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Original Articles

HIPEC treatment in advanced and recurrent ovarian cancer: a meta-analysis of observational studies

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Summary

This meta-analysis summarizes survival outcomes of advanced and recurrent ovarian cancer patients undergoing hyperthermic intraperitoneal chemotherapy (HIPEC), from published studies between 1990 and 2015. *Objective:* The authors performed a meta-analysis on outcomes of patients with advanced (primary) and recurrent epithelial ovarian cancer (EOC) treated with cytoreductive surgery and HIPEC. *Materials and Methods:* Studies evaluating HIPEC in EOC patients published between January 1, 1990 and January 1, 2015 were identified using PubMed. Eligible studies had ≥ 10 patients and reported overall survival (OS). The authors performed multivariate analysis of OS and progression-free survival (PFS) based on modeling the point estimates with weighted fixed effects models. *Results:* Twenty-six studies met criteria with extractable statistics (n=1608): 13 advanced (n=534) and 14 recurrent EOC (n=1074). For primary advanced EOC, five-year OS was 39.7% (95% CI: 37.8-41.7%), with a 63-month median OS. For recurrent EOC, five-year OS was 32.0% (95% CI: 30.3-33.7%), with a 39-month median OS. Optimal cytoreduction was achieved in 79% of advanced and 77% of recurrent EOC patients. Mortality was 1.4% (advanced) and 3.9% (recurrent). *Conclusions:* HIPEC treatment in ovarian cancer in the primary or recurrent setting has favorable survival outcomes as compared to surgical cytoreduction alone, with comparable mortality rates.

Key words: Hyperthermic intraperitoneal chemotherapy; Ovarian cancer; Meta-analysis.

Introduction

Peri-operative hyperthermic intraperitoneal chemotherapy (HIPEC) has an established role in appendiceal cancer and pseudomyxoma peritonei, yielding improved survival rates and acceptable morbidity and mortality in patients undergoing this procedure [1, 2]. In epithelial ovarian cancer (EOC), however, HIPEC has remained an experimental treatment strategy, despite its growing use and interest [3, 4]. The theoretical rationale for using HIPEC to treat EOC is to combine the demonstrated pharmacological activity of intraperitoneal (IP) chemotherapy in EOC with the advantages of intra-operative hyperthermia to enhance chemotherapy cytotoxicity after cytoreductive surgery [5, 6]. The similarities in peritoneal spread patterns between pseudomyxoma peritonei and EOC suggest similar benefits among these two peritoneal surface malignancies. Nonetheless, no prospective, randomized phase III trials examining the impact of HIPEC on EOC have not yet been completed. Despite this lack of evidence, HIPEC use and interest has grown among surgical oncologists and recurrent EOC patients in search for alternative therapies.

A number of retrospective and phase II trials have suggested a survival benefit associated with HIPEC and secondary cytoreductive surgery (CRS) in patients with recurrent EOC [7, 8] and more recently, in primary advanced stage (advanced) EOC (upfront and interval CRS) [9-12]. While the toxicity of HIPEC is higher than that of surgical cytoreduction alone, studies in recent years have reported lower morbidity and mortality rates from these procedures, likely due to improved supportive care measures and the expanding surgical skills of gynecologic oncologic surgeons [8, 13, 14]. Current evidence thus suggests that complete cytoreductive surgery and HIPEC is a feasible option for patients with EOC with potential benefits that may exceed the survival outcomes of current standard of care treatment options, especially in platinum-resistant recurrences [15]. Unfortunately, wide variability exists in the indications, administration, and chemotherapy drug selection of HIPEC procedures in EOC. To address the broad variability of reported clinical and peri-operative outcomes and diverse indications and administration techniques associated with HIPEC in EOC, the authors analyzed class II and III level literature on the effects of HIPEC

