Survival Benefit of Adding Hyperthermic IntraPEritoneal Chemotherapy (HIPEC) at the Different Time-points of Treatment of Ovarian Cancer: Review of Evidence

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Abstract: The standard treatment for advanced ovarian cancer consists in complete cytoreductive surgery (CRS) and intravenous combination chemotherapy with a platinum compound and a taxane. Although response rates to initial therapy are high, many patients will recur and die of peritoneal carcinomatosis. The addition of Hyperthermic IntraPEritoneal Chemotherapy (HIPEC) to the standard therapy aims at increasing survival by reducing peritoneal recurrence.

This review describes the survival results of HIPEC at the different time-points of the treatment of ovarian cancer: at upfront CRS, at interval CRS, at consolidation CRS after complete response to initial therapy, at secondary CRS after incomplete response, at salvage CRS for recurrence and as palliative treatment without CRS for unresectable ovarian cancer with chemotherapy resistant ascites.

The available evidence suggests that a potential survival benefit of adding HIPEC may be largest in the settings of secondary CRS for stage III ovarian cancer and salvage CRS for recurrent ovarian cancer, two time-points representing failure of initial standard therapy. There is much less evidence for a potential benefit of HIPEC for less advanced stages (I-II) and for earlier time-points in the treatment of ovarian cancer (upfront, interval and consolidation). Postoperative mortality is not higher after CRS and HIPEC (0.7%) than after CRS only (1.4%). Four randomised trials are ongoing and their results are eagerly awaited.

Palliative HIPEC without CRS might be used more in patients with incapacitating ascites due to recurrent ovarian cancer which has become resistant to systemic chemotherapy.

Keywords: Hyperthermic intraperitoneal chemotherapy (HIPEC); cytoreductive surgery, ovarian cancer; survival, time-points, review.

INTRODUCTION

Ovarian cancer has a high tendency for early peritoneal spread so that many patients present peritoneal carcinomatosis at diagnosis. On the other hand, it tends to stay confined to the peritoneal cavity for a long time before seeding to other organs. The early spread to the peritoneal cavity without hematogenous metastases for a long period makes ovarian cancer very suitable for aggressive locoregional therapies.

Since the mid-1980s, cytoreductive surgery (CRS) and intravenous combination chemotherapy with a platinum compound and a taxane have become the standard of care for patients with ovarian cancer [1]. Although response rates to initial therapy are high, many patients will recur, mainly in the peritoneal cavity, resulting in an overall 5-year survival of only 50% for FIGO III ovarian cancer [1]. The addition of Hyperthermic IntraPEritoneal Chemotherapy (HIPEC) to the standard therapy aims at increasing survival by reducing peritoneal recurrence. This paper provides an update of the survival results after CRS and HIPEC and discusses its potential role at the different time-points of the treatment of ovarian cancer.

MATERIALS AND METHODS

A PubMed search of the world literature published between January 1st, 1980, to January 31st, 2012 was performed using the key words [hyperthermic intraperitoneal chemotherapy] and [ovarian cancer]. All papers in English and French reporting results of HIPEC in ovarian cancer were included. Additional papers were identified by a cross-reference search. In case of multiple publications on the same group of patients, only the most recent and complete paper was retained. All types of study design were included. There was no restriction on the patient number except for single case reports that were excluded. Studies on both primary and recurrent ovarian cancer were included, as well as studies on the palliative use of HIPEC for recurrent malignant ascites. Only studies describing HIPEC exclusively for ovarian cancer were considered. Studies that did not report separate results for distinct time-points were not included.

The following data were analyzed: type of study design, year of publication, number of patients, FIGO stage, timing of HIPEC in the course of the disease (Table **1**), percentage of patients with Sugarbaker's completeness of cytoreduction (CC) scores CC0 (no macroscopic tumor visible), CC1 (largest residual tumor nodules < 2.5 mm), CC2 (largest residual tumor nodules between 2.5 mm and 2.5 cm), CC3 (largest residual tumor nodules > 2.5 cm) [2], hospital mortality, follow-up (median and range), disease free survival (DFS) (median, at 5 years), overall survival (OS) in the whole patient group (median, at 5 years) and OS in the subgroup of patients with CC0 CRS (median, at 5 years). Morbidity could not be compared in a meaningful way between CRS and HIPEC versus CRS only because of absent or different definitions of morbidity between series.

