J Cancer Res Clin Oncol (2009) 135:1637–1645
DOI 10.1007/s00432-009-0667-4

REVIEW

Intraoperative hyperthermic intraperitoneal chemotherapy after cytoreductive surgery in ovarian cancer peritoneal carcinomatosis: systematic review of current results

Terence C. Chua · Greg Robertson · Winston Liauw · Rhonda Farrell · Tristan D. Yan · David L. Morris

Received: 18 July 2009 / Accepted: 7 August 2009 / Published online: 23 August 2009

Abstract
Background Advanced and recurrent ovarian cancer results in extensive spread of tumor on the peritoneal surfaces of the abdomen and pelvis. We collectively review studies in the literature that report the efficacy of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) for ovarian cancer peritoneal carcinomatosis.
Methods An electronic search of all relevant studies published in peer-reviewed journals before May 2009 was performed on three databases. The quality of each study was independently assessed and classified according to the time point of HIPEC use in various setting of ovarian cancer from the consensus statement of the Peritoneal Surface Oncology Group. Clinical efficacy was synthesized through a narrative review with full tabulation of the results of each included study.
Results Nineteen studies each of more than ten patients reporting treatment results of HIPEC of patients with both advanced and recurrent ovarian cancer were included and data were extracted. All studies were observational case series. The overall rate of severe perioperative morbidity ranged from 0 to 40% and mortality rate varied from 0 to 10%. The overall median survival following treatment with HIPEC ranged from 22 to 64 months with a median disease-free survival ranging from 10 to 57 months. In patients with optimal cytoreduction, a 5-year survival rate ranging from 12 to 66% could be achieved.
Conclusion Despite the heterogeneity of the studies reviewed, current evidence suggest that complete CRS and HIPEC may be a feasible option with potential benefits that are comparable with the current standard of care. A randomized trial is required to establish the role of HIPEC in ovarian cancer.

Keywords Ovarian cancer · Peritoneal neoplasm · Hyperthermia · Cytoreductive surgery · Intraperitoneal chemotherapy · Hyperthermic intraperitoneal chemotherapy

T. C. Chua (✉) · T. D. Yan · D. L. Morris (✉)
Department of Surgery, St George Hospital,
University of New South Wales, Kogarah,
Sydney, NSW 2217, Australia
e-mail: Terence.Chua@unsw.edu.au

D. L. Morris
e-mail: David.Morris@unsw.edu.au

G. Robertson · R. Farrell
Department of Gynaecology Oncology,
St George Hospital, Kogarah,
Sydney, NSW 2217, Australia

W. Liauw
Cancer Care Centre, St George Hospital, Kogarah,
Sydney, NSW 2217, Australia

Introduction

Ovarian cancer is the third commonest and most lethal malignancy gynecological malignancy (Jemal et al. 2007). Epithelial ovarian tumors account for majority (>70%) of all ovarian cancers. It typically presents with vague gastrointestinal and constitutional symptoms of abdominal bloating, distension, weight loss, and fatigue (Goff et al. 2000). Owing to the heterogeneity of these clinical symptoms, early diagnosis is often delayed. Late presentation results in the majority of patients being diagnosed with advanced

disease (Stage III/IV). The 5-year survival rate of patients with advanced ovarian cancer is <25% (Ozols 2005). In the final stages of this disease, patients suffer from severe anorexia, dyspnea and pain from malignant bowel obstruction, ascites, and pleural effusion as a result of the extensive burden of tumor.

Epithelial ovarian tumor arises from the serosal lining of the ovary. This covering of the ovary communicates with the serosal lining of the abdominopelvic cavity, and is known as the peritoneum. Tumor growth results in the exfoliation of malignant cells into the peritoneal fluid. They circulate freely and typically implant in the pelvis and subdiaphramatic recesses owing to gravity and the incumbent position. This spread of tumor within the peritoneum is termed peritoneal carcinomatosis (Sugarbaker 1996). Intraoperatively, it is characterized by the extensive presence of macroscopic whitish tumor nodules of variable sizes and consistency that may coalesce to form plaques or masses within the abdominopelvic cavity. Tumor dissemination from the peritoneal cavity into the pleural cavity may also occur through the lymphatic lacunae present within the diaphragmatic peritoneum (Abu-Hijleh et al. 1995; Carmignani et al. 2003). This results in severe pleural effusion which compromises lung and cardiac functions. In the past, peritoneal carcinomatosis was regarded as a terminal condition and patients were treated symptomatically. However, as this disease is largely confined to the peritoneal surfaces, it is now considered a loco-regional disease.