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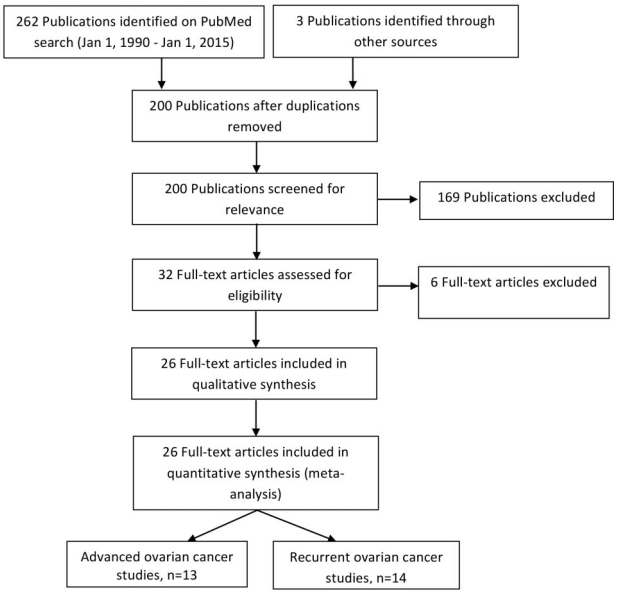

Figure 1. – Prisma flow diagram of study identification

for the two most common indications in EOC: advanced (primary) EOC, and recurrent EOC, and report the results separately for each disease type.

Materials and Methods

A National Center for Biotechnology Information (NCBI) PubMed search of studies published between January 1, 1990 and January 1, 2015 was performed using the key words: *hyperthermic intraperitoneal chemotherapy*, *ovarian cancer*, and *cytoreductive surgery*. Additional studies were identified through review of the identified manuscripts. Eligible studies were defined as those with ≥ 10 patients that reported overall survival (OS) curves or point estimates. Studies on both advanced and recurrent EOC were included; studies that included other cancers were not considered. In the case of multiple publications on the same group of patients, only the most recent publication was included in the analysis (Figure 1).

The authors reviewed each study to determine whether the patients were characterized as having advanced or recurrent cancer. A small number of studies reported results for both advanced and recurrent cancers. The authors excluded studies in which advanced and recurrent cancer results were reported only as pooled statistics. Details on the use of HIPEC, such as neoadjuvant versus adjuvant timing, number of cycles administered, was not widely available in the analyzed studies, and therefore, uniform analyses could not be performed using these data.

For three- and five-year OS estimates, the authors performed weighted fixed effects meta-analyses on each study's estimates; the weights were the study sample sizes. From available data, the authors extracted the survival percentages at three- and five-years and the median survival, if reached. For reporting the results in the forest plots, each individual study's estimate of the standard errors and confidence intervals were derived from the crude standard errors for proportions. The weighted mean estimates of three- and five-year survival were derived from the inverse standard errors of the study. OS estimates and prediction intervals were plotted based on the fixed effects models of logarithmically-transformed percentages as the outcome, and the corresponding survival or PFS time as the independent variable. The authors performed a multivariate analysis of OS and PFS using available point estimates, considering: minutes of administration, HIPEC temperature, and study year. The present multivariate model had an endpoint of OS or PFS percentage, and the authors fitted a log-log transformed model weighted by sample size.

Results

Thirty-two studies initially met criteria, of which six full text-articles were excluded, including two studies which used pooled statistics for both advanced and recurrent EOC [10, 17], and others which did not meet the defined eligibility. To avoid double-counting patients, one study was excluded from the analysis [16] because it was updated in 2013 [8]. Twenty-six of the remaining studies had extractable statistics (n=1608), of which one study included separate statistics for advanced EOC and recurrent EOC [39], and therefore was counted twice, for a total of 13 advanced EOC studies (n=534) and 14 recurrent EOC studies (n=1074).

Eleven studies were published between 2000 and 2006 (n=308 patients) and 15 were published between 2007 and 2015 (n=1,292 patients). No eligible studies were identified for the time period between 1990 and 2000. There were 15 prospective case series (including 193 advanced and 322 recurrent EOC patients) and 11 retrospective studies (including 356 advanced and 729 recurrent EOC patients). The mean number of patients included in advanced EOC studies was 39.2 (range 10-92) and mean number of patients included in recurrent EOC studies was 70.9 (range 18-474). The list of all included published studies is available in Table 1 [10, 11, 15-41].

Characteristics of EOC patients are listed in Table 2. Over half of all recurrent EOC studies reported on chemoresistant EOC patients. The definition of optimal cytoreduction varied from 0.5 to 2 cm, with earlier reports using ≤ 2 cm as optimal debulking threshold. Seventy-one percent of recurrent EOC studies utilized < 0.5 cm as cut-off for optimal cytoreduction, compared to 43% of advanced EOC studies. The majority of EOC studies used a 90-minute administration of HIPEC (50% of advanced EOC and 43% of recurrent EOC studies), with 120 minutes and 30-60 minutes as other selected duration times. The most commonly used hyperthermic chemotherapy agent used in both recurrent and advanced EOC was cisplatin, with a broad range in dose (15-100 mg/m^2), with carboplatin as the second most commonly used chemotherapy in advanced EOC patients, while the second most commonly used chemotherapy agent in recurrent EOC was doxorubicin (Table 2).

