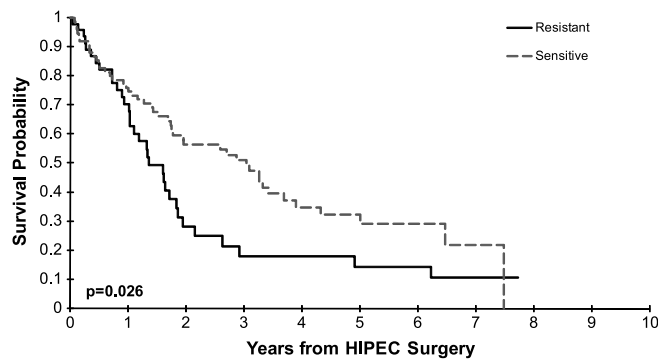


FIGURE 2. Kaplan-Meier curve survival probability by platinum response.

HIPEC and risk of death or recurrence. The chance of surviving 5 years (33.8% vs 16.7%) was significantly greater if the duration of perfusion was 90 minutes or shorter ($P = 0.047$ for 1-sided Z test).

DISCUSSION

Despite more than 400 reported cases of EOC treated with HIPEC, there are still major gaps in knowledge about its role in treating this disease. Reported studies are mostly small, containing heterogeneous populations, and data are difficult to interpret (reviewed in³⁴). A recent abstract reports on a combined nonrandomized series from 2 centers in France,⁴⁰ and the full peer-reviewed results are eagerly awaited. There are no completed RCTs, and to our knowledge, there is only a single, open RCT of HIPEC at interval debulking at the Netherlands Cancer Center (W. van Driel personal communication). Because RCTs looking at outcome in EOC can require several hundred patients, the possibility of many such trials taking place in the near future seems slim.

Surgery with HIPEC has been used for EOC by surgical oncologists in the United States and elsewhere since the 1990s,^{41–43} but much of the experience has never been published. HYPER-O represents an attempt to fill the knowledge gap about treatment of EOC using HIPEC, pending higher level evidence. This is the largest series of patients treated with HIPEC in the United States allowing for in-depth analysis of the current practice of HIPEC delivery in this country and prognostic factors and outcomes. There are clearly problems related to a study such as this including that there was no specified protocol for HIPEC delivery, the data are retrospective coming from different centers with varying selection criteria and does not include information on patients with EOC who were treated in the collaborating centers who did not receive HIPEC or declined treatment with HIPEC. Despite these shortcomings, we believe that analysis of HYPER-O data can contribute to better understanding of this methodology and further research into its efficacy and role.

No difference in outcome has been reported between the use of open and closed methods for HIPEC delivery, and none was found in this series. Interestingly, the temperature of the perfusate between 38.5 and 43.6°C (median, 41.9°C) did not affect outcome, but the duration of perfusion did, with

benefit demonstrated in perfusions of 90 minutes or shorter as opposed to longer than 90 minutes.

There are clearly difficulties in comparing our results with those in the literature because of the heterogeneity of the data set and our inability to compare the median OS and PFS times because of lack of similar studies with the actual data set. Use of approximated CIs for the median survival times from the published reports would lead to misleading comparisons. However, we were able to compare OS and PFS for patients treated with FL HIPEC in relation to those reported for Gynecologic Oncology Group (GOG) protocol⁵ No. 172 in which median survival in the investigational arm was extended by 16 months because of the large number of events in that study. Of the 26 patients treated with FL HIPEC, 20 had similar criteria to eligibility for GOG 172 being cytoreduced to no larger than 1-cm greatest residual lesion size. The 2-year OS and PFS and the median OS time were not significantly different using 95% CI (ie, 5% significance level; Table 6). Although clearly our numbers are small, the data do suggest that HIPEC does not have outcomes that are out of range of those reported for GOG 172.

