

Cytoreduction and intraperitoneal heated chemotherapy for the treatment of endometrial carcinoma recurrent within the peritoneal cavity

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Abstract. Helm CW, Toler CR, Martin RS III, Gordinier ME, Parker LP, Metzinger DS, Edwards RP. Cytoreduction and intraperitoneal heated chemotherapy for the treatment of endometrial carcinoma recurrent within the peritoneal cavity. *Int J Gynecol Cancer* 2007;17:204–209.

Our experience with hyperthermic intraperitoneal chemotherapy (IPHC) in conjunction with surgical resection for endometrial cancer recurrent within the abdominal cavity was reviewed. Eligible patients underwent exploratory laparotomy with the aim of resecting disease to ≤ 5 mm maximum dimension followed immediately by intraperitoneal perfusion of cisplatin (100 mg/m^2) heated to $41\text{--}43^\circ\text{C}$ ($105.8\text{--}109.4^\circ\text{F}$) for 1.5 h. Data for analysis was extracted from retrospective chart review. Five patients underwent surgery and IPHC between September 2002 and January 2005 for abdomino-pelvic recurrence. Original stage and histology were 1A papillary serous (1), 1C endometrioid with clear cell features (1), and 1B endometrioid (3). Mean age was 61 (41–75) years, mean prior laparotomies were 1.4 (1–2), and mean chemotherapy agent exposure was 1.6 (0–4). Mean time from initial treatment to surgery and IPHC was 47 (29–66) months. Mean length of surgery was 9.8 (7–11) h after which three patients had no residual disease and two had ≤ 5 mm disease. The mean duration of hospital stay was 12.6 (6–20) days. Postoperative surgical complications included wound infection with septicemia in one patient. Mean maximum postoperative serum creatinine was 1.02 (0.6–1.70) mg/dL. There was no ototoxicity or neuropathy and no perioperative mortality. No patients have been lost to follow-up. Two are living disease free at 28 and 32 m and two are living with disease at 12 and 36 m. One patient died at 3 m without evidence of cancer. Two patients who had no residual macroscopic disease at the end of surgery are alive at 32 and 36 m. The combination of IPHC with surgery for recurrent endometrial carcinoma is relatively well tolerated. The unexpectedly long survival seen in this cohort supports a phase II trial of IPHC with cisplatin for recurrent endometrial cancer.

KEYWORDS: cisplatin, hyperthermia, intraperitoneal chemotherapy, IPHC, recurrent endometrial cancer.

In the United States, endometrial carcinoma is the most common invasive malignancy of the female genital tract⁽¹⁾. The majority of patients present with early disease and because of this the overall cure rate is high⁽²⁾. However, when endometrial carcinoma does recur, it has a poor prognosis⁽³⁾. Only patients with isolated endometrial cancer recurrence are considered

potentially curable, and results are poor even when this is only a vaginal cuff recurrence^(4,5).

Normothermic intraperitoneal therapy has been shown to be effective in ovarian cancer^(6–8), and thus, we hypothesize that small-volume endometrial carcinoma within the peritoneal cavity should be a similarly good target.

The addition of hyperthermia to the chemotherapy is supported by *in vitro* and *in vivo* animal data, which demonstrate that not only is heat alone tumoricidal⁽⁹⁾ but it also increases the cytotoxicity of many chemotherapeutic agents, including agents active in endometrial cancer such as cisplatin, carboplatin, and doxorubicin, both in human cell culture and in animal

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models^(10–15). It has been reported that heat may reverse cisplatin resistance⁽¹⁶⁾.

The possible synergy between hyperthermia and chemotherapy treatment in patients with peritoneal disease has sparked clinical trials in many disease types including gastric cancer⁽¹⁷⁾, malignant mesothelioma⁽¹⁸⁾, appendix cancer⁽¹⁹⁾, as well as colorectal and ovarian cancer^(20–30); all have shown promising results. A phase III randomized study of hyperthermic intraperitoneal chemotherapy (IPHC) following debulking 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⁽³¹⁾.