The feasibility of hyperthermic intraperitoneal chemotherapy (HIPEC) as a treatment for peritoneal carcinomatosis was first demonstrated by Spratt et al. (1980) in the early 1980s. Its development continued under Dr. Sugarbaker from the Washington Cancer Institute in the mid-1990s who advocated this combined procedure of surgical resections and hyperthermic chemoperfusion to achieve complete intraoperative cytoreduction. This procedure involves cytoreductive surgery (CRS) with peritonectomy procedures aimed at resecting peritoneal surfaces with tumor implants and visceral dissections with a maximal surgical effort to remove as much tumor as possible macroscopically, followed by direct instillation of heated chemotherapy which together serves as a synergistic medium to enhance cytotoxicity to address microscopic residual disease (Witkamp et al. 2001). The results of this treatment have been shown to be beneficial for patients with peritoneal carcinomatosis from appendiceal cancer (Yan et al. 2007a), colorectal cancer (Yan et al. 2006), and peritoneal mesothelioma (Yan et al. 2007b).

This study aims to provide a collective review of the current evidence available for the combined regimen of CRS and HIPEC for ovarian cancer peritoneal carcinomatosis.

Methods

Literature search strategy

A literature search was conducted using the MEDLINE (1966 to August May 2009), PubMed (January 1980 to May 2009) and EMBASE (1974 to May 2009) databases. The reference lists of articles identified were manually searched to locate other articles of relevance. The search was limited to English language articles and to humans. The search terms used to locate studies were 'Ovarian cancer', 'Intraperitoneal', and 'Cytoreductive surgery'. All relevant articles identified were assessed with application of inclusion and exclusion criteria.

Selection criteria

The selection criteria were as follows: all studies >10 patients, adopting the combined CRS and HIPEC treatment with a diagnosis of advanced (Stage III/IV) or recurrent ovarian cancer. Studies which included the results of other gastrointestinal and pelvic malignancies were included if the results of the ovarian cancer subjects were analyzed separately and clearly reported. We excluded studies reporting the pharmacokinetic data (Phase I studies). Where multiple publications from the same institution were identified, only the most recent update with the largest number of patients or longer follow-up group was included. CRS consisted of peritonectomy procedures (anterior parietal peritonectomy, omentectomy ± splenectomy, right and left subphrenic peritonectomy, pelvic peritonectomy, and lesser omentectomy with stripping of the omental bursa ± cholecystectomy) and visceral resections (rectosigmoidectomy, right colectomy, total abdominal colectomy, hysterectomy, and small bowel resection) (Sugarbaker 1995). The type and extent of peritonectomy procedures were not uniformly performed in all the studies included. HIPEC was administered intraoperatively after CRS. Studies were selected for evaluation if they were level I evidence: randomized controlled trials (RCTs); level II evidence: nonrandomized controlled clinical trials or well-designed cohort studies; level III evidence: observational studies, as described by the US Preventive Services Task Force.

Data extraction and critical appraisal

The studies were independently and critically appraised using a standard protocol. Data extracted include the methodology, quality criteria, perioperative variables, and the morbidity and mortality outcomes. All data were extracted and tabulated from the relevant articles' texts, tables, and figures.

The patient group treated in each study was classified according to the indications for treatment for CRS and HIPEC at five time points in the natural history of ovarian cancer as described by the consensus of the Peritoneal Surface Oncology Group: (1) at the time of primary treatment where optimal cytoreduction is achieved, (2) at the time of interval debulking, (3) as a consolidation therapy following complete pathological response following initial therapy as confirmed by a second-look laparotomy, (4) at the time of first recurrence, and (5) as salvage therapy (Helm et al. 2008).

