

Hyperthermic intraperitoneal chemotherapy in conjunction with surgery for the treatment of recurrent ovarian carcinoma[☆]

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Abstract

Objectives. To review experience of secondary surgical cytoreduction (SSC) with hyperthermic intraperitoneal chemotherapy (IPHC).

Methods. Eligible patients with ovarian cancer in whom pre-operative evaluation indicated that there was a good possibility that disease could be resected to ≤ 5 mm underwent surgery followed by intraperitoneal perfusion of cisplatin (100 mg/m²) or mitomycin C (30–40 mg total dose) heated to 41–43°C (105.8–109.4°F) for 90 min. Data for analysis were extracted from retrospective chart review.

Results. Eighteen patients underwent surgery and IPHC between 9/02 and 3/05. Characteristics were median age 64 (37–77) years, mean prior laparotomies 1.4 (0–3), mean chemotherapy regimens 3.2 (0–7), mean time from initial therapy to IPHC 30.6 (1–88) months. Original histology: papillary serous 12, poorly differentiated adenocarcinoma 1, serous low malignant potential 2, mucinous 1 and mixed subtypes 2. 13 had recurrent disease and 5 had persistent disease following front-line therapy. 15 received cisplatin and 3 mitomycin C. The mean duration of surgery was 9.8 (5–16) h. The maximum dimension of residual lesions at the end of surgery prior to IPHC was nil ($n=11$), ≤ 2 mm ($n=4$), ≤ 5 mm ($n=2$) and ≤ 10 mm ($n=1$). Mean time to return of bowel function was 7 (5–20) days and mean time to hospital discharge 11.5 (5–49) days. All patients developed CTEP grade 1 or 2 metabolic or hematologic toxicities. CTEP grade 3 or 4 metabolic toxicity occurred in 72% and a hematologic toxicity in 28%. There was one peri-operative death due to pulmonary embolus. Median progression-free interval was 10 months and median overall survival was 31 months. Improved outcome was significantly related to the size of residual disease prior to IPHC and postoperative chemotherapy.

Conclusions. IPHC is a relatively well-tolerated procedure with the majority of the morbidity being related to associated surgery. When combined with SSC it has the potential to extend quality life in some patients with recurrent ovarian cancer and warrants continued research. Randomized studies are needed earlier in the course of the disease.

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Introduction

In the United States, ovarian carcinoma affects over 20,000 women annually, causing the death of approximately 15,000 women. [1] Standard front-line therapy has been surgery followed by intravenous chemotherapy with a platinum and taxane

combination. Although response rates to this treatment are high, 60–70% of all patients with ovarian carcinoma will recur [2–5] and the overall 5-year survival still only approximates 50%. In ovarian cancer recurrent disease has a very poor prognosis.

Intraperitoneal delivery of chemotherapy in ovarian cancer has been shown to be effective in front-line treatment. Three large, randomized studies investigating the intraperitoneal delivery of cisplatin, carboplatin or paclitaxel in combination with intravenous delivery have shown a survival advantage for patients treated with intraperitoneal chemotherapy [6–8].

Hyperthermia, on its own, is tumoricidal [9]. In addition, it increases the cytotoxicity of cisplatin and other chemothe-

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therapeutic agents both in human cell culture and animal models [10–14] and may reverse cisplatin resistance. [15] While the precise underlying molecular mechanism of these effects is unknown, studies of hyperthermia in combination with chemotherapy have demonstrated increased DNA cross-linking and increased DNA adduct formation [11,16]. Cisplatin has also been shown to penetrate more deeply into tumor implants when delivered intraperitoneally with hyperthermia [16].