The authors analyzed advanced versus recurrent EOC,

Table 1. — *Ovarian cancer HIPEC studies.*

Study	Pub. year	Ref.	N	Disease	Med. age	Med. OS	Opt. criteria (cm)	Opt. cytored. (%)	Duration (min.)	Temp. (°C)
Cavaliere *et al.*	2000	[18]	26	Recurrent	52	25	< 0.25		90	42
Hager *et al.*	2001	[19]	36	Advanced	55	49				43
Chatzigeorgiou *et al.*	2003	[20]	20	Recurrent	59		< 1.5		120	39
de Bree *et al.*	2003	[21]	19	Recurrent	65	54	< 0.5			41
Look *et al.*	2004	[22]	28	Advanced	54	46	< 0.25	(57)	90	
Ryu *et al.*	2004	[23]	57	Advanced	46	41	< 1	(84)	90	44
Piso *et al.*	2004	[10]	19	Both		33	< 0.25	(77)	90	
Zanon *et al.*	2004	[24]	30	Recurrent	60	28	< 0.25	(77)	60	42
Reichman *et al.*	2005	[25]	13	Advanced	64		< 0.25	(85)	90	40
Gori *et al.*	2005	[26]	29	Advanced	56		< 2	(100)	60	42
Yoshida *et al.*	2005	[27]	10	Advanced	44	70				
Rufian *et al.*	2006	[17]	33	Both		48	< 1	(52)	60	42
Raspagliesi *et al.*	2006	[28]	40	Recurrent	53	32	CC-0	(82)		43
Bae *et al.*	2007	[29]	67	Advanced	50		< 1	(72)	90	44
Cotte *et al.*	2007	[30]	81	Recurrent	54	28	CC-0	(55)	90	44
Helm *et al.*	2007	[31]	18	Recurrent	64	31	< 0.5	(61)	90	41
Ceelen *et al.*	2008	[32]	42	Recurrent	54	37		(50)	30-90	41
Pavlov *et al.*	2009	[11]	56	Advanced	61	29	CC-0		120	40
Lim *et al.*	2009	[33]	30	Advanced		53			90	42
Fagotti *et al.*	2009	[34]	25	Recurrent	52		< 0.25	(92)	100	41
Guardiola *et al.*	2009	[35]	47	Advanced	60		< 1	(100)	120	37
Helm *et al.*	2010	[36]	141	Recurrent	58	24			100	39
Deraco *et al.*	2011	[37]	26	Advanced	64		CC-0	(57)	60	43
Melis *et al.*	2011	[38]	43	Advanced	60	54	CC-0	(83)	60-90	42
Bakrin *et al.*	2012	[16]	246	Recurrent	58	49	CC-0	(92)	90	42
Deraco *et al.*	2012	[39]	56	Recurrent	55	26		(84)	90	43
Bakrin *et al.*	2013	[15]	474	Recurrent	57	46	CC-0	(74)	90	42
Bakrin *et al.*	2013	[15]	92	Advanced	57	35	CC-0	(74)	90	42
Gonz.-Bayon *et al.*	2013	[40]	42	Recurrent			CC-0	(75)	60-90	43
Spiliotis *et al.*	2015	[41]	60	Recurrent	58		CC-0 & CC-1	(85)	60	43

Pub. year = year of publication; Ref. = reference; N = # patients in study; Med. = median, CC-0 = no macroscopic tumor visible; CC-1 = ≤ 0.25 cm visible disease remaining; Opt. criteria. = optimal cytoreduction criteria; Optimal cytored. % = % of patients optimally cytoreduced in each study per optimal cytoreduction criteria; Duration = duration of HIPEC; Temp. = temperature of HIPEC administration.

year of publication, number of patients, HIPEC administration time and temperature, duration of procedure, temperature, residual disease, hospital mortality, PFS, OS, and follow-up. The definition of an optimal cytoreductive surgical resection varied across studies from CC-0 (no macroscopic disease visible) to < 1 cm. Optimal cytoreduction, defined by residual disease < 1 cm, was achieved in a mean of 79% of advanced EOC patients (range 57-100%) and a mean of 77% of recurrent EOC patients (50-92%).