Discrepancies were resolved by discussion and consensus. Following tabulation of the results, study design, year of publication, number of patients, criteria used to define CRS, completeness of cytoreduction, HIPEC protocol, treatment outcomes, treatment-related morbidity and mortality, and prognostic factors associated with outcomes were synthesized. Meta-analysis was inappropriate because of the heterogeneous nature of the included studies and the lack of a comparative arm in most studies. Clinical effectiveness was synthesized through a narrative review with full tabulation of results of all included studies.

Results

The search revealed a total of 132 abstracts from which 19 studies employed a combined regime of CRS and HIPEC in the treatment of patients with ovarian cancer peritoneal carcinomatosis. These were retrieved and appraised in this review. None of the studies reviewed were randomized trials. The level of evidence in the studies reviewed were mostly class II or class III (nonrandomized comparative studies and observational studies). In addition, the patient cohort treated was of a heterogeneous group. Most studies included patients with either advanced or recurrent ovarian cancer who have undergone previous surgery and chemotherapy. A significant proportion of the patients within these studies also had documented chemoresistance and had undergone multiple treatments (time point 5). The full details are listed in Tables 1 and 2.

Time-point of use of HIPEC

All 19 studies reviewed performed HIPEC as part of the combined treatment with cytoreduction. However, the HIPEC protocol varied in each institution. The most commonly used

Table 1 Patient characteristics from 19 studies comprising of 895 patients

First author	Level of evidence	Patients, *n*	Patient's disease status	Patients with chemoresistance	Previous surgery	Previous chemotherapy
Bereder et al. (2009)	Class III	246	Advanced (62) and recurrent (184) ovarian cancer	Yes	Yes	Yes
Pavlov (2009)	Class III	56	Advanced (31) and recurrent (25) ovarian cancer	NR	Yes	Yes
Fagotti (2009)	Class III	25	Recurrent ovarian cancer (25)	Yes	Yes	Yes
Guardiola et al. (2009)	Class III	47	Advanced ovarian cancer (47)	NR	Yes	Yes
Di Giorgio et al. (2008)	Class II	47	Advanced (22) and recurrent (25) ovarian cancer	NR	Yes	Yes
Bae et al. (2007)	Class II	67	Advanced ovarian cancer	No	Yes	Yes
Cottee (set al. 2007)	Class III	81	Recurrent ovarian cancer	Yes	Yes	Yes
Helm et al. (2007)	Class III	18	Recurrent ovarian cancer	Yes	Yes	Yes
Rufian et al. (2006)	Class III	33	Advanced (19) and recurrent (14) ovarian cancer	Yes	Yes (14), no (19)	Yes (14), no (19)
Raspagliesi et al. (2006)	Class III	40	Recurrent ovarian cancer	Yes	Yes	Yes
Reichman et al. (2005)	Class III	13	Advanced ovarian cancer	NR	No	Yes
Gori et al. (2005)	Class III	29	Advanced ovarian cancer	NR	Yes	Yes
Look et al. (2004)	Class III	28	Advanced ovarian cancer	NR	Yes (24), no (4)	Yes (18), no (6)
Ryu et al. (2004)	Class II	57	Advanced ovarian cancer	No	Yes	Yes
Piso et al. (2004)	Class III	19	Advanced (8) and recurrent (11) ovarian cancer	NR	NR	Yes (13)
Zanon et al. (2004)	Class II	30	Recurrent ovarian cancer	NR	NR	Yes
Chatzigeorgiou et al. (2003)	Class III	20	Recurrent ovarian cancer	Yes	Yes	Yes
de Bree et al. (2003)	Class III	19	Recurrent ovarian cancer	Yes	NR	Yes
Cavaliere et al. (2000)	Class III	20	Recurrent ovarian cancer	Yes	Yes	Yes