The possible synergy between hyperthermia and chemotherapy agents has sparked clinical trials utilizing this combination in many disease types. With regard to situations analogous with ovarian carcinoma in which disease may be widespread within the peritoneal cavity, studies in gastric cancer [17], malignant mesothelioma [18], appendix cancer [19], and colorectal cancer have shown promising results. [20] A phase III randomized study of hyperthermic intraperitoneal chemotherapy following cytoreductive surgery compared with traditional intravenous chemotherapy and palliative care in patients with peritoneal spread of colorectal carcinoma showed a statistically significant prolongation of life in the experimental arm. [20] This study was not designed to evaluate the relative contributions of the surgery and intraperitoneal hyperthermic chemotherapy to the improvement in outcome.

Ovarian carcinoma is a logical target for directed intraperitoneal therapy in combination with heat and there are reports of clinical studies looking at hyperthermic intraperitoneal chemotherapy following surgical debulking in this disease [21–27], however, they are few and contain relatively small numbers of patients.

Methods

After obtaining Institutional Review Board approval from the University of Louisville we performed a retrospective review of patients treated with IPHC for recurrent or persistent ovarian, peritoneal or Fallopian tube carcinoma at the University of Louisville Hospital between September 2002 and March 2005.

To be eligible for this treatment patients had to have recurrent or persistent disease confined to the peritoneal cavity, or disease within the lymph nodes or liver amenable to surgical resection, which pre-operative evaluation indicated a good possibility of resection to ≤ 5 mm residual. All patients underwent exploratory laparotomy with the aim of resecting disease down to ≤ 5 mm largest residual lesion size. Following surgical resection IPHC was delivered in the following manner: after induction of anesthesia the anesthesiologist placed an esophageal heat sensor. A urethral catheter with heat sensor probe was placed in the bladder. Following initial draping of the chest and legs a large sterile Ioban™-2 adhesive drape (3M Corp, St Paul, MN) was placed over the entire operative field.

Cytoreductive surgery was performed and 1 h prior to completion of surgery, the patient's core temperature was gradually lowered to about 34°C as assessed by the bladder and esophageal probes in order to reduce the risk of core body hyperthermia during the hyperthermic intraperitoneal perfusion. Upon completion of the surgery (apart from bowel anastomoses) the patient was readied for hyperthermic intraperitoneal chemotherapy (SGO video presentation, San Diego, 2004). Two inflow tubes were placed, one above the right lobe of the liver with a temperature probe attached to the tip and the other in the left upper quadrant. Two outflow tubes were placed, one on either side of the pelvic floor with a temperature probe connected to the end of one. The skin of the abdominal incision was closed using a free Richard-Allan 2090-1 3/8in needle connected to a 96in PDS #1 loop in a running, locking 'baseball' fashion. Care was taken to ensure that the skin edges were not inverted and that the skin was tightly apposed around the tubing.

The inflow and outflow tubing was connected to a Thermochem™ HT-1000 modified heat-exchange pump (ViaCirq, Pittsburgh, PA). Pre-heated Deflex™

peritoneal dialysis solution (Fresenius Medical Care, Lexington, MA) was allowed to fill the peritoneal cavity with the patient in steep Trendelenburg position allowing air to be expelled through the outflow tubing. Once the abdomen was distended (usually with 2–3 l) and a flow rate of approximately 1500 cm³/min was achieved the patient was leveled out. When the temperature probes showed a consistent inflow temperature of 43°C and outflow of 42°C the chemotherapy agent was added to the perfusate and allowed to circulate within the abdominal cavity for 90 min with an assistant on each side of the patient gently kneading the abdomen to encourage good distribution. Care was taken to watch for leakages from the wound and secure them with sutures.

At the completion of perfusion the perfusate was drained into the waste container attached to the Thermochem™ HT-1000 machine. The abdomen was carefully opened with a disposable sump sucker 'at the ready' to aspirate residual fluid. The abdomen and pelvis were gently irrigated with 2–3 l of saline to wash away any residual chemotherapy agent and avoid contamination during the remainder of the procedure. All contaminated instruments and tubing were passed off and placed in biohazard containers according to standard chemotherapy protocol. Gowns and gloves were changed and the surgery was completed including bowel anastomoses. When resection of part of the diaphragm was performed the defect was closed as soon as possible, and prior to the hyperthermic perfusion, following aspiration of any intraperitoneal fluids to minimize contamination.