Total duration of the surgical cytoreduction and HIPEC procedure ranged from five to ten hours in advanced (mean of 7.5 hours) and four to ten hours in recurrent EOC patients (mean of 7.4 hours) (Table 3). Length of stay was 15.7 ± 6.8 days for advanced and 15.0 ± 5.5 days for recurrent EOC patients. The peri-operative mortality rate was reported in all studies, with a mean mortality rate of 1.5% (0-4%) in advanced and 3.4% (0-10%) in recurrent EOC studies. Some studies reported the rate of significant peri-operative morbidity, however this was not uniformly reported, and was therefore not analyzed in this meta-analysis.

Median follow-up for advanced and recurrent EOC were 40 and 21 months, respectively. Three-year OS for advanced EOC patients was 61.7% (95% CI: 60.7-62.6%); five-year OS was 39.7% (95% CI: 37.8-41.7%) with a median OS of 63 months (Figure 1a). For recurrent EOC, three-year OS was 47.7% (95% CI: 46.8-48.8%), and five-year OS was 32.0% (95% CI: 30.3-33.7%), with a median OS of 39 months (Figure 1b). On multivariate analysis, more recent studies showed improved OS in recurrent EOC patients, whereas no factors correlated with OS in advanced patients (Table 4).

The authors performed a weighted fixed effects non-linear meta-analysis model with OS for both advanced and recurrent EOC patients (Figure 2). They first performed variable selection where the variable weighting was proportionate to the number of patients. The follow-up time in each study was statistically significant in both advanced and recurrent EOC patients, and year of publication was statistically significant in the recurrent cohort. The non-lin-

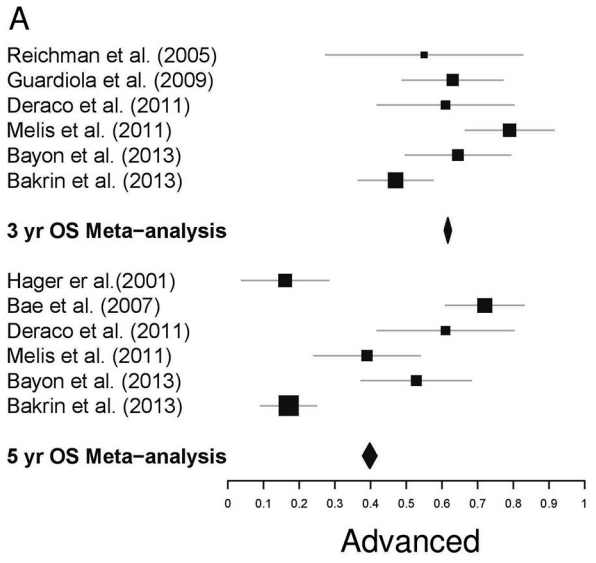

Figure 1a. — Impact of HIPEC on three- and five-year overall survival rates in advanced ovarian cancer as reported by recent retrospective studies.

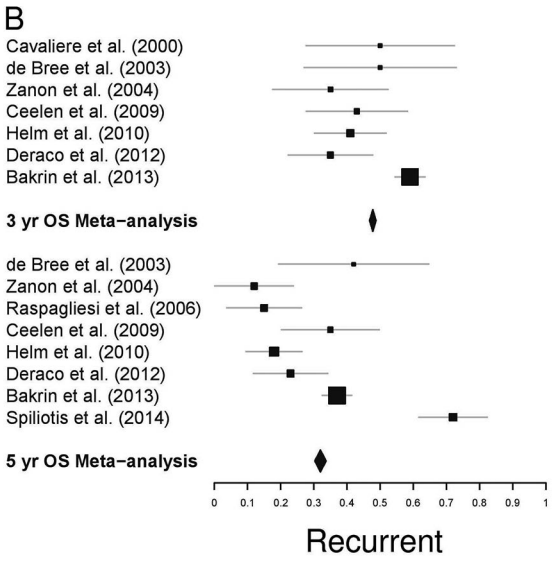

Figure 1b. — Impact of HIPEC on three- and five-year overall survival of recurrent ovarian cancer as reported by recent retrospective studies.