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Table 1. Timing of HIPEC in the Course of Ovarian Cancer Treatment

in combination with cytoreductive surgery (CRS):
1. upfront CRS and HIPEC: as first treatment for newly diagnosed ovarian cancer
2. interval CRS and HIPEC: after neo-adjuvant chemotherapy without previous resection except for biopsies
3a. consolidation CRS and HIPEC: after upfront (near) complete CRS and a full course of chemotherapy in patients with a clinically complete response
3b. secondary CRS and HIPEC: after upfront incomplete CRS followed by chemotherapy in patients with a partial response or stable disease
4. salvage CRS and HIPEC: for recurrent ovarian cancer after initial complete response to CRS and chemotherapy
without cytoreductive surgery (CRS):
5. palliative HIPEC without CRS for unresectable ovarian cancer with refractory ascites

RESULTS

Upfront CRS and HIPEC

Eight papers described the results of (sub)groups of patients who underwent CRS and HIPEC as first treatment for newly diagnosed stage III/IV ovarian cancer [3-10] (Table **2**).

Median and 5 year overall survival (OS) were 14.5-41.7 months and 28-60.7% for the whole group respectively and 47 months [4] and 60.0% [7] after complete resection (CC0). Median and 5 year DFS were 5-30 months and 15.2-19.7% respectively.

The results were compared with ten papers published in the same period on comparable (sub)groups of patients who underwent CRS without HIPEC as first treatment for newly diagnosed stage III/IV ovarian cancer [11-20] (Table **2**).

Median and 5 year OS were 29-58.2 months and 19.5-49% for the whole group and 45-78 months and 31.3% in case of complete resection (CC0). Median and 5 year DFS were 12-33.2 months and 31.0% respectively.

Interval CRS and HIPEC

Six papers described the results of (sub)groups of patients who underwent CRS and HIPEC after neo-adjuvant chemotherapy without previous resection for stage III/IV ovarian cancer [3, 8, 10, 21-23] (Table **3**). Median and 5 year OS were 38.0-68.6 months and 50.2-62%. Median DFS was 8.4-16.9 months.

The results were compared with six papers published in the same period on comparable (sub)groups of patients who underwent CRS without HIPEC after neo-adjuvant chemotherapy without previous resection for advanced ovarian cancer [11, 12, 17, 24-26] (Table **3**). Median and 5 year OS were 26-53 months and 21.2%. Median DFS was 12-15 months.

Consolidation CRS and HIPEC

Three papers described the results of consolidation CRS and HIPEC in (sub)groups of patients with a clinically complete response after (near) complete CRS and adjuvant chemotherapy for ovarian cancer [3, 8, 27] (Table **4**). Median and 5 year OS were 53.7-130.3 months and 42.4%. Median and 5 year DFS were 29.6-82.8 months and 24.2% respectively.

One of these studies compared CRS and HIPEC with no treatment in a prospective non randomised study [27] ((Fig. **1**), Table **4**). Median overall survival was 64.4 months in the CRS and HIPEC group versus 46.4 months for the control group (p = 0.056, NS).

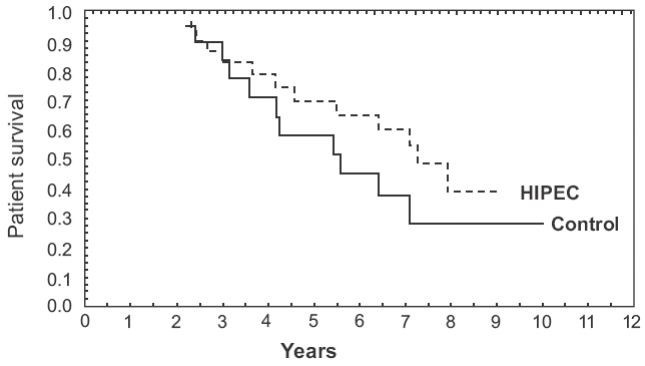

Fig. (1). Overall survival after consolidation CRS and HIPEC (IPCT + HT) versus no treatment (control) in stage III ovarian cancer with a residual mass less than 2 cm after initial surgery; p = NS (reproduced with permission from 27)

We found one paper published in the same period on a comparable (sub)group of patients with a clinically complete response after (near) complete CRS and adjuvant chemotherapy for ovarian cancer [28] (Table **4**). Patients were randomised between 3 and 12 cycles of paclitaxel as consolidation therapy. They did not receive consolidation CRS and HIPEC. Median OS and DFS were 48 versus 53 months and 14 versus 22 months for the groups receiving 3 and 12 cycles respectively.

Secondary CRS and HIPEC

Four papers described the results of (sub)groups of patients who underwent secondary CRS and HIPEC after upfront incomplete CRS followed by chemotherapy in patients with a partial response or stable disease [29-32] (Table **5**). Median and 5 year OS for stage III ovarian cancer were at least 60 months [29, 30] and 53.8-66.1% [29, 30]. Median and 5 year DFS for stage III ovarian cancer were 26.4-56 months and 26.9% respectively.

Two of these papers compared CRS and HIPEC with CRS alone in a retrospective study [29, 30]. In both studies, disease-free and overall survival were significantly better for CRS and HIPEC versus CRS alone in stage III ovarian cancer but not in stage I-II (Figs. **2** and **3**, Table **5**).