Postoperatively patients were routinely monitored in the Intensive Care Unit. Following cisplatin administration a target urine output of at least 100 ml/h for the first 72 h was sought. All other postoperative care was that routinely given to patients after major surgery.

Following discharge from hospital patients were treated with adjuvant chemotherapy if indicated and followed closely. Since the patients had advanced/recurrent disease it was considered unlikely that the surgery and a single intraperitoneal treatment would be sufficient treatment. We considered it prudent to give further chemotherapy to try and consolidate the benefits of the procedure, particularly the small disease volume at the end of surgery. Chemotherapy agents were selected with the assistance of drug resistance assays performed on tumor samples taken at the time of surgery (Oncotech, Palo Alto, CA). Routine follow-up was by clinical examination and CA125 three monthly with radiological investigations when indicated. Recurrence and progression were evaluated using the Response Evaluation Criteria in Solid Tumors Committee (RECIST) and Rustin criteria [28,29]. Overall survival and progression-free survival were analyzed using the Kaplan–Meier method. The logrank and Chi-squared tests were used where appropriate. Metabolic and hematologic complications were graded according to CTEP v3.0 guidelines [30].

Results

Between September of 2002 and March of 2005 eighteen patients underwent surgery with IPHC with a median age of 64 (37–77) years. The patients had been heavily pre-treated with the mean number of prior laparotomies being 1.4 (0–3) and the mean number of chemotherapy agents 3.2 (0–7). One patient had received no prior chemotherapy because her original tumor had been diagnosed as serous LMP, however, she recurred with widespread invasive carcinoma and was treated by surgical cytoreduction and IPHC. Two patients had received prior pelvic radiation, one with intraperitoneal P³² and one with external beam therapy. The mean time from completion of initial therapy to IPHC was 30.6 (1–88) months. Fourteen patients had widespread recurrent disease involving the abdomen and pelvis, one patient had disease confined only to the abdomen, two patients had disease confined to the pelvis and one had no visible disease. The details of the original primary site, histology and stage are given in Table 1. The mean duration of surgery was 9.8 (5–16) h with a mean blood loss of 1260 (150–3500) ml. The maximum dimension of residual lesions at

Table 1
Tumor characteristics

	Primary site	Original stage	Original histology	Situation
1	Ovary	3C	Serous	Recurrent
2	Ovary	3C	Serous	Recurrent
3	Ovary	3C	Serous	Recurrent
4	Ovary	3	Serous	Recurrent
5	Ovary	3C	pd ^a Adenocarcinoma	Persistent
6	Ovary	4	Serous	Recurrent
7	Peritoneal	3C	Serous	Recurrent
8	Peritoneal	3C	Serous	Persistent
9	Ovary	3A	Serous LMP	Recurrent
10	Ovary	1B	Serous LMP	Recurrent
11	Fallopian tube	3C	Serous	Recurrent
12	Ovary	4	Serous	Recurrent
13	Ovary	3C	Endometrioid/Clear cell	Persistent
14	Ovary	1C	Mucinous	Recurrent
15	Ovary	3C	Serous	Persistent
16	Ovary	3C	Serous/Endometrioid	Recurrent
17	Ovary	3C	Serous	Recurrent
18	Ovary	4	Serous	Persistent

^a pd= Poorly differentiated.

the end of surgery prior to IPHC was nil ($n=11$), ≤ 2 mm ($n=4$), ≤ 5 mm ($n=2$) and ≤ 10 mm ($n=1$). Details of the surgical procedures performed are given in Table 2.