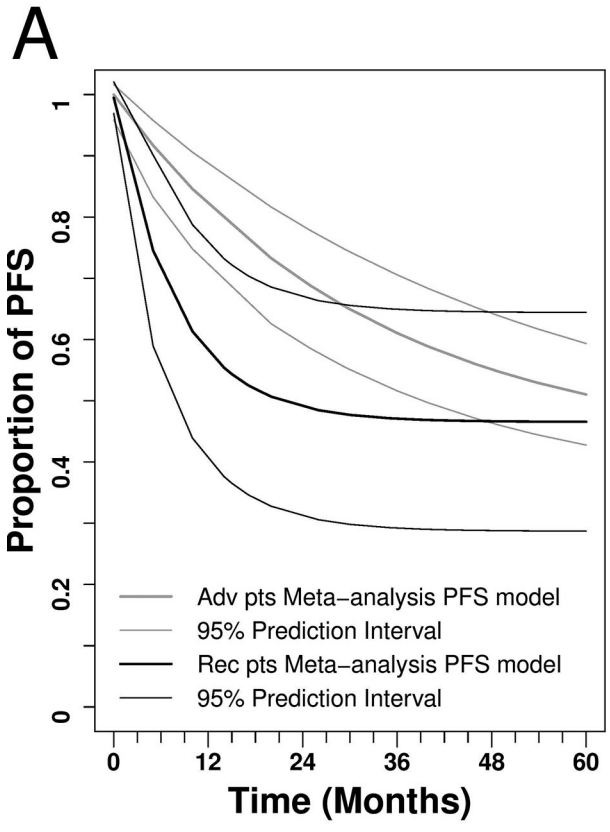

Figure 2a. — Weighted fixed effects meta-analysis for overall survival in advanced and recurrent ovarian cancer patients.

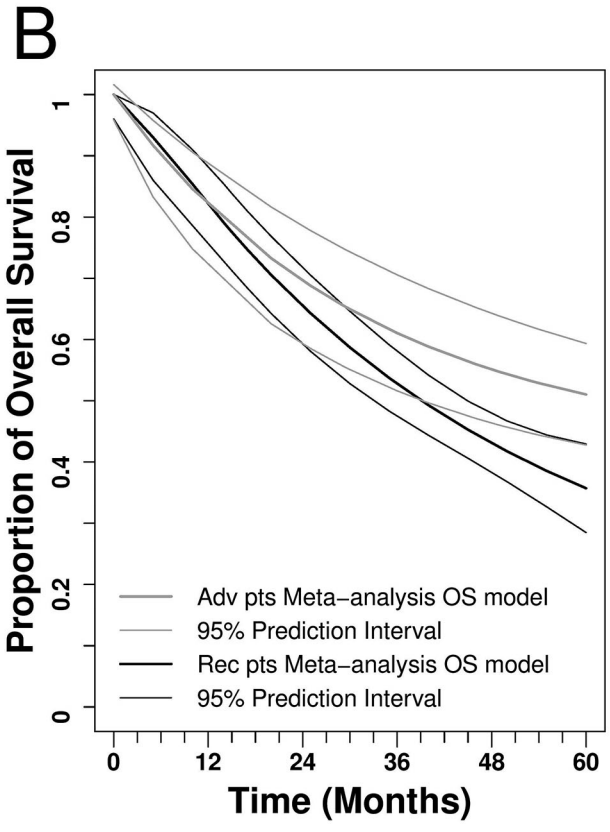

Figure 2b. — Weighted fixed effects meta-analysis for progression-free survival in advanced and recurrent ovarian cancer patients.

Table 2. — *Characteristics of primary advanced versus recurrent HIPEC studies.*

Factor	Advanced studies (N =13)		Recurrent studies (N = 14)	
Chemoresistance	N	(%)	N	(%)
Yes	0		7	(50)
No	2	(14)	0	
Both	0		5	(36)
NR	12	(86)	2	(14)
Prior surgery				
Yes	5	(36)	11	(79)
No	2	(14)	0	
Both	1	(7)	0	
NR	6	(43)	3	(21)
Prior chemotherapy				
Yes	6	(43)	13	(93)
No	1	(7)	0	
Both	1	(7)	0	
NR	6	(43)	1	(7)
Def. of opt. cytoreduction (cm)				
<0.5	6	(43)	10	(71)
0.5 < 2.0	4	(28)	1	(7)
NR	4	(28)	3	(21)
Dur. of procedure (HIPEC)(min.)				
30-60	2	(14)	3	(21)
90	7	(50)	6	(43)
120	2	(14)	3	(21)
NR	3	(21)	2	(14)
Year				
2000-2005	6	(43)	4	(29)
2006-2010	4	(28)	7	(50)
2011-2014	4	(28)	3	(21)
HIPEC Agent				
Taxol based				
Doxetaxel			1	(7)
Platinum-taxane combo	1	(7)	2	(14)
Doxorubicin	1	(7)		
Platinum based (mg/m^2)				
Cisplatin (15 – 50)	4	(29)	5	(36)
Cisplatin (> 50 – 100)	6	(43)	2	(14)
Cisplatin (>100)			2	(14)
Carboplatin (350)	2	(15)		
Oxaliplatin (460)			2	(14)