Based on the hypothesis that recurrent endometrial cancer with disease confined to the peritoneal cavity should be a good target for intraperitoneal therapy in combination with heat, we treated five patients with IPHC following surgical cytoreduction.

Materials and methods

After obtaining Institutional Review Board approval, a retrospective chart review was performed to obtain data on patients who had undergone IPHC after secondary surgical cytoreduction for recurrent endometrial carcinoma.

Inclusion criteria were the presence of pathologically proven, recurrent endometrial carcinoma of any histologic subtype with disease confined to the peritoneal cavity, and cytoreduced to ≤ 5 mm. Patients with liver or retroperitoneal lymph nodal involvement were eligible provided the disease was amenable to surgical resection. Patients needed to be medically fit for surgery and chemotherapy.

After giving informed consent, patients underwent exploratory laparotomy with the aim of resecting all disease down to no visible disease or at most the largest lesion size to ≤ 5 mm. Lesion size was measured with a ruler on sterile paper tape or scalpel handle.

Following the optimal surgical resection, IPHC was delivered in the following manner: After induction of anesthesia, a urethral catheter with heat sensor probe was placed in the bladder (Precision 400; Tyco Healthcare Group, Mansfield, MA) and the anesthesiologist placed an esophageal heat sensor (DeRoyal, Powell, TN). Following initial draping of the chest and legs, a large sterile IobanTM-2 adhesive drape (3M Corp., St Paul, MN) was placed over the entire operative area extending laterally beyond the anterior superior iliac

spine—mid-axillary line on each side. One hour 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 by turning the warming blanket off and lowering the air temperature in the operating room.

Upon completion of debulking surgery, the patient was prepared for IPHC (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 3/8 inch needle connected to a 96 inch PDS #1 loop (Ethicon Inc., Somerville, NJ) in a running, "baseball" fashion. Care was taken to ensure that the skin edges were not inverted, and that the skin was tightly apposed around the tubing.

About 30 min prior to placement of the tubing, the perfusionist prepared the ThermochemTM HT-1000 modified heat-exchange pump (ViaCirq Inc., Pittsburgh, PA). With the wound closed, the inflow and outflow tubing was connected and the preheated DeflexTM peritoneal dialysis solution (Fresenius Medical Care, Lexington, MA) allowed to fill the cavity. The patient was placed in steep Trendelenberg to allow air to be expelled through the outflow tubing. Between 2 and 3 L were required to distend the cavity and achieve a flow rate of approximately 1500 cc/min. The patient was leveled when equilibrium was reached. Once the temperature probes showed a consistent inflow temperature of 43°C and outflow of 42°C, the cisplatin was added to the perfusate. The perfusion was 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, and these were secured with sutures of 0 polyglactin 910 (Vicryl; Ethicon Inc., Somerville, NJ).

At the completion of perfusion, the perfusate was drained into the waste container attached to the ThermochemTM HT-1000 machine. The abdomen was carefully opened with a 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 discarded by placing in dangerous substance containers. Gowns and gloves were changed and the surgery was completed.

Postoperatively patients were routinely followed in the intensive care unit and attempts were made to maintain a urine output of at least 100 mL/h for the first 72 h. Following discharge from hospital, patients were treated with adjuvant chemotherapy directed by drug resistance assays (Oncotech Inc., Palo Alto, CA) usually followed by progestagen. All patients were followed with clinical examination and CA125 and radiologic investigations when indicated. In the absence of disease, routine follow-up was performed every 3 months. Overall survival and progression-free survival were analyzed using the Kaplan–Meier method.

Results

Between September 2002 and January 2005, five patients underwent IPHC following secondary surgical cytoreduction for recurrent endometrial carcinoma. The mean age of the patients was 61 (41–75) years. All were originally early stage at the time of initial presentation, and the stage and histologic types were papillary serous 1A ($n = 1$), endometrioid 1B ($n = 3$), and endometrioid 1C ($n = 1$). The mean interval from initial surgery to IPHC was 47 (26–66) months. Three patients had received prior chemotherapy. One patient had received prior whole-pelvis radiation and another vaginal brachytherapy (Table 1). No patients received adjuvant chemotherapy following initial surgery. The mean time to recurrence from completion of initial treatment was 36.6 (22–52) months. Preoperative work-up included computed tomography (CT) ($n = 2$) and positron emission tomography (PET)/CT ($n = 3$). All patients had disease in both the abdomen and pelvis.