Fifteen patients received intraperitoneal cisplatin at 100 mg/m² and three received mitomycin C at a total dose of 40 mg (30 mg initially followed by 10 mg at 60 min). Mitomycin was given because of prior platinum hypersensitivity or resistance. In all cases the total duration of infusion was 90 min. The mean core temperature prior to infusion was 34.6 (32.4–36.1) °C, the mean inflow temperature 42.5 (40.4–43.6) °C, the mean outflow temperature 41.3 (39.9–42.3) °C and mean core temperature after transfusion 38.8 (36.3–40.5) °C. No patient required emergency cooling measures to be taken during the perfusion.

In the postoperative period the mean hourly urine output for the first 72 h was 162 (89–290) ml, the mean time to return of bowel function was 7 (5–20) days and the mean time to discharge was 11.5 (5–49) days.

Postoperative morbidity is detailed in Tables 3 and 4. All patients developed CTEP grade 1 or 2 metabolic or hematologic toxicities. Thirteen of the 18 patients (72%) experienced a CTEP grade 3 or 4 metabolic toxicity and five (28%) a hematologic toxicity. [30] All patients had a pre-operative creatinine below the institutional upper limit of normal (ULN), 1.2 mg/dl. Eight of 15 (53%) receiving cisplatin had a rise in

Table 2
Surgical procedures performed

$n=17$			
Right hemicolectomy	5	Splenectomy	5
Anterior resection	6	Resection of metastasis in or on liver	4
Colostomy/Ileostomy	3	Resection of diaphragmatic disease	2
Small bowel resection	2	Distal pancreatectomy	1
Cholecystectomy	2	Partial ureteral resection with neocystostomy	1
Node resection	11	Repair of abdominal ureter	1
Upper vaginectomy	2		

Table 3
Post-operative morbidity—metabolic and hematologic CTEP v3.0 (CTCAE) grading [30]

	Grade 3	Grade 4
	n	n
Raised creatinine	1	1
Hyponatremia	3	
Hypnatremia	1	
Hypokalemia	4	
Hypocalcemia	6	
Hypoalbuminemia	8	
Raised liver enzymes	4	
Hemoglobin	4	
Platelets	1	
Leucocytes	2	
Absolute neutrophil count	2	

creatinine above the ULN in the early postoperative period, the range of maximum postoperative values being 1.4–9.9 mg/dl. Although the levels remained above the ULN in 75% during the follow-up period no patients required chronic dialysis. No patient receiving mitomycin had an abnormal creatinine level. Sixteen of 18 (89%) experienced other toxicities (Table 4).

Seven of 18 (39%) patients developed pleural effusions in the postoperative period with drainage being necessary in 4 cases. There was a significant correlation between the development of pleural effusions and the presence of disease on the diaphragm ($p=0.006$) and the length of surgery ≥ 10 h versus <10 h ($p=0.016$). Surgery on the diaphragm per se was not significantly associated ($p=0.09$), Chi-squared test. Five of 6 patients with diaphragmatic disease at surgery developed postoperative effusions. Four had disease resected and 3 developed effusions whereas two patients had small volume disease that was not resected and both developed effusions. Both patients with partial resection of the diaphragm developed significant effusions requiring drainage in the postoperative period. Only two of twelve patients without disease on the diaphragms developed postoperative effusions.

Nine of 18 patients (50%) developed one or more infection complications detailed in Table 4. There was a non-significant trend towards the occurrence of infection in patients undergoing

Table 4
Post-operative morbidity—other

	n		n
Pleural effusion drained	4	Fistula (uretero-rectal stump)	1 ^a
Pneumonia	1	Intra-abdominal hematoma	1 ^a
Heart arrhythmia	2	Small bowel obstruction	1 ^a
Heart failure	2	Tissue necrosis	1 ^a
Central vein thrombosis	2	Femoral neuropathy	1
Pulmonary embolus	1		
Septicemia	2	Death within 30 days	1
Line sepsis	2		
Wound infection	5		
Pelvic abscess	1		
Wound seroma	1		
Urinary infection	2		

^a Requiring further surgery.

bowel surgery versus those that did not, 6/9 versus 3/9 ($p=0.16$, Chi-squared test).