N = number of studies; % = % of all studies; NR= not recorded; Def. of opt. cytoreduction = definition of optimal cytoreduction used in each study

ear fit was better in recurrent EOC patients compared with advanced EOC patients (R^2 of 78.4% *vs*. 34.0%). Figures 2a and 2b show the predicted OS and PFS curves for advanced and EOC patients. These predicted estimates were derived from the log transformed models weighted by sample size, assuming constant hazards.

Discussion

Hyperthermic intraperitoneal chemotherapy is currently considered experimental in EOC treatment [3]. Nonetheless, interest in HIPEC for EOC has increased over the last several years with numerous single-institutional retrospective studies published [36, 42, 43]. Critics of HIPEC cite its high mortality and morbidity rates, as well as an unproven survival advantage due to the lack of completed prospective randomized large multi-institutional trials. A number of these trials are currently underway for interval, secondary, and salvage cytoreduction [44], however, with results likely not available for several years, it is essential to analyze the available evidence to determine the utility and potential benefits of HIPEC in the treatment of EOC.

The present authors performed a meta-analysis including 1,608 patients from 26 single- and multi-institutional studies reporting survival data and characteristics of HIPEC treatment in patients with advanced or recurrent EOC. Five hundred thirty-four patients with advanced EOC and 1,074 patients with recurrent EOC were included in this meta-analysis. The outcome data showed that the five-year median OS of 63 months for HIPEC treatment in advanced disease is similar to that achieved for optimal cytoreduction combined with intraperitoneal chemotherapy (65.6 months) [45, 46]. If confirmed in a prospective trial, this raises an interesting question of whether HIPEC therapy in the upfront setting could replace IP chemotherapy, which is uncommonly used despite its superior survival outcomes, due to its toxicities and need for specialized nursing training [47]. For recurrent EOC, the five-year OS of 39 months appears to be longer than the rates reported for secondary cytoreduction alone from recent studies conducted during the same time period, with median OS of 30 months reported by Bristow *et al.* [8], and 29 months by the DESKTOP I study [48]. One drawback to the present study includes the variability of the definition of optimal debulking used in the analyzed studies (ranging from no gross residual disease to less than 2 cm), thus not allowing for individual survival curves based on residual disease status.

The question of whether patients included in HIPEC studies have better performance status than those not being offered HIPEC remains unanswered, and introduces a selection bias, which is however likely true of most surgical cytoreduction studies. Since the advent of radical surgical cytoreduction methods in ovarian cancer surgery, extensive contributions to the literature have reported the observed peri-operative morbidity and mortality, and the safety of upper abdominal and diaphragmatic debulkings [49, 50]. For HIPEC procedures, the data is less extensive. Recently, a retrospective analysis of HIPEC in both advanced and recurrent EOC reported a 25% and 19% morbidity rate [51]. Data regarding mortality rates in large ovarian cancer groups undergoing HIPEC are scarce. The present meta-analysis shows that the peri-operative mortality (1.4% for

Table 3. — *Mean characteristics of HIPEC studies.*

	Advanced studies (N =13)		Recurrent studies (N = 13)	
Characteristics	Mean (SD)	Range	Mean (SD)	Range
Number of patients	39.4 (21.6)	10–92	70.9 (118)	18–474
Optimal cytoreduction (%)	79% (17%)	57–100%	77% (15%)	50–92%
Temperature (°C)	41 (1.9)	37–43	41 (1.5)	38–44
Duration of procedure (hours)	7.5 (2.7)	5–10	7.4 (2.3)	4–10
Length of stay (days)	15.7 (6.8)	8–21	15.0 (5.5)	12–28
Mortality	1.4% (1.8%)	0–4%	3.9% (4.1%)	0–10 %
Follow-up (months)	41 (20)	14–70	23 (9)	16–47