All patients underwent exploratory laparotomy with surgical resection of recurrent disease. Three patients had no residual disease, one patient had maximum residual lesion size of 2 mm, and one patient had 5 mm. All patients were treated with intraperitoneal perfusion of cisplatin 100 mg/m² at a temperature of 41–43°C for 90 min. The mean maximum

inflow temperature was 43°C (42.7–43.5) and mean minimum outflow temperature 41.5°C (39.9–42.7). The mean core temperature before IPHC was 33.98°C (32.4–35.3) and mean maximum core temperature during IPHC was 38.02°C (36.7–38.8). Tumor was sent for drug resistance assay.

All bowel anastomoses were performed after the IPHC. The mean hourly urine output for the first 72 h postoperatively was 158 (115–220) mL. Details of the surgical procedure are given in Table 2.

Complications were graded by CTEP v3.0 guidelines⁽³²⁾. There were no significant intraoperative complications, and there were no perioperative deaths within 28 days of surgery. One patient died at 3 months post-surgery of unrelated causes. All patients experienced grade 1 metabolic disturbances, which were easily corrected. The peak mean postoperative serum creatinine was 1.02 mg/dL (0.6–1.7), and all were within the institutional normal range by discharge. Grade 3 metabolic disturbances included hyponatremia ($n = 1$), hypoalbuminemia ($n = 2$), and hypokalemia ($n = 1$). One patient developed congestive heart failure, with cytologically negative pleural effusions, ventricular tachycardia, and cardiogenic shock. One patient developed pneumonia and metabolic alkalosis, and one developed septicemia probably related to chronic infection from mesh placement at previous ventral hernia repair. Her wound responded to local treatment and eventually healed 9 months after IPHC. This patient experienced incisional discomfort and exacerbation of chronic diarrhea that had been present since cholecystectomy 4 years prior to IPHC. All these complications responded to therapy.

Postoperative treatment and outcome are detailed in Table 3. One patient died of natural causes without evidence of disease 3 months following IPHC and did not receive additional adjuvant therapy. Of the 4 surviving patients, 2 are without disease. Two of the 3 without macroscopic residual at the end of surgery prior to IPHC are alive at 32 and 36 months. Recurrence in the upper abdomen in one responded to chemotherapy.

Table 1. Patient detail

Patient	Age (years)	Original FIGO stage	Original histology	Months from initial surgery to IPHC	Prior laparotomy	Prior chemotherapy	Prior radiation
1	75	1A	Papillary serous	47	2	4	No
2	67	1C g2	Endometrioid	26	1	2	Whole pelvis
3	66	1B g3	Endometrioid	63	2	2	No
4	41	1B g1	Endometrioid	35	1	0	No
5	55	1B g2	Endometrioid	66	1	0	Vaginal

Table 2. Surgical detail

Patient	Duration of surgery (h)	Bowel procedures	Largest residual (mm)	Blood loss (mL)	Return of flatus (days)	Hospital stay (days)
1	10	Right hemicolectomy	0	500	5	12
2	7	Rectotomy repair ^a	0	350	3	12
3	11	0	0	800	7	13
4	11	Sigmoid serosa repair	2	1900	6	6
5	10	Right hemicolectomy	5	1500	9	20

^aPerformed prior to IPHC.

Discussion

To our knowledge, this is the first report of the use of IPHC at the time of secondary surgical debulking for recurrent endometrial carcinoma.