Three patients required re-operation. One was anticoagulated for a central vein thrombosis and developed a hematoma in the left abdomen which was drained at laparotomy. Following this procedure a small bowel obstruction developed and was relieved by adhesiolysis at a third surgery. Another patient developed extensive necrosis of the tissues of the anterior abdominal wall in the left lower quadrant during the post-operative period which required debridement and skin grafting. The cause of this necrosis was postulated to be poor vasculature associated with diabetes exacerbated by the ligation of the inferior mesenteric artery at the time of surgery. A third patient developed a uretero-rectal stump fistula which required re-implantation of the ureter.

There was one peri-operative death within 30 days of surgery. The patient had a St. Jude’s valve as well as atrial fibrillation. She experienced an ileus in the postoperative period which resolved, however, she collapsed and died on day 16. The cause of death was thought to be a massive pulmonary embolus.

At the time of last follow-up 8/18 patients (44%) were dead of disease, 2 patients were dead of other causes without evidence of disease, and 8 (44%) were alive: 6 with recurrence and 2 free of disease. Mean follow-up among those still alive is 16.2 months range 6–33 months. Recurrence occurred in 14 patients with a median progression-free interval of 10 months. Progression-free survival is shown in Fig. 1. The sites of recurrence were abdomen and pelvis 6, pelvis alone 1, abdomen alone 7. Overall median survival was 31 months (Fig. 2). The Kaplan–Meier survival curves were almost identical when the patients with original LMP histology and no disease at surgery were excluded. Median survival was significantly related to the size of the largest residual lesion: 31 versus 8 months (≤ 2 mm versus >2 mm disease, $p=0.02$ logrank test) and 31 versus 5.5 months (<5 mm versus ≥ 5 mm disease, $p=0.0014$ logrank test) (Fig. 3). There was no significant difference between the median survival of patients treated with IPHC more than 9 months versus ≤ 9 months from completion of initial therapy, 31 versus 12 months ($p=0.09$ logrank test) or of patients with platinum-sensitive versus platinum-refractory/resistant disease 31 months versus 12 months ($p=0.06$ logrank test) (Fig. 4).

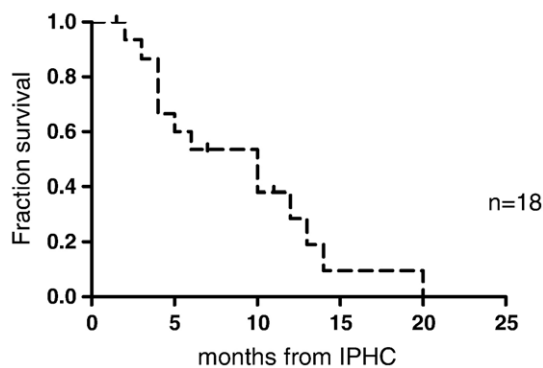


Fig. 1. Progression-free survival.

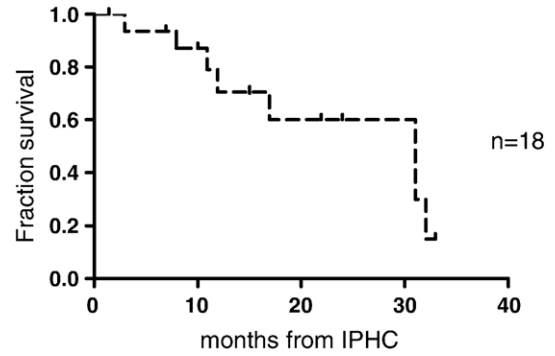


Fig. 2. Overall survival.

Twelve of 18 patients received postoperative chemotherapy following recovery from surgery with a median survival 31 months versus 8 months for the 6 patients who did not receive postoperative chemotherapy ($p=0.0037$). Of these 6 patients one died on postoperative day 11, one died at 1.5 months of medical problems and one with localized completely resected disease, declined. Three others died of disease at 3, 8, 14 months, one had had extensive 5 mm residual at surgery and another developed a brain metastasis and died at 8 months.