Although the outcome for patients with recurrent EOC is universally considered to be poor, there are some patients who appear to do well with secondary cytoreductive surgery alone.^{44,45} However, because many patients selected for secondary cytoreductive surgery in these series fall into a good prognosis group with platinum-sensitive disease, small number of recurrence sites, and long interval to recurrence, the results of our unselected group seem interesting. For instance, in the most recent meta-analysis of secondary cytoreductive surgery,⁴⁵ the weighted mean percentage of patients having localized disease was 35% (in those studies where the data were available) compared with 15% of the 83 patients treated with HIPEC for recurrent disease having localized disease, with 28.6% overall being platinum resistant, suggesting that they are a somewhat different and worse prognostic group than would be normally selected for surgery in this setting.

The prognostic factors significant for increased survival in the multivariable analysis were sensitivity to platinum response ($P = 0.048$), CC scores of 1 or 0 ($P = 0.025$), carboplatin alone or a combination chemotherapy agents used ($P = 0.011$), and duration of hospital stays of 10 days or less ($P = 0.021$). Although platinum response is established as a major prognostic factor in the treatment of EOC,^{46,47} it

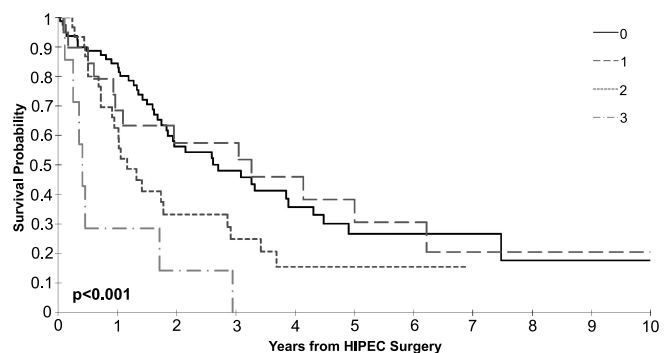


FIGURE 3. Kaplan-Meier curve by CC score.

TABLE 6. OS and PFS probability (percentage) comparison between GOG 172 and HYPER-O in Frontline group

Study	Characteristic	n	OS		PFS	
			Median	2-yr	Median	2-yr
GOG 172*	Therapy					
	Intravenous	210	49.7	75†	18.3	42†
	IP	205	65.6	82†	23.8	53†
HYPER-O	FL‡	20	57.5 (18.8–96.2)§	66.4 (42.5–90.3)§	36.5 (9.9–63.1)§	47.6 (23.7–71.5)§

*Time measured from randomization.

†The numbers are estimated from Figure 4 in GOG 172.⁵

‡Largest residual lesion size before HIPEC perfusion is not larger than 1 cm.

§95% CI.

has not previously been reported as being of significance in patients treated with HIPEC possibly because surgical oncologists have not recognized the importance of this factor in their reports. In a smaller study, the numbers were not large enough to establish any more than a trend.⁴⁸

The demonstration that in platinum-sensitive patients, outcome was significantly better with carboplatin than the other agents is interesting, although the numbers in this group were small. Because carboplatin has a lower adverse-effect profile than cisplatin, it may be preferable in platinum-sensitive patients. For those that are platinum resistant, the choice of an agent remains difficult and our data reveal no agent having an edge. Although a combination of 1 or more chemotherapy agents was significantly associated with survival in the multivariable analysis, the number of patients was again small and no meaningful interpretation can be given about association with prior platinum response and natural history time point used.

The significant prognostic effect of the CC score originally described by Jacquet and Sugarbaker³⁶ confirms previous reports in EOC.^{49,50} The importance of the CC score has been underscored by others using different scoring systems.^{51–53} There has been debate about whether an upper

age limit for the performance of cytoreductive surgery and HIPEC should be set. Interestingly, age was not a factor in outcome in either the univariable or multivariable analyses (groupings: younger than 50 years [n = 27], 50 to younger than 60 years [n = 50], 60 to younger than 70 years [n = 47], and older than 70 years [n = 17]), and it appears that patients should be selected for this procedure based on their fitness for surgery rather than absolute age.

CONCLUSIONS

This large data set shows that HIPEC is a viable additional treatment option for patients with EOC and may extend life in selected groups. It warrants further study in RCTs.

ACKNOWLEDGMENTS

The authors thank Ms Cathy Buckley and Aaron Howell for secretarial and administrative assistance; Hana Gragg, Clinical Trials Office, University of Louisville, and Vaquita Bunton, Contracts Office, University of Louisville, for regulatory and contract support; and Lee Hagendoorn, Advertex Inc, for expert assistance in the design and running of HYPER-O.