Possible treatments in patients with recurrent endometrial carcinoma have included intravenous chemotherapy, hormonal therapy, radiation, and surgery. Pelvic irradiation alone has a limited role for abdominal disease but has been used for isolated pelvic, para-aortic, and vaginal cuff recurrence. It is rarely effective for bulky disease⁽³³⁾. Initial response to single-agent chemotherapy is relatively good, doxorubicin 31%, epirubicin 26%, cisplatin 29%, carboplatin 31%, and paclitaxel 31%⁽³⁴⁾, but responses are more commonly partial than complete, lasting between 3–6 months with a mean time to progression of 4–6 months and median survival of only 7–10 months⁽³⁵⁾. The combination of doxorubicin, cisplatin, and paclitaxel with growth colony-stimulating factor was associated with a 57% response rate in a study including 263 patients. Despite this high response rate, there was only an 8.3 month progression-free interval and 15.3 months median survival and that with significant toxicity⁽³⁾. Although combination of paclitaxel and carboplatin have been reported to have good response rates^(36,37) when these agents were given in combination with amifostine to 47 women with advanced, recurrent, or refractory endometrial adenocarcinoma, the median

progression-free survival was only 7 months and overall survival 14 months⁽³⁸⁾. Response rates to hormonal therapy are between 21–31% with low-dose medroxyprogesterone acetate 26%⁽³⁹⁾, megestrol acetate 26%⁽⁴⁰⁾, and arzoxifen 31%⁽⁴¹⁾. Most remissions are partial in extent and short lasting, but when megestrol acetate was given sequentially with tamoxifen citrate, although the overall response rate was 27%, there were some long-term responders⁽⁴²⁾. Best responses are in those who are progesterone receptor positive and grade 1^(39,43).

For patients with a central pelvic recurrence following radiation therapy, pelvic exenteration gives a survival ranging from 20% to 45%^(44,45). Surgery has been used combined with other modalities to treat selected patients with recurrent disease including radiation⁽⁴⁶⁾ and hepatic intra-arterial chemotherapy at the time of maximal cytoreductive effort⁽⁴⁷⁾.

We chose to use intraperitoneal cisplatin for these patients because of its known *in vivo* activity in advanced, recurrent endometrial carcinoma, a wide experience reported for its use intraperitoneally both with heat^(20–30) and without heat^(7,8) in ovarian carcinoma, and the large *in vitro* data suggesting a strong synergistic effect with heat^(10–14,48). Investigations of the mechanism of the synergistic effect of heat on cisplatin activity have shown increased DNA cross-linking and increased DNA adduct formation^(11,48) and deeper penetration into peritoneal tumor implants⁽⁴⁸⁾.

Table 3. Postoperative treatment and outcome

Patient	Treatment post-IPHC	ER/PR status	Site of recurrence	Time to recurrence	Time since IPHC	Current status
1	Nil	Not known	n/a	3	3	Dead
2	Cyclophosphamide progestagen	+ / +	Right upper abdomen	18	36	Alive with cancer
3	Carboplatin progestagen	Not known	Nil	32	32	Alive disease free
4	WART, cis/doxo/taxol, progestagen	+ / +	Right upper abdomen, porta hepatis	7	28	Alive disease free
5	Anastrozole	+ / -	Abdomen/pelvis	0	12	Alive with cancer

ER, estrogen receptor; PR, progesterone receptor; n/a, not applicable, WART, whole abdomen radiation; cis, cisplatin; doxo, doxorubicin; taxol, paclitaxel.

Our experience with these five patients mirrors reports in other cancers that the delivery of IPHC is relatively safe and most of the morbidity is associated with the radical surgery and not with the IPHC. Despite surgeries lasting between 7 and 11 h, the mean time to discharge from the hospital was 12.6 days, and there were few long-term complications.

These five patients all had disease recurrent within the abdomen and pelvis and would otherwise have had a very poor prognosis with standard therapy (3,33–35,38–41).

Despite the advanced nature of these intraperitoneal recurrences, four of the five patients are still alive at 12, 28, 32, and 36 months from surgery and IPHC (Fig. 1). Of the three patients who were completely cytoreduced prior to IPHC, one died at 3 months, but the progression-free survival in the other two was 18 and 32 months (Fig. 2). The patients with visible disease at the end of surgery had much shorter times to progression, suggesting that the aim of surgery should be to achieve microscopic residuals only. Despite the disease recurrence, all patients are alive with good performance status.