Discussion

This report documents the experience of a single institution with the use of surgery and IPHC for recurrent/persistent ovarian carcinoma. Research into the intraperitoneal delivery of chemotherapy combined with hyperthermia for ovarian carcinoma has lagged behind research in other cancers causing peritoneal carcinomatosis including appendiceal carcinoma, [19] mesothelioma [18] and colorectal carcinoma. [20] This is somewhat surprising since ovarian carcinoma is a classic peritoneal surface malignancy with relatively high sensitivity to chemotherapy agents and where intraperitoneal delivery of normothermic chemotherapy has been shown to be effective. [6–8] Patients with recurrent ovarian cancer usually die with intra-abdominal recurrence of chemotherapy resistant disease [31].

The first instance of IPHC being used to treat advanced ovarian carcinoma was in 1994 [32] when a single case of

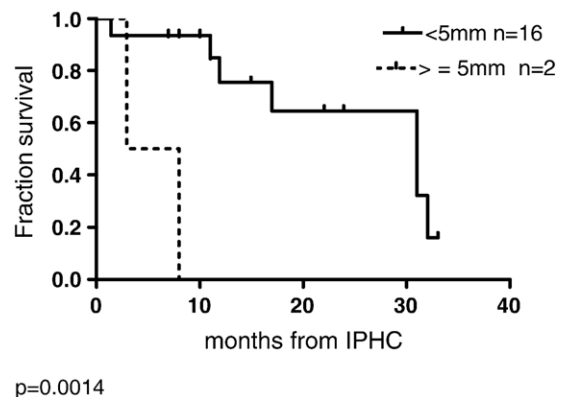


Fig. 3. Survival by extent of residual disease.

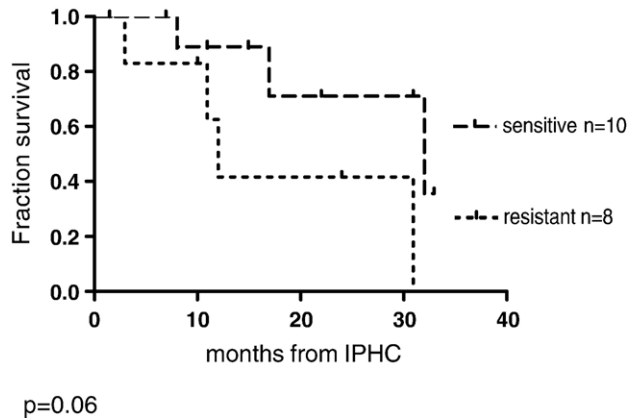


Fig. 4. Survival by initial platinum response.

ovarian carcinoma was included in a series of seven cases of intraperitoneal carcinoma predominantly of gastro-intestinal origin. Since that time several reports have examined experience with IPHC in recurrent ovarian cancer mainly from surgical oncology centers in Europe, though there have been some reports recently from the USA [23–26,33–36].

The results from these non-randomized studies are difficult to interpret because of the variability among patients studied, the range of clinical situations studied and the treatments administered. In order to compare experience with IPHC in recurrent or persistent ovarian carcinoma following front-line treatment two of the above reports have been excluded and the remainder are shown in Table 5 as the ‘comparison group’. Cavaliere et al. [23] reported on 20 patients with ovarian cancer in a mixed series of 40 patients with ovarian, colorectal, appendiceal and mesothelial peritoneal carcinomatosis. All had been previously treated with surgery and/or chemotherapy and were no longer responsive to conventional therapies. However, only a proportion of the patients received IPHC and separate data on this group are not given. Look and colleagues [35] reported on 28 patients treated with advanced and recurrent ovarian carcinoma. Four of the 28 were treated front-line and only 16 of the 28 had had prior chemotherapy. Patients were treated either with early postoperative intraperitoneal normothermic chemotherapy or IPHC but were not separately analyzed.