REFERENCES

1. Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics. *CA Canc J Clin.* 2005;55:74–108.
2. Dedrick RI, Myers CE, Bungay PM, et al. Pharmacokinetic rationale for peritoneal drug administration in the treatment of ovarian cancer. *Canc Treat Rep.* 1978;62:1–11.
3. Markman M. Intraperitoneal chemotherapy in the management of malignant disease. *Exp Rev Anticanc Ther.* 2001;1:142–148.
4. Alberts DS, Liu PY, Hannigan EV, et al. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer [see comment]. *N Eng J Med.* 1996;335:1950–1955.
5. Armstrong DK, Bundy BN, Wenzel L, et al; Gynecologic Oncology Group. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Eng J Med.* 2006;354:34–43.
6. Markman M, Bundy BN, Alberts DS, et al. Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III

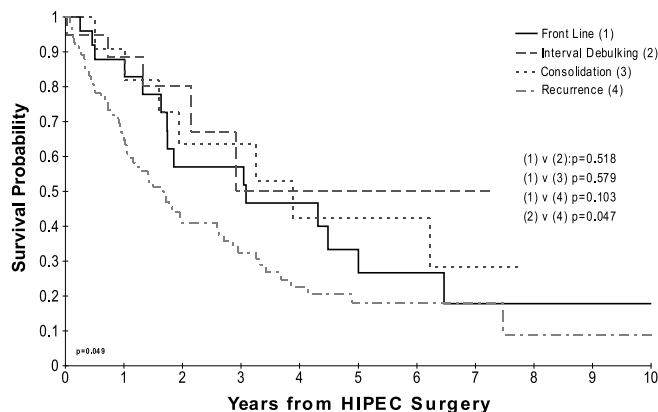


FIGURE 4. Kaplan-Meier curve survival probability by time point HIPEC used. ID, interval debulking; CON, consolidation; REC, recurrence.