NR not reported

Table 2 Time-point of use of HIPEC and protocol reported in 19 studies

First author	Time-point of HIPEC use[a]	Definition of optimal cytoreduction (cm)	HIPEC drug and dose	Temperature (°C)	Duration (min)
Bereder et al. (2009)	2, 4, 5	0	Cisplatin, Cisplatin and Doxorubicin, Cisplatin and Mitomycin C	43	90
Pavlov et al. (2009)	1, 4, 5	0	Doxorubicin 0.1 mg/kg, Cisplatin 15 mg/m^2	40	120
Fagotti et al. (2009)	4, 5	<0.25	Oxaliplatin 460 mg/m^2	42	30
Guardiola et al. (2009)	2	<1	Cisplatin 90 mg/m^2	37	120
Di Giorgio et al. (2008)	1, 4, 5	<0.25	Cisplatin 75 mg/m^2	42–43	60
Bae et al. (2007)	2, 3	<1	Carboplatin 350 mg/m^2 or Paclitaxel 175 mg/m^2	43–44	90
Cotte et al. (2007)	5	<0.25	Cisplatin 20 mg/m^2	44–46	90
Helm et al. (2007)	5	≤0.5	Cisplatin 100 mg/m^2 or Mitomycin C 30–40 mg	41–43	90
Rufian et al. (2006)	1, 4	≤1	Paclitaxel 60 mg/m^2	41–43	60
Raspagliesi et al. (2006)	3, 5	0	Cisplatin 25 mg/m^2/l and Mitomycin C 3.3 mg/m^2/l or Cisplatin 43 mg/l and Doxorubicin 15.25 mg/l	42.5	NR
Reichman et al. (2005)	1, 4	<0.25	Cisplatin 50 mg/m^2	40	90
Gori et al. (2005)	3	<2	Cisplatin 100 mg/m^2	41–43	60
Look et al. (2004)	1, 5	<0.25	Cisplatin and Doxorubicin or Mitomycin C and 5FU	NR	90
Ryu et al. (2004)	2, 3	<1	Carboplatin 350 mg/m^2 and Interferon-α, 5,000,000 IU/m^2	43–44	90
Piso et al. (2004)	1, 4, 5	<0.25	Cisplatin 75 mg/m^2 or Mitoxantrone 15 mg/m^2	NR	90
Zanon et al. (2004)	2	<0.25	Cisplatin 100-150 mg/m^2	41.5	60
Chatzigeorgiou et al. (2003)	5	<1.5	Cisplatin 50-75 mg/m^2	39–40	120
de Bree et al. (2003)	4, 5	≤0.5	Doxetaxel 75 mg/m^2	41	NR
Cavaliere et al. (2000)	NR	<0.25	Mitomycin C 3.3 mg/m/L and Cisplatin 25 mg/m^2/l	41.5–42.5	90

NR not reported

[a] Time-points for use of HIPEC from the consensus of the Peritoneal Surface Oncology Group: (1) at the time of primary treatment where optimal cytoreduction is achieved, (2) at the time of interval debulking, (3) as a consolidation therapy after complete pathological response following initial therapy as confirmed by a second-look laparotomy, (4) at the time of first recurrence and (5) as salvage therapy

chemoperfusate was Cisplatin. The median intraabdominal temperature was 42°C with a range of 38–48°C. The median duration of infusion was 90 min with a range of 60–120 min. Eleven out of 19 studies employed the use of CRS and HIPEC as primary treatment for a proportion of their patients with advanced ovarian cancer. Eleven out of 19 studies employed the use of CRS and HIPEC as salvage therapy for patients with recurrent or persistent ovarian cancer peritoneal carcinomatosis, indicating that this group of patients have failed conventional treatment. The full details are listed in Table 2.