Our data confirm that secondary surgical cytoreduction and IPHC can be given to patients relatively safely. Although the incidence of complications following the surgery was high,

many of these were attributable to the surgery itself, few were long-standing and there was only one peri-operative death from a pulmonary embolus. Four patients had either prolonged hospital stays or complications which delayed the start of adjuvant chemotherapy. The ‘comparison group’ do not report a high level of complications and Panteix et al. [26] and Reichman et al. [36] do not report complications.

In the ‘comparison group’ there were 4 peri-operative deaths one each due to disseminated intravascular coagulation, pulmonary embolus, gram-negative sepsis and colorectal anastomotic leak/bleeding [25,33,34] giving a mortality rate of 4.9% (4 of 81 patients). This is comparable to our series where there was one peri-operative death attributable to pulmonary embolus out of 18 patients (5.5%). These results are in line with the 5% mortality associated with cytoreductive surgery and IPHC in peritoneal carcinomatosis associated with colorectal and appendiceal cancer. [37] In contrast to our series in which 72% of patients experienced a CTEP grade 3 or 4 metabolic toxicity and 28% a hematologic toxicity, in the ‘comparison group’ grade 3 hematologic toxicity including thrombocytopenia was reported in only 2 patients (2%) [25,34] and there were no reported grade 3 metabolic toxicities. In contrast to a single case of grade 2 renal toxicity in the ‘comparison group’ [25] we found that eight of 15 (53%) had a raised creatinine in the early postoperative period with one grade 3 and one grade 4.

The reason for this higher occurrence of toxicities may be related to the dose of cisplatin used. We used 100 mg/m² over 90 min whereas others used smaller doses. Zanon et al. [34] treated 9 patients with cisplatin 100 mg/m² and 21 with 150 mg/m² at a mean temperature of 41.8°C for 60 min using sodium thiosulphate intravenously in 16 of the 30 patients. There were two cases of transient polyuria postoperatively in patients who did not receive sodium thiosulphate but raised creatinine is not reported. Panteix et al. [26] treated 9 patients at 41–43°C for 90 min with a maximum 100 mg total dose and without any reported renal toxicity. Recognizing the need to try and avoid renal toxicity we made every effort to keep urine output high in the postoperative period and only failed to keep up average hourly output for the first 72 h above 100 ml in a single patient.

Surgical complications reported in the ‘comparison group’ included an ileocolic anastomotic leak and a spontaneous ileal perforation [34] and a colorectal anastomosis leak. [33] We had no anastomotic leaks out of 10 unprotected anastomoses but we

Table 5
Comparison group

Authors	Type	n	Chemotherapy	Dose	Minutes	Temperature (°C)
van der Vange et al. [24]	Pilot	5	Cisplatin	50/75 mg/m ²	90	40
Deraco et al. [25]	Prospective	27	Cisplatin	25 mg/m ² /L	60	42.5
Panteix et al. [26]	Pharmacokinetic	16	Cisplatin	60/80/100 mg	90	41–43
Zanon et al. [34]	Phase II	30	Cisplatin	100/150 mg/m ²	60	41.5–42.5
de Bree et al. [33]	Prospective	19	Docetaxel	75 mg/m ²	120	41–43
Reichman et al. [36]	Retrospective	13	Cisplatin	50 mg/m ²	90	40
Current series	Retrospective	18	Cisplatin Or mitomycin	100 mg/m ² 40 mg	90	42–43

recognized the reported increased risk of impaired healing with IPHC and 3 additional patients had temporary diversions. Wound complications were surprisingly low in the comparison group with a single dehiscence and 3 wound infections. [33] The incidence of pleural effusion was also low with only two significant effusions reported [24,34] in comparison with our series with 4/18 patients having significant effusion requiring drainage.