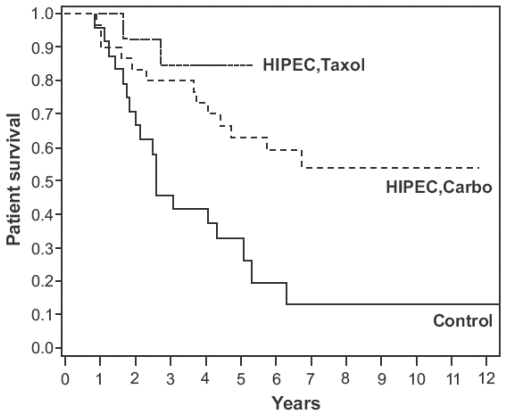

Fig. (2). Overall survival after secondary CRS and HIPEC with either Taxol or Carboplatin versus CRS only (control) in stage III ovarian cancer with a residual mass less than 1 cm after secondary surgery; p = 0.003 (reproduced with permission from 29)

The results were compared with those of a trial published in the same period on a comparable group of patients who were randomised between secondary CRS without HIPEC versus chemotherapy alone after upfront maximal but incomplete CRS followed by chemotherapy in patients with a partial response or stable disease [33] (Table **5**). Median OS and DFS were 33.9 versus 33.7 months and 10.5 versus 10.7 months for the groups receiving CRS without HIPEC versus chemotherapy alone respectively.

Salvage CRS and HIPEC for Recurrent Ovarian Cancer

Seventeen papers described the results of (sub)groups of patients who underwent salvage CRS and HIPEC for recurrent ovarian cancer after initial complete response to CRS and chemotherapy [5-8, 10, 21, 23, 31, 34-42,] (Table **6**). Median and 5 year OS were 15.5-57 months and 18-57% for the whole group and 97.4 months [39] and 63-67% [7, 34] after macroscopically complete resection (CC0). Median and 5 year DFS were 3-48 months and 0-12.5% respectively.

Two of these papers compared CRS and HIPEC with CRS alone in a prospective study [34, 35]. Disease-free [34] and overall survival [34, 35] were significantly better for CRS and HIPEC versus CRS alone ((Fig. **4**), Table **6**).

The results were compared with three papers published in the same period on comparable (sub)groups of patients who underwent salvage CRS without HIPEC for recurrent ovarian cancer [43-45] (Table **6**). Median and 5 year OS were 16-29.2 months and 11.5% for the whole group and 19-45.2 months and 53% in case of complete resection (CC0).

Palliative HIPEC without CRS for Unresectable Ovarian Cancer with Refractory Ascites

One paper described the results of palliative HIPEC without CRS in seventeen patients with chemotherapy resistant ovarian cancer with ascites [46]. The average number of chemotherapy

Table 2. Upfront CRS and HIPEC

Reference	treatment	n	FIGO III-IV	FIGO III	FIGO IV	CC0	mortality	follow-up	5 y PFS	PFS	5 y OS (all)	5 y OS (CC0)	OS (all)	OS (CC0)
3	**CRS and HIPEC**	2	100%	100%	0%		0%			5 m			14.5 m	
4	**CRS and HIPEC**	51	100%			40%		98 m			28%		28.5m	47 m
5	**CRS and HIPEC**	8	100%	75%	25%								29 m *	
6	**CRS and HIPEC**	31	100%	100%	0%								34.1 m	
7	**CRS and HIPEC**	19	100%	100%	0%	47%	0%			25 m	37%	60%	38 m*	
8	**CRS and HIPEC**	26							19.7%	24.8 m	33.3%		41.7 m	
8	**CRS and HIPEC**	26	100%	96%	4%	58%	3.8%	25 m	15.2%	30 m	60.7%		NR	
10	**CRS and HIPEC**	14	100%	100%	0%	79%	0%				55%			NR
11	**CRS only**	336	100%	76%	24%	20%	2.6%	56 m		12 m	19.5%	31.3 %	29 m	45.0 m
12	**CRS only**	68	100%					42 m		15 m			39 m	
13	**CRS only**	279	100%	100%	0%	26%							41 m	
14	**CRS only**	55	100%	100%	0%		0%	74 m					48 m	
15	**CRS only**	210	100%	100%	0%	68%		48 m		18.3 m			49.7 m	
16	**CRS only**	285	100%	87%	13%	24%	0.7%			17 m			50 m	78 m
17	**CRS only**	332	100%	78%	22%	60%	2.7%	23 m*		33.2 m			51.3 m	65.4 m
18	**CRS only**	227	100%	100%	0%	36%	0.9%			22.2 m			52.2 m	
19	**CRS only**	210	100%	83%	17%	27%	1.0%	54 m	31.0%		47.0%		54.0 m	
20	**CRS only**	408	100%	100%	0%	86%		33 m			49.0%		58.2 m	76.2 m

follow-up and survival figures are expressed as median values in months unless specified otherwise
n = number of patients
* = mean
CC0: macroscopically complete cytoreduction
5 y = 5 year
DFS = disease free survival
OS = overall survival
NR = not reached