Increased use of PET scanning and serum CA125 levels may help identify patients earlier in their recurrence at a time when they would be theoretically even better candidates for this aggressive therapy. In our series, three of the five patients underwent PET scanning to exclude metastatic disease outside of the abdominal cavity so that surgery would not be performed without chance of complete resection of disease.

Although the numbers are small, our results suggest a possible role for IPHC in patients with endometrial carcinoma recurrent within the peritoneal cavity. In addition, consideration might be given to using this combined modality therapy for patients with poor

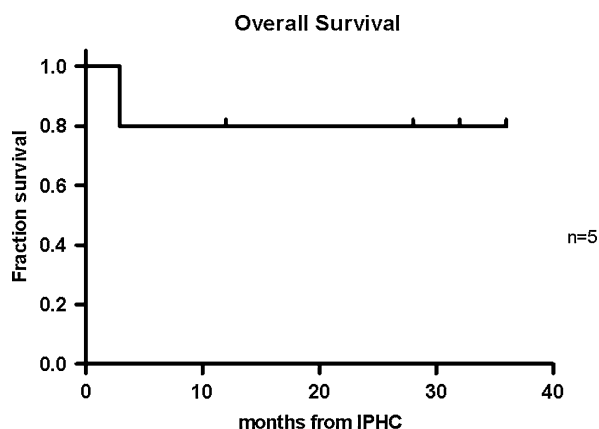


Figure 1. Overall survival.

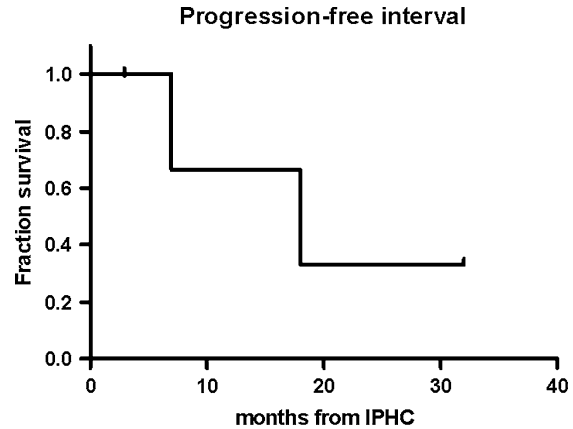


Figure 2. Progression-free interval.

prognostic histologic subtypes such as papillary serous carcinoma at the time of initial surgery. This is a technique that requires further research.

References

- American Cancer Society. *Cancer facts and figures 2005*. Atlanta, GA: American Cancer Society, 2005.
- Creasman WT, Odicino F, Maisonneuve P *et al*. Carcinoma of the corpus uteri. *Int J Gynaecol Obstet* 2003;**1**:79–118.
- Fleming GF, Filiaci VL, Bentley RC *et al*. Phase III randomized trial of doxorubicin + cisplatin versus doxorubicin + 24-h paclitaxel + filgrastim in endometrial carcinoma: a Gynecologic Oncology Group study [see comment]. *Ann Oncol* 2004;**15**:1173–8.
- Kuten A, Grigsby PW, Perez CA, Fineberg B, Garcia DM, Simpson JR. Results of radiotherapy in recurrent endometrial carcinoma: a retrospective analysis of 51 patients. *Int J Radiat Oncol Biol Phys* 1989;**17**:29–34.
- Barakat R, Grigsby PW, Sabbatini P, Zaino RJ. Corpus: epithelial tumors. In: Hoskins WJ, Perez CA, Young RC, eds. *Principles and practice of gynecologic oncology*. Philadelphia, PA: Lippincott Williams and Wilkins, 2000:919–79.
- 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 Engl J Med* 1996;**335**:1950–5.
- 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 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**:1001–7.
- Armstrong DD, Bundy B, Wenzel L *et al*. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med* 2006;**354**:34–43.
- Giovanella BC, Stehlin JS Jr, Morgan AC. Selective lethal effect of supranormal temperatures on human neoplastic cells. *Cancer Res* 1976;**36**(Pt 1):3944–50.
- Hahn GM. Potential for therapy of drugs and hyperthermia. *Cancer Res* 1979;**39**(Pt 2):2264–8.
- Meyn RE, Corry PM, Fletcher SE, Demetriades M. Thermal enhancement of DNA damage in mammalian cells treated with cis-diamminedichloroplatinum(II). *Cancer Res* 1980;**40**:1136–9.
- Alberts DS, Peng YM, Chen HS, Moon TE, Cetas TC, Hoeschele JD. Therapeutic synergism of hyperthermia-cis-platinum in a mouse tumor model. *J Natl Cancer Inst* 1980;**65**:455–61.
- Los G, van Vugt MJ, Pinedo HM. Response of peritoneal solid tumours after intraperitoneal chemohyperthermia treatment with cisplatin or carboplatin. *Br J Cancer* 1994;**69**:235–41.