- ovarian carcinoma: an intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group [see comment]. *J Clin Oncol*. 2001;19:1001–1007.
7. Jaaback K, Johnson N. Intraperitoneal chemotherapy for the initial management of primary epithelial ovarian cancer. *Coch Data Syst Rev*. 2006;CD005340.
 8. National Cancer Institute. NCI clinical announcement on intraperitoneal therapy for ovarian cancer. Available at: <http://www.cancer.gov/clinicaltrials/developments/IPchemo-digest>. Accessed July 8, 2009.
 9. Giovanella BC, Stehlin JS Jr, Morgan AC. Selective lethal effect of supranormal temperatures on human neoplastic cells. *Canc Res*. 1976;36:3944–3950.
 10. Alberts DS, Peng YM, Chen HS, et al. Therapeutic synergism of hyperthermia-cis-platinum in a mouse tumor model. *J Natl Canc Inst*. 1980;65:455–461.
 11. Barlogie B, Corry PM, Drewinko B. In vitro thermochemotherapy of human colon cancer cells with cis-dichlorodiammineplatinum(II) and mitomycin C. *Canc Res*. 1980;40:1165–1168.
 12. Wang BS, Lumanglas AL, Silva J, et al. Effect of hyperthermia on the sensitivity of human colon carcinoma cells to mitoxantrone. *Canc Treat Rep*. 1987;71:831–836.
 13. Xu MJ, Alberts DS. Potentiation of platinum analogue cytotoxicity by hyperthermia. *Canc Chemother Pharmacol*. 1988;21:191–196.
 14. Los G, van Vugt MJ, Pinedo HM. Response of peritoneal solid tumours after intraperitoneal chemohyperthermia treatment with cisplatin or carboplatin. *Brit J Canc*. 1994;69:235–241.
 15. Maymon R, Bar-Shira Maymon B, Holzinger M, et al. Augmentative effects of intracellular chemotherapy penetration combined with hyperthermia in human ovarian cancer cells lines. *Gynecol Oncol*. 1994;55:265–270.
 16. Haveman J, Rietbroek RC, Geerdink A, et al. Effect of hyperthermia on the cytotoxicity of 2',2'-difluorodeoxycytidine (gemcitabine) in cultured SW1573 cells. *Int J Cancer*. 1995;62:627–630.
 17. Rietbroek RC, van de Vaart PJ, Haveman J, et al. Hyperthermia enhances the cytotoxicity and platinum–DNA adduct formation of lobaplatin and oxaliplatin in cultured SW 1573 cells. *J Canc Res Clin Oncol*. 1997;123:6–12.
 18. Hermisson M, Weller M. Hyperthermia enhanced chemosensitivity of human malignant glioma cells. *Anticancer Res*. 2000;20:1819–1823.
 19. Urano M, Ling CC. Thermal enhancement of melphalan and oxaliplatin cytotoxicity in vitro. *Int J Hypertherm*. 2002;18:307–315.
 20. Mohamed F, Marchettini P, Stuart OA, et al. Thermal enhancement of new chemotherapeutic agents at moderate hyperthermia. *Ann Surg Oncol*. 2003;10:463–468.
 21. Takemoto M, Kuroda M, Urano M, et al. The effect of various chemotherapeutic agents given with mild hyperthermia on different types of tumours. *Int J Hypertherm*. 2003;19:193–203.
 22. de Bree E, Theodoropoulos PA, Rosing H, et al. Treatment of ovarian cancer using intraperitoneal chemotherapy with taxanes: from laboratory bench to bedside. *Cancer Treat Rev*. 2006;32:471–482.
 23. Istomin YP, Zhavrid EA, Alexandrova EN, et al. Dose enhancement effect of anticancer drugs associated with increased temperature in vitro. *Exp Oncol*. 2008;30:56–59.
 24. Meyn RE, Corry PM, Fletcher SE, et al. Thermal enhancement of DNA damage in mammalian cells treated with cis-diamminedichloroplatinum(II). *Cancer Res*. 1980;40:1136–1139.
 25. van de Vaart PJ, van der Vange N, Zoetmulder FA, et al. Intraperitoneal cisplatin with regional hyperthermia in advanced ovarian cancer: pharmacokinetics and cisplatin–DNA adduct formation in patients and ovarian cancer cell lines. *Eur J Cancer*. 1998;34:148–154.
 26. Spratt JS, Adcock RA, Muskovin M, et al. Clinical delivery system for intraperitoneal hyperthermic chemotherapy. *Cancer Res*. 1980;40:256–260.
 27. Spratt JS, Adcock RA, Sherrill W, et al. Hyperthermic peritoneal perfusion system in canines. *Cancer Res*. 1980;40:253–255.
 28. Fujimoto S, Takahashi M, Mutou T, et al. Improved mortality rate of gastric carcinoma patients with peritoneal carcinomatosis treated with intraperitoneal hyperthermic chemoperfusion combined with surgery. *Cancer*. 1997;79:884–891.
 29. Loggie BW, Fleming RA, McQuellon RP, et al. Prospective trial for the treatment of malignant peritoneal mesothelioma. *Am Surg*. 2001;67:999–1003.
 30. Sugarbaker PH, Chang D. Results of treatment of 385 patients with peritoneal surface spread of appendiceal malignancy. *Ann Surg Oncol*. 1999;6:727–731.
 31. Helm CW, Toler CR, Martin RS III, et al. Surgical cytoreduction and intraperitoneal heated chemotherapy (IPHC) for endometrial carcinoma recurrent within the peritoneal cavity. *Int J Gynecol Cancer*. 2007;17:204–209.
 32. Witkamp AJ, de Bree E, Kaag MM, et al. Extensive cytoreductive surgery followed by intra-operative hyperthermic intraperitoneal chemotherapy with mitomycin-C in patients with peritoneal carcinomatosis of colorectal origin. *Eur J Cancer*. 2001;37:979–984.
 33. Verwaal VJ, Bruin S, Boot H, et al. 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. [see comment]. *Ann Surg Oncol*. 2008;15:2426–2432.
 34. Helm CW, Bristow RE, Kusamura S, et al. Hyperthermic intraperitoneal chemotherapy with and without cytoreductive surgery for epithelial ovarian cancer. *Journal of Surgical Oncology*. 2008;98:283–290.
 35. Oxford-Center for Evidence Based Medicine. http://www.cebm.net/levels_of_evidence.asp. Accessed March 11, 2009.
 36. Jacquet P, Sugarbaker PH. Current methodologies for clinical assessment of patients with peritoneal carcinomatosis. *J Exp Clin Cancer Res*. 1996;15:49–58.
 37. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Assoc*. 1958;53:457–481.
 38. Kalbfleisch JD, Prentice RL. *The Statistical Analysis of Failure Time Data*. Second Edition ed. New York: Wiley and Sons; 2002.
 39. Cox DR. Regression models and life tables. *Journal of the Royal Statist Soc*. 1972;34:187–220.
 40. Bereder J, Glehen O, Habre J. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from ovarian cancer: A multi-institutional study of 246 patients. *Journal of Clinical Oncology*. 2009;27:Abstr 5542.
 41. Loggie BW, Sterchi JM, Rogers AT, et al. Intraperitoneal hyperthermic chemotherapy for advanced gastrointestinal and ovarian cancers. *Reg Cancer Treat*. 1994;2:78–81.
 42. Steller MA, Egorin MJ, Trimble EL, et al. A pilot phase I trial