Table 3. Interval CRS and HIPEC

Reference	Treatment	n	FIGO III-IV	FIGO III	FIGO IV	CC0	Mortality	Follow-up	5 y DFS	DFS	5 y OS (all)	5 y OS (CC0)	OS (all)	OS (CC0)
21	**CRS and HIPEC**	4	100%				0%			8.4 m				
3	**CRS and HIPEC**	4	100%	100%	0%		0%			17.8 m			38.0 m	
8	**CRS and HIPEC**	19							9.6%	16.8 m	50.2%		68.6 m	
10	**CRS and HIPEC**	31	100%	100%	0%	65%	0%				58%			NR
22	**CRS and HIPEC**	9	100%	100%	0%	78%	1/9	39 m*			62%		NR	
23	**CRS and HIPEC**	10	100%	100%	0%	80%	0%			16.9 m				
24	**CRS only**	34	100%	88%	12%		0%	>24 m					26 m	
11	**CRS only**	334	100%	76%	24%	47%	0.7%	56 m		12 m	21.1%	27.5%	30 m	38.2 m
17	**CRS only**	40	100%	78%	22%	88%	0%	23 m*		14.6 m			36.5 m	37.9 m
12	**CRS only**	71	100%					42 m		15 m			41 m	
25	**CRS only**	53	100%	66%	34%	55%	0%	39 m		14 m			45 m	
26	**CRS only**	18	100%	89%	11%		0%	20 m		15 m			53 m	

follow-up and survival figures are expressed as median values in months unless specified otherwise
n = number of patients
* = mean
CC0: macroscopically complete cytoreduction
5 y = 5 year
DFS = disease free survival
OS = overall survival
NR = not reached

Table 4. Consolidation CRS and HIPEC

Reference	Treatment	n	FIGO III-IV	FIGO III	FIGO IV	CC0	mortal-ity	follow-up	5 y DFS	DFS	5 y OS (all)	5 y OS (CC0)	OS (all)	OS (CC0)	p value
27	**CRS and HIPEC**	29	100%	100%	0%	100%	0%	73 m					64.4 m	64.4 m	(1)
27	**no treatment**	19	100%	100%	0%			73 m					46.4 m		(1)
8	**CRS and HIPEC**	12							24.2%	29.6 m	42.4%		53.7 m		
3	**CRS and HIPEC**	4	100%	100%	0%		0%			82.8 m			130.3 m		
28	**paclitaxel IV x 3**	146	100%							14 m			48 m		
28	**paclitaxel IV x 12**	150	100%							22 m			53 m		

follow-up and survival figures are expressed as median values in months unless specified otherwise
n = number of patients
* = mean
CC0: macroscopically complete cytoreduction
5 y = 5 year
DFS = disease free survival
OS = overall survival
NR = not reached
(1) p not significant for OS after CRS and HIPEC versus after no treatment

Table 5. Secondary CRS and HIPEC

Reference	Treatment	n	FIGO III-IV	FIGO III	FIGO IV	CC0	Mortality	Follow-up	5 y DFS	DFS	5 y OS (all)	5 y OS (CC0)	OS (all)	OS (CC0)	p value
29	**CRS and HIPEC stage I-II**	23	0%	0%	0%		0%	62*		NR	82.4%		NR		(1)
29	**CRS only stage I-II**	5	0%	0%	0%		0%	52*		NR	60.0%		NR		(1)
29	**CRS and HIPEC stage III**	44	100%	100%	0%		0%	62*		56 m	66.1%		>60 m		(2)
29	**CRS only stage III**	24	100%	100%	0%		0%	52*		15 m	32.8%		31 m		(2)
30	**CRS and HIPEC (all)**	57	61.4%	61.4%	0%		3.5%	47*		48.7 m	63.4%		76.1 m		(3)
30	**CRS only (all)**	60	65%	65%	0%		0%	46*		19.8 m	52.8%		62.9 m		(3)
30	**CRS and HIPEC stage I-II**	22	0%	0%	0%			47*	69.6%		78.4%				(4)
30	**CRS only stage I-II**	21	0%	0%	0%			46*	77.8%		89.6%				(4)
30	**CRS and HIPEC stage III**	35	100%	100%	0%			47*	26.9%	26.4 m	53.8%		60.9 m		(5)
30	**CRS only stage III**	39	100%	100%	0%			46*	10.3%	6.1 m	33.3%		22.3 m		(5)
31	**CRS and HIPEC**	16								8 m			24.3 m		
32	**CRS and HIPEC**	31	100%	100%	0%		0%			14.1 m			NR		
33	**CRS and IV chemotherapy only**	216	100%	93%	7%			47 m		10.5 m			33.9 m		
33	**IV chemotherapy only**	208	100%	96%	4%			48 m		10.7 m			33.7 m		