It is not surprising that most patients in our series have recurred considering the extent of recurrent disease and the heavy pre-treatment before IPHC. The median progression-free interval of 10 months reflects the nature of the population treated. Within the ‘comparison group’ median time to progression when stated, ranged between 15.4 and 21.8 months. [25,34,36] Our completeness of cytoreduction, as measured by the size of the largest residual lesion, 83% \leq 2 mm and 94% \leq 5 mm was comparable with those studies where the rate of residual disease $<$ 2.5 mm was 70–85% [25,34,36] and $<$ 5 mm 75% [33]. Our rate of complete cytoreduction to no visible disease was 65% compared with 100% (5/5) [24] and 55% [25]. Our experience that recurrence within the abdomino-pelvic cavity is predominant is confirmed by the ‘comparison group’: while 3 authors did not report the site of recurrence [26,34,36] in those that did 4/4 (100%) were peritoneal, [33] 9/13 (69%) were loco-regional [25] and 3 of 4 (75%) were intra-abdominal including liver. [24] This confirms that while the combination of surgery and IPHC may be delaying the time to progression of disease it is not permanently clearing all disease.

Our overall median survival of 31 months is interesting when measured against the extent of disease and pre-treatment given to a group of patients with historically very poor survival. In the ‘comparison group’ overall 2-year survival was reported as 55% [25] and 60% [34] and 3-year survival 55% [36] and 37.5%. [26] Some long-term survivors were reported by Panteix et al. [26] with 12.5% 7-year survival and De Bree et al. [33] who reported 25% (3 of 12) patients surviving a mean of 74 (72–79) months. We found that survival was significantly related to the amount of residual disease prior to IPHC with a trend to longer survival with the interval from initial treatment to IPHC $>$ 9 months. Among the ‘comparison group’ the following were found to be significantly related to outcome: extent of residual disease, [25,34,36] patient age [25] and the interval from diagnosis to IPHC. [25] Reflecting performance of studies in surgical oncology centers, the peritoneal cancer index (PCI) was also reported to be of significance. [25,34,36] The PCI is a clinical integration of peritoneal implant size and lesion distribution within the abdominal cavity widely used by surgical oncologists managing peritoneal surface malignancies [38].

In total these results confirm that in some patients with extensive recurrence of ovarian carcinoma extended survival can be obtained using a combination of surgical cytoreduction and intraperitoneal chemotherapy delivered with hyperthermia. It is not possible to differentiate the relative contributions of these three modalities in small non-randomized studies. In vitro data demonstrating synergy between chemotherapy and heat as well as the relatively low toxicity of IPHC suggest that further research should be performed using this combination. The use

of IPHC earlier in the natural history of ovarian carcinoma might yield even better outcomes. If outcome is related to the completeness of eradication of disease front-line then IPHC given at the time of front-line surgery is intuitively a better choice. This idea was first reported by Steller et al. [22] in a phase I study of 6 patients at the National Cancer Institute investigating the use of carboplatin. Little has been reported on this front-line use [35,39]. If treatment is given at this time disease volume is minimal, all peritoneal surfaces are exposed to the heat and chemotherapy and treatment would be started many days prior to conventional treatment. Within the surgical oncology field there has been interest in giving extended normothermic chemotherapy in the early postoperative period for the same reasons [35,40] and this field is open for further research in ovarian cancer. The challenge would be to integrate these treatments into an emerging normothermic intraperitoneal front-line treatment program.

Another time to consider giving IPHC is as consolidation at second look surgery. Notwithstanding the excellent prolongation of life demonstrated by the incorporation of intraperitoneal delivery of cisplatin and paclitaxel into front-line therapy [8] no less than 65% of the patients receiving this form of treatment recurred. This reinforces the need for continued research into methods of reducing recurrence rates. The use of IPHC in this fashion has been reported [41,42] but further work is needed.

Conclusion

Secondary surgery and intraperitoneal hyperthermic chemotherapy can extend survival in selected patients with recurrent/persistent ovarian cancer. Further research is needed to develop better selection criteria and more effective agents.

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