- of continuous hyperthermic peritoneal perfusion with high-dose carboplatin as primary treatment of patients with small-volume residual ovarian cancer.[erratum appears in *Cancer Chemother Pharmacol*. 1999;44(1):90]. *Cancer Chemotherapy & Pharmacology*. 1999;43:106–114.
43. Look M, Chang D, Sugarbaker PH. Long-term results of cytoreductive surgery for advanced and recurrent epithelial ovarian cancers and papillary serous carcinoma of the peritoneum. *Int J Gynecol Cancer*. 2004;14:35–41.
 44. Munkarah AR, Coleman RL. Critical evaluation of secondary cytoreduction in recurrent ovarian cancer. *Gynecol Oncol*. 2004;95:273–280.
 45. Bristow RE, Puri I, Chi DS. Cytoreductive surgery for recurrent ovarian cancer: a meta-analysis. *Gynecol Oncol*. 2009;112:265–274.
 46. Gore ME, Fryatt I, Wiltshaw E, et al. Cisplatin/carboplatin cross-resistance in ovarian cancer. *Brit J Cancer*. 1989;60:767–769.
 47. Markman M, Rothman R, Hakes T, et al. Second-line platinum therapy in patients with ovarian cancer previously treated with cisplatin. *J Clin Oncol*. 1991;9:389–393.
 48. Helm CW, Randall-Whitis L, Martin RS, III, et al. Hyperthermic intraperitoneal chemotherapy in conjunction with surgery for the treatment of recurrent ovarian carcinoma. *Gynecol Oncol*. 2007;105:90–96.
 49. Deraco M, Rossi CR, Pennacchioli E, et al. Cytoreductive surgery followed by intraperitoneal hyperthermic perfusion in the treatment of recurrent epithelial ovarian cancer: a phase II clinical study. *Tumori*. 2001;87:120–126.
 50. Zanon C, Clara R, Chiappino I, et al. Cytoreductive surgery and intraperitoneal chemohyperthermia for recurrent peritoneal carcinomatosis from ovarian cancer. *World J Surg*. 2004;28:1040–1045.
 51. Cotte E, Glehen O, Mohamed F, et al. Cytoreductive surgery and intraperitoneal chemo-hyperthermia for chemo-resistant and recurrent advanced epithelial ovarian cancer: prospective study of 81 patients. [see comment]. *World J Surg*. 2007;31:1813–1820.
 52. Rufian S, Munoz-Casares FC, Briceno J, et al. Radical surgery-peritonectomy and intraoperative intraperitoneal chemotherapy for the treatment of peritoneal carcinomatosis in recurrent or primary ovarian cancer. *J Surg Oncol*. 2006;94:316–324.
 53. Reichman TW, Cracchiolo B, Sama J, et al. Cytoreductive surgery and intraoperative hyperthermic chemoperfusion for advanced ovarian carcinoma. *J Surg Oncol*. 2005;90:51–56.