follow-up and survival figures are expressed as median values in months unless specified otherwise
n = number of patients
* = mean
CC0: macroscopically complete cytoreduction
5 y = 5 year; DFS = disease free survival; OS = overall survival
NR = not reached
(1) p not significant for DFS and OS after CRS and HIPEC versus after CRS only
(2) p = 0.003 for DFS and OS after CRS and HIPEC versus after CRS only
(3) p = 0.002 for DFS; p = 0.008 for OS after CRS and HIPEC versus after CRS only
(4) p not significant for DFS and OS after CRS and HIPEC versus after CRS only
(5) p = 0.007 for DFS; p = 0.002 for OS between CRS and HIPEC versus after CRS only

cycles given before the first HIPEC was 12.5. The patients' average Karnofsky performance status was 60%. HIPEC was performed by circulating dialysate with cisplatin or carboplatin at 42-43° C in the peritoneal cavity for one hour through a specially designed needle. One cycle of HIPEC consisted of two to three treatments at intervals of 5-7 days. The next cycle of HIPEC was performed after 4-6 weeks. The treatments were repeated as long as the treatment was feasible and convenient for the patient. The adverse effects were mild especially compared to systemic chemotherapy with nausea and vomiting in 70%, peritoneal irritation in 5% and subileus in 2% of treatments. Malignant ascites frequently diminished after a single HIPEC treatment and vanished within less than 3-5 administrations. Quality of life could be improved. It was concluded that HIPEC was safe and associated with a marked improvement in quality of life. Even heavily pretreated patients could be treated safely. Some patients did respond to HIPEC even after 25 HIPEC treatments.

Mortality after HIPEC and CRS Versus CRS only

Mean postoperative mortality was 0.7% (4/547) after CRS and HIPEC versus 1.4% (31/2206) after CRS only for all series taken together.

DISCUSSION

In 1978, Dedrick proposed the intraperitoneal administration of chemotherapy which allowed a significantly higher intraperitoneal concentration than by the intravenous route [47]. Because ovarian cancer remains confined to the peritoneal cavity for much of its natural history and is relatively sensitive to chemotherapy, it should be a good target for intraperitoneal treatment. For drugs most active in ovarian cancer, the ratio of their intraperitoneal to plasma concentrations varies from 18-20 times for carboplatin and cisplatin to 500-1000 times for docetaxel and paclitaxel [48]. The addition of postoperative normothermic intraperitoneal administration of chemotherapy to standard upfront CRS for patients with FIGO III ovarian cancer and intravenous chemotherapy was analysed in 3 phase III trials, all suggesting a survival benefit for patients treated with intraperitoneal chemotherapy [13, 15, 18]. These trials have been contested however because drugs and doses used in the control arms were different from the standard chemotherapy regimen (carboplatin dosed to an area under the concentration-time curve (AUC) of 5-7.5, in combination with paclitaxel at a dose of 175 mg/m^2

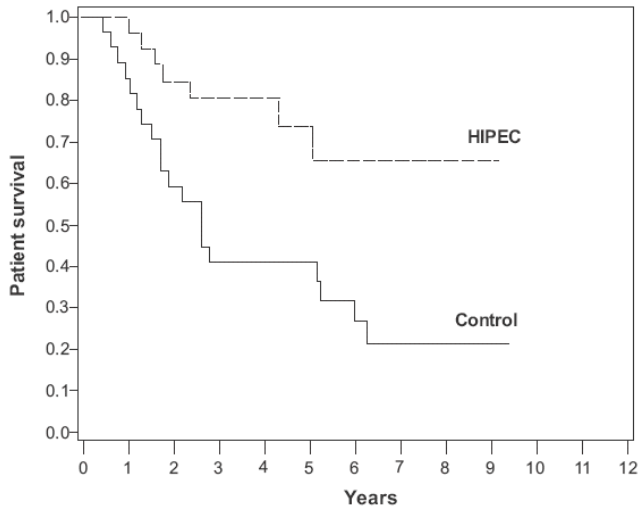

Fig. (3). Overall survival after secondary CRS and HIPEC (IPHC group) versus CRS only (control group) in stage III ovarian cancer with a residual mass less than 1 cm after secondary surgery; p = 0.002 (reproduced with permission from 30).