- 14 Akaboshi M, Tanaka Y, Kawai K, Akuta K, Masunaga S, Ono K. Effect of hyperthermia on the number of platinum atoms binding to DNA of HeLa cells treated with ^{195m}Pt-radiolabelled cis-diaminedichloroplatinum(II). *Int J Radiat Biol* 1994;**66**:215–20.
- 15 Mohamed F, Marchettini P, Stuart OA, Urano M, Sugarbaker PH. Thermal enhancement of new chemotherapeutic agents at moderate hyperthermia. *Ann Surg Oncol* 2003;**10**:463–8.
- 16 Herman TS, Teicher BA, Cathcart KN, Kaufmann ME, Lee JB, Lee MH. Effect of hyperthermia on cis-diaminedichloroplatinum(II) (rhodamine 123)2[tetrachloroplatinum(II)] in a human squamous cell carcinoma line and a cis-diaminedichloroplatinum(II)-resistant subline. *Cancer Res* 1988;**48**:5101–5.
- 17 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**:884–91.
- 18 Loggie BW, Fleming RA, McQuellon RP, Russell GB, Geisinger KR, Levine EA. Prospective trial for the treatment of malignant peritoneal mesothelioma. *Am Surg* 2001;**67**:999–1003.
- 19 Sugarbaker PH, Chang D. Results of treatment of 385 patients with peritoneal surface spread of appendiceal malignancy. *Ann Surg Oncol* 1999;**6**:727–31.
- 20 Bartlett DL, Buell JF, Libutti SK *et al*. A phase I trial of continuous hyperthermic peritoneal perfusion with tumor necrosis factor and cisplatin in the treatment of peritoneal carcinomatosis [erratum appears in *Cancer* 1998;**83**:2241]. *Cancer* 1998;**83**:1251–61.
- 21 Loggie BW, Sterchi JM, Rogers AT *et al*. Intraperitoneal hyperthermic chemotherapy for advanced gastrointestinal and ovarian cancers. *Reg Cancer Treat* 1994;**2**:78–81.
- 22 Cavaliere F, Perri P, Di Filippo F *et al*. Treatment of peritoneal carcinomatosis with intent to cure. *J Surg Oncol* 2000;**74**:41–4.
- 23 van der Vange N, van Goethem AR, Zoetmulder FA *et al*. Extensive cytoreductive surgery combined with intra-operative intraperitoneal perfusion with cisplatin under hyperthermic conditions (OVHIPEC) in patients with recurrent ovarian cancer: a feasibility pilot. *Eur J Surg Oncol* 2000;**26**:663–8.
- 24 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**:120–6.
- 25 Panteix G, Beaujard A, Garbit F *et al*. Population pharmacokinetics of cisplatin in patients with advanced ovarian cancer during intraperitoneal hyperthermia chemotherapy. *Anticancer Res* 2002;**22**:1329–36.
- 26 Helm CW, Martin RS, Metzinger DS, Edwards RP. Secondary surgical cytoreduction and hyperthermic intraperitoneal chemotherapy for recurrent ovarian and endometrial cancer. *International Gynecologic Cancer Society* 2004;**14**(Suppl. 1):167.
- 27 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**:1040–5.
- 28 Reichman TW, Cracchiolo B, Sama J *et al*. Cytoreductive surgery and intraoperative hyperthermic chemoperfusion for advanced ovarian carcinoma. *J Surg Oncol* 2005;**90**:51–6.
- 29 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.
- 30 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**:90]. *Cancer Chemother Pharmacol* 1999;**43**:106–14.
- 31 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**:979–84.