Table 4. — *Multivariate fixed effects model for OS included terms: time, study year, HIPEC temp, and minutes of HIPEC.*

Statistically significant terms	Advanced disease parameter estimates		Recurrent disease parameter estimates	
Term	Estimates	*p*-value	Estimates	*p*-value
Intercept	-1.46	0.0001	163.37	0.0029
Follow-up	0.021	0.0035	0.038	<0.0001
Year of publication	n/a	n/a	0.077	0.0026
R-square	34.0%		78.4%	

OS = overall survival.

advanced EOC and 3.9% for recurrent EOC) is similar or superior to that reported with optimal debulking alone [8, 52].

The variability of HIPEC administration remains a key issue. There is no standard chemotherapy agent, procedure duration, or temperature currently considered optimal or required. Furthermore, the ideal tumor histology and disease distribution indicated for HIPEC are also not well established. The present study did not address the issue of consolidation therapy as a role for HIPEC and the authors did not distinguish between HIPEC at interval versus upfront cytoreduction; these are important considerations to determine the ideal role of HIPEC. This is particularly important in recurrent EOC patients who are a heterogeneous patient cohort and factors such as type of cytoreduction (such as secondary or tertiary), platinum-sensitive status, and prior and subsequent chemotherapies may have a significant prognostic impact but were beyond the scope of this meta-analysis. Interestingly, the largest retrospective analysis of HIPEC in EOC to date suggests that both platinum-sensitive and platinum-resistant EOC patients benefit equally as well from HIPEC, and thus both should be offered HIPEC as therapy [8].

There are some statistical limitations to the present study that deserve mention. First, time-to-endpoint data was not available in all studies included in the analysis. Therefore, the authors extracted data from point estimates and modeled these with a weighted linear model. Since many point estimates did not include a standard deviation estimate, the authors' weighting was based on the overall number of advanced and recurrent EOC patients and not on inverse variance weighting. By not having a full complement of data, this may have biased the findings by narrowing the variance estimates and confidence intervals. Second, there is a risk that the present study had publication and selection biases, causing these meta-analysis estimates to be anti-conservative [53]. Although this is a concern in the present data set, the selected studies were single-arm case series instead of comparative trials. Third, the authors could not compare OS in either advanced or recurrent EOC patients to reasonable contemporaneous non-HIPEC historical cohorts in EOC. Comparison of the advanced HIPEC treatment group to an advanced ovarian cancer SEERs cohort is limited due to the absence of data on residual disease (optimal cytoreduction). Fourth, the present analysis of perioperative morbidity was limited due to the non-uniform reporting of complications, and thus restricts the present assessment of the toxicity resulting from HIPEC, and therefore was not reported. Similarly, the timing of HIPEC (neoadjuvant versus adjuvant), and number of cycles given in the adjuvant setting, could not be extracted due to lack of reporting in the analyzed studies. Lastly, there are other suggested indications for HIPEC, such as consolidation or palliative therapies, which were not addressed in this analysis, due to limited available data.

In conclusion, the present meta-analysis, while limited, sheds light on the overall optimal cytoreduction rate achieved in HIPEC, and average mortality rates in patients undergoing this procedure. These data are meaningful given the large number of patients investigated, and add to the literature and counseling of ovarian cancer patients contemplating HIPEC. Nonetheless, HIPEC is still considered investigational in ovarian cancer patients, and whether survival benefits are present, needs to be deduced from prospective randomized clinical trials. This study's results point towards favorable outcomes with acceptable mortality rates. Ongoing randomized prospective phase III trials, including recurrent EOC HIPEC trials in Italy (Scambia *et al.*) and France (Classe *et al.*), as well as advanced EOC HIPEC trials (DiBergamo *et al.*, Park *et al.*, Van Driel *et al.*) are ongoing abroad, and are eagerly awaited.

HIPEC treatment in ovarian cancer in the primary upfront setting results in survival outcomes similar to those reported for optimally cytoreduced patients followed by IV/IP chemotherapy, and may thus be an attractive alternative to postoperative IP chemotherapy, which in itself has considerable toxicity. In the recurrent setting, HIPEC appears to show favorable OS outcomes possibly exceeding those seen in secondary cytoreduction alone, with no excessive mortality rates.

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