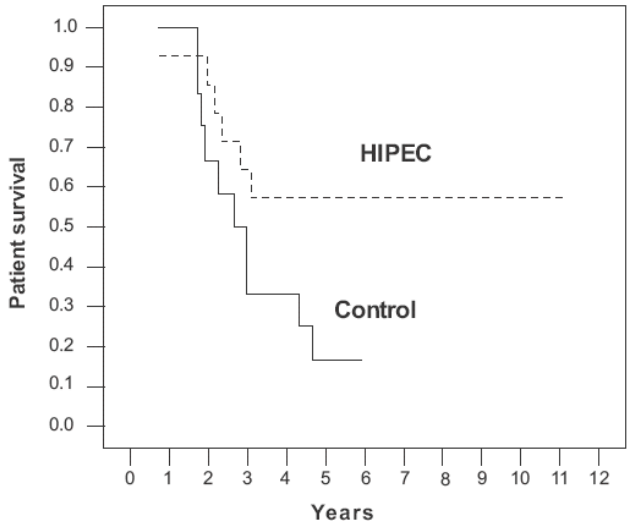

Fig. (4). Overall survival after salvage CRS and HIPEC versus CRS only in stage III recurrent ovarian cancer with a residual mass less than 1 cm after salvage surgery; p = p = 0.046 (reproduced with permission from 34).

every 3 weeks for 6 cycles) [49]. In addition, significant rates of catheter complications were noted with postoperative intraperitoneal chemotherapy [50].

The administration of intraperitoneal chemotherapy during in stead of after the operation and the combination with hyperthermia has first been proposed by Spratt [51, 52]. HIPEC has several theoretical advantages over postoperative intraperitoneal chemotherapy. The intraoperative administration, especially during an open abdomen approach (Coliseum technique) guarantees the homogeneous spread of the drug and a good exposure of the whole peritoneal surface. It also avoids catheter related complications. While hyperthermia in itself is tumoricidal [53], it has also been shown to increase the cytotoxicity of many chemotherapeutic agents in human cell culture and animal models [54, 55]. Furthermore, hyperthermia deepens penetration into peritoneal tumor implants of intraperitoneally delivered chemotherapy [56].

A survival benefit of HIPEC + CRS versus CRS alone has been shown very recently in digestive cancers. In animal models of colorectal peritoneal carcinomatosis in rats [57-59] and gastric peritoneal carcinomatosis in rabbits [60], a better survival was found in the HIPEC groups. In humans, the results of the first phase III randomised trial studying this question has been published in 2011 [61]. Sixty-eight gastric peritoneal carcinomatosis patients were randomized to CRS alone or to CRS + HIPEC receiving cisplatin 120 mg and mitomycin C 30 mg. Median overall survival was 6.5 months after CRS versus 11.0 months after CRS + HIPEC (P = 0.046). The authors concluded that CRS + HIPEC improved survival compared to CRS alone.

HIPEC for ovarian cancer was first reported in 1993 [62]. Up till November 1st 2011, 37 series have been published reporting on the results of HIPEC in 1362 patients [3-10, 21-23, 27, 29-32, 34-42, 46, 63-72]. Most studies are retrospective. Only a few studies have analysed the results of HIPEC with CRS versus CRS alone in non randomized studies [29, 30, 34, 35]. Several randomised trials have been initiated but it will take some years for their results to be known. In the mean time, this review tries to summarise the available evidence for the potential benefit of HIPEC at the different time-points of treatment of ovarian cancer.

Upfront CRS and HIPEC

No studies were found directly comparing upfront CRS and HIPEC with CRS alone in their patient population. Median overall survival is < 38.5 months in 5 out of 6 papers on CRS and HIPEC while it is > 38.5 months in 9 out of 10 papers on CRS alone (Table **2**). Although it is impossible to reach firm conclusions out of this comparison, there doesn't seems to be a striking survival advantage by adding HIPEC to upfront CRS, rather on the contrary.

Interval CRS and HIPEC

No studies were found directly comparing interval CRS and HIPEC with CRS alone in their patient population. Overall survival seems to be somewhat better after CRS and HIPEC than after on CRS alone (Table **3**). Patient numbers however are very small and FIGO stages seem more favourable in the CRS and HIPEC studies.

A phase III randomised trial in the interval setting is ongoing at the Netherlands Cancer Institute (OVHIPEC trial; Clinical Trials.gov identifier NCT00426257). The study started in February 2007 and is estimated to close in December 2013. Two hundred eighty patients with epithelial ovarian cancer FIGO stage III in whom upfront CRS was not feasible due to tumour extension or general condition (group 'interval CRS') or patients treated with incomplete upfront CRS with residual disease > 1 cm (group 'secondary CRS') will receive 3 courses of carboplatin or cisplatin combined with taxol. In case of tumour response, they will be randomised to undergo a second CRS with or without HIPEC. This trial therefore studies the effect of adding HIPEC to CRS in two distinct patient populations: patients undergoing interval CRS after neoadjuvant chemotherapy and patients receiving secondary CRS after upfront incomplete CRS followed by chemotherapy.