- 32 National Cancer Institute: Cancer Therapy Evaluation Program common terminology criteria for adverse events v3.0. Available at: <http://ctep.cancer.gov/forms/CTCAEv3.pdf>
- 33 Lin LL, Grigsby PW, Powell MA, Mutch DG. Definitive radiotherapy in the management of isolated vaginal recurrences of endometrial cancer. *Int J Radiat Oncol Biol Phys* 2005;**63**:500–04.
- 34 Thigpen JT, Brady MF, Homesley HD *et al*. Phase III trial of doxorubicin with or without cisplatin in advanced endometrial carcinoma: a gynecologic oncology group study. *J Clin Oncol* 2004;**22**:3902–8.
- 35 Levine DA, Hoskins WJ. Update in the management of endometrial cancer. *Cancer J* 2002;**8**(Suppl. 1):31–40.
- 36 Price FV, Edwards RP, Kelley JL, Kunschner AJ, Hart LA. A trial of outpatient paclitaxel and carboplatin for advanced, recurrent and histologic high-risk endometrial carcinoma: preliminary report. *Semin Oncol* 1997;**24**:S15–78–82.
- 37 Hoskins PJ, Swenerton KD, Pike JA *et al*. Paclitaxel and carboplatin, alone or with irradiation, in advanced or recurrent endometrial cancer: a phase II study. *J Clin Oncol* 2001;**19**:4048–53.
- 38 Scudder SA, Liu PY, Wilczynski SP *et al*. Paclitaxel and carboplatin with amifostine in advanced, recurrent, or refractory endometrial adenocarcinoma: a phase II study of the Southwest Oncology Group. *Gynecologic Oncology* 2005;**96**:610–5.
- 39 Thigpen JT, Blessing JA, Hatch KD, Barrett R, Adelson M, DiSaia PJ. Oral medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial carcinoma. *J Clin Oncol* 1999;**17**:1736–44.
- 40 Lentz SS, Brady MF, Major FJ, Reid GC, Soper JT. A phase II trial of high dose megestrol acetate (Megace) in advanced or recurrent endometrial carcinoma. *J Clin Oncol* 1996;**14**:357–61.
- 41 McMeekin DS, Gordon A, Fowler J *et al*. A phase II trial of arzoxifene, a selective estrogen response modulator, in patients with recurrent or advanced endometrial cancer. *Gynecologic Oncology* 2003;**90**:64–9.
- 42 Fiorica JV, Brunetto VL, Hanjani P *et al*. Phase II trial of alternating courses of megestrol acetate and tamoxifen in advanced endometrial carcinoma: a Gynecologic Oncology Group study [see comment]. *Gynecologic Oncology* 2004;**92**:10–4.
- 43 Markman M. Hormonal therapy of endometrial cancer. *Eur J Cancer* 2005;**41**:673–5.
- 44 Barakat RR, Goldman NA, Patel DA, Venkatraman ES, Curtin JP. Pelvic exenteration for recurrent endometrial cancer. *Gynecologic Oncology* 1999;**75**:99–102.
- 45 Morris M, Alvarez RD, Kinney WK, Wilson TO. Treatment of recurrent adenocarcinoma of the endometrium with pelvic exenteration. *Gynecologic Oncology* 1996;**60**:288–91.
- 46 Aalders JG, Abeler V, Kolstad P. Recurrent adenocarcinoma of the endometrium: a clinical and histopathological study of 379 patients. *Gynecologic Oncology* 1984;**17**:85–103.
- 47 Scarabelli C, Campagnutta E, Giorda G *et al*. Maximal cytoreductive surgery as a reasonable therapeutic alternative for recurrent endometrial carcinoma. *Gynecologic Oncology* 1998;**70**:90–3.
- 48 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**:148–54.

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