A similar multicenter phase III randomised trial in the interval setting has just started in Italy (CHORINE: Cytoreduction and Hipec in the treatment of OvaRIaNcancEr) [73]. This study compares CRS+HIPEC (cisplatin+paclitaxel) vs. CRS alone in Stage IIIC unresectable ovarian cancer with partial or complete response after 3 systemic cycles of carboplatin and paclitaxel, followed by 3 further cycles of carboplatin and paclitaxel. The primary outcome is two year disease-free survival.

Consolidation CRS and HIPEC

In a prospective non randomised study, consolidation CRS and HIPEC (29 patients) was compared with no treatment (19 patients in the same period who refused CRS and HIPEC) in patients with FIGO stage III ovarian cancer after upfront (near) complete CRS

followed by adjuvant systemic chemotherapy [27] (Fig. **1**). Median overall survival was 64.4 months in the CRS and HIPEC group versus 46.4 months for the control group but the difference failed to reach statistical significance (p = 0.56).

Secondary CRS and HIPEC

In contrast to the previous time-points, there is more evidence for a potential benefit in adding HIPEC to CRS for ovarian cancer in the setting of secondary CRS after upfront incomplete CRS followed by chemotherapy in patients with a partial response or stable disease. Two retrospective but well stratified studies compared CRS and HIPEC with CRS alone [29, 30]. In both studies, disease-free and overall survival were impressive and significantly better for CRS and HIPEC versus CRS alone in stage III ovarian cancer but not in stage I-II (Table **5**). Of note, a randomised trial in the same period showed no survival benefit in adding secondary CRS alone to systemic chemotherapy in a comparable group of patients [33] (Table **5**).

Table 6. Salvage CRS and HIPEC

Reference	treatment	n	FIGO III-IV	FIGO III	FIGO IV	CC0	mortality	follow-up	5 y DFS	DFS	5 y OS (all)	5 y OS (CC0)	OS (all)	OS (CC0)	p value
34	**CRS and HIPEC**	14	100%	100%	0%	64%	0%			48 m*	57%	67%	NR	NR	(1)
34	**CRS only**	12	100%	100%	0%	58%	0%			24 m*	17%	29%			(1)
35	**CRS and HIPEC**	24	100%			46%	0%	24					19.4 m		(2)
35	**CRS only**	24	100%			25%	0%	24					11.2 m		(2)
36	**CRS and HIPEC**	25	100%							22.5 m			15.5 m		
37	**CRS and HIPEC**	5	100%				0%	16		3 m			16 m		
8	**CRS and HIPEC**	83							9.6%	13.7 m	18.0%		23.5 m		
38	**CRS and HIPEC**	30	100%				0%	19*		17.1 m			28.1 m		
31	**CRS and HIPEC**	65								8.5 m			28.4 m		
5	**CRS and HIPEC**	11	100%	73%	27%								30 m*		
39	**CRS and HIPEC**	42	100%			50%	0%	20.8*	12.5 %	13 m	41.3%		37 m	97.4 m*	
40	**CRS and HIPEC**	43	100%			95%	0%	29		24 m			38 m		
6	**CRS and HIPEC**	25	100%										40.1 m		
7	**CRS and HIPEC**	14	100%	100%	0%	57%	0%			31 m	51%	63%	57 m*		
41	**CRS and HIPEC**	31	100%	97%	3%	65%	0%	27	0%	13.3 m			NR		
10	**CRS and HIPEC**	8	100%	100%	0%	75%	0%				44%			NR	
23	**CRS and HIPEC**	8	100%	100%	0%	100%	0%			10 m					
42	**CRS and HIPEC**	12	100%	8/12	0%	100%	0%	14		14.3 m					
21	**CRS and HIPEC**	9	100%				0%			20.3 m					
43	**CRS only**	267	69%	65%	4%	50%		19					29.2 m	45.2 m	
44	**CRS only**	44	100%	100%	0%	77%	0						16 m	19 m	
45	**CRS only**	149	79%	69%	10%	36%	3.3%	27			11.5%	53%			

follow-up and survival figures are expressed as median values in months unless specified otherwise
n = number of patients; * = mean
CC0: macroscopically complete cytoreduction
5 y = 5 year; DFS = disease free survival; OS = overall survival; NR = not reached
(1) p not mentioned for DFS; p = 0.046 for OS after CRS and HIPEC versus after CRS only
(2) p < 0.05 for OS after CRS and HIPEC versus after CRS only

Table 7. Summary of Evidence for the Potential Benefit of HIPEC at the Different Time-points of Ovarian Cancer Treatment

Time-point	Non Comparative Trials*	Comparative Trials	Randomized Phase 3 Trials
upfront CRS	(-)		
interval CRS	(+)		1 ongoing (the Netherlands) 1 ongoing (Italy)
consolidation CRS	(0)	(+)	
secondary CRS stage I-II		0	
secondary CRS stage III	0	+	1 ongoing (the Netherlands)
salvage CRS	+	+	2 ongoing (France, Italy)
palliative (HIPEC only)	quality of life ↑		

* versus contemporary studies on CRS only
- survival worse after HIPEC
0 no survival difference
+ survival better after HIPEC

The setting of secondary CRS therefore seems to be a very interesting time-point to conduct a randomised trial between CRS and HIPEC versus CRS alone in stage III ovarian cancer. Such a trial is ongoing at the Netherlands Cancer Institute (OVHIPEC trial; ClinicalTrials.gov identifier NCT00426257; see above). There is no evidence for a potential benefit of adding HIPEC to secondary CRS in stage I-II ovarian cancer.

Salvage CRS and HIPEC for Recurrent Ovarian Cancer

There is also more evidence for a potential benefit in adding HIPEC to CRS in the setting of recurrent ovarian cancer. Two prospective non randomised trials compared CRS and HIPEC with CRS alone [29, 30] (Table **6**). In the first study on 26 patients, median DFS (48 m) and 5 year OS (67%) were impressive for CRS and HIPEC and significantly better than after CRS alone (24 m and 29% respectively) [34]. In the second study on 48 patients, survival figures were less favourable. Nevertheless, median OS was significantly better for CRS and HIPEC (19.4 m) than for CRS alone (11.2 m) [35]. When comparing the results in the seventeen papers on CRS and HIPEC with the results of three contemporary papers on CRS only in the setting of recurrent ovarian cancer, survival figures after CRS and HIPEC tend to be better than after CRS alone in many studies. For all these reasons, the setting of recurrent ovarian cancer seems to be a promising time-point to conduct a randomised trial between CRS and HIPEC versus CRS alone. Such a trial is ongoing in France sponsored by the Fédération Nationale des Centres de Lutte Contre le Cancer (CHIPOR trial; ClinicalTrials.gov identifier NCT01376752).

The study started in April 2011 and is estimated to close in December 2018. Four hundred forty four patients with FIGO III recurrent epithelial ovarian cancer will receive six courses of carboplatin - paclitaxel or carboplatin - caelyx. In case of tumour response and if a (near) complete (CC0-1) CRS seems possible, they will be randomised to undergo a second CRS with or without HIPEC. A second randomised trial in patients with recurrent ovarian cancer is ongoing in Rome [40].

Palliative HIPEC without CRS for Unresectable Ovarian Cancer with Refractory Ascites

Despite all surgical and medical efforts, ovarian cancer will recur in many patients, often leading to a miserable situation of refractory ascites with discomfort, dyspnoea and anorexia. In patients with refractory ascites as main complaint, palliative HIPEC without CRS may be a safe and effective palliative treatment to improve quality of life. Good results of the palliative (laparoscopic) administration of HIPEC without CRS have been reported recently in patients with refractory ascites due to recurrent gastric cancer, colorectal cancer, ovarian cancer, breast cancer and peritoneal mesothelioma with limited morbidity, complete clinical and radiological disappearance of ascites in 94% of cases, and improvement of the Karnofsky index [74-76].

Morbidity and Mortality After HIPEC and CRS Versus After CRS Only

Morbidity could not be compared in a meaningful way between CRS and HIPEC versus after CRS only because of absent or different definitions of morbidity between series. Postoperative mortality however was not higher after CRS and HIPEC (0.7%) versus after CRS only (1.4%). The morbidity analysis of the ongoing and planned randomized controlled trials will have to be awaited to allow a correct comparison of morbidity rates after HIPEC and CRS versus CRS only.

CONCLUSION

The addition of HIPEC to CRS for peritoneal carcinomatosis has a sound theoretical rationale which has been confirmed in survival experiments in animal models and in one randomised trial in patients with gastric cancer. More specifically for ovarian cancer, indirect evidence for a potential benefit of adding HIPEC to CRS comes from three randomised trials on postoperative normothermic intraperitoneal chemotherapy, a handful of non randomised comparative trials and about thirty non comparative trials on HIPEC. A summary of the current clinical evidence (Table **7**) suggests that the most interesting settings first to explore in randomised trials are secondary CRS after upfront incomplete CRS for stage III ovarian cancer and salvage CRS for recurrent ovarian cancer, two time-points representing failure of initial standard therapy. There is much less indirect evidence for a potential benefit of HIPEC for less advanced stages (I-II) and for earlier time-points in the treatment of ovarian cancer (upfront, interval and consolidation). Postoperative mortality is not higher after CRS and HIPEC (0.7%) than after CRS only (1.4%). Four randomised trials are ongoing and their results are eagerly awaited. Palliative HIPEC without CRS might be used more in patients with incapacitating ascites due to recurrent ovarian cancer which has become resistant to systemic chemotherapy.

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CONFLICTS OF INTEREST

None declared.

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