Perioperative mortality and morbidity results

In total, 895 patients from 19 different studies were reviewed. The mortality rate associated with treatment ranged from 0 to 10%. The median duration of operation and HIPEC treatment ranged from 4 to 10 h. The median length of hospital stay ranged from 8 to 25 days. Morbidity was analyzed and reported according to the National Cancer Institute, common toxicity criteria. Briefly, grade I postoperative complication was where the diagnosis was established but no intervention was required for resolution. Grade II postoperative complication was where medical treatments were required for resolution. Grade III postoperative complications required an invasive intervention such as a radiological intervention were required for resolution. Grade IV postoperative complication required urgent definitive intervention such as returning to the operating room or ICU were required for resolution. Grade I morbidity ranged from 6 to 70%, grade II morbidity ranged from 3 to 50%,

grade III morbidity ranged from 0 to 40% and grade IV morbidity ranged from 0 to 15%. Common postoperative complications include ileus, anastomotic leakage, bleeding, wound infection, toxicity, pleural effusion, infections, fistula, transient hepatitis, and thrombocytopenia. The full details are listed in Table 3.

Survival results

Although the use of CRS and HIPEC was at different time-points during the natural history of ovarian cancer, a tabulation approach to consolidate results of this treatment is presented to provide an indication of the treatment efficacy. The median time of follow-up ranged from 14 to 64 months, the median disease-free survival ranged from 10 to 57 months, the median overall survival ranged from 22 to 64 months, median overall survival for patient with an optimal cytoreduction ranged from 29 to 66 months, overall 3- year survival rate ranged from 35 to 63%, and 5-year survival rate ranged from 12 to 66%. The full details are listed in Table 4.

Discussion

Traditionally, patients with extensive ovarian cancer peritoneal carcinomatosis are often labeled as having terminal disease. Efforts at aggressive treatment are abandoned and treatment is largely palliative. Palliative surgery, where debulk or by-pass procedures are performed, or systemic chemotherapy is administered, both of which are not performed with a curative intent. The true result of whether this improves symptoms or extends survival is largely unknown (Ozols 2005). Presently, despite its availability in specialized surgical oncology institutions, HIPEC has not been advocated as a treatment option to existing 'curative' therapy in ovarian cancer.

Evident from our review, the use of the term CRS in the ovarian cancer literature has been shown to indicate varying extent of cytoreduction with residual tumor volume of 1–2 cm. Groups performing CRS using peritonectomy procedures assess the completeness of cytoreduction based on Jacquet and Sugarbaker's criteria of complete cytoreduction being $\leq$0.25 cm (Jacquet and Sugarbaker 1996). In addition, HIPEC was also performed at various time-points during the natural history of the disease and thus the treated group within this review comprised patients that have the following: newly diagnosed and treatment-naive advanced ovarian cancer, patients with their first recurrence following primary treatment, patients who have responded to primary treatment and are currently disease free, as well as patients who have recurrent and persistent ovarian cancer that have failed conventional treatment. This heterogeneity precluded the definitive conclusion of the survival results. However, efforts have been made to collectively tabulate and narrate the results of HIPEC in this heterogeneous group of patients with ovarian cancer peritoneal carcinomatosis to demonstrate the efficacy of this treatment.

Interest in the use of intraperitoneal chemotherapy for ovarian cancer was revived following the publication of results of the Gynecologic Oncology Group (GOG-172) phase III trial which compared intravenous chemotherapy with intravenous plus intraperitoneal chemotherapy in primary stage III ovarian cancer (Armstrong et al. 2006); the National Cancer Institute and GOG performed a meta-analysis of this treatment and made an announcement that this should become the standard of care (Trimble and Christian 2008). The treatment employed in this trial compared maximal cytoreduction followed by administration of adjuvant chemotherapy, cisplatin, and paclitaxel via both the intraperitoneal (IP) and intravenous (IV) route versus a group which only had IV chemotherapy. Although there were obvious survival benefits in the IP group, only 40% of patients were able to complete six cycles of chemotherapy due to high rates of IP catheter complications (Walker et al. 2006). Despite the low rates of treatment completion, survival benefits were still achieved, suggesting that limited use of IP chemotherapy is still purposeful. Therefore in clinical practice, this treatment is not routinely administered and has not become standard (Rowan 2009; Walker 2009).

In recurrent ovarian cancer, options for treatment are more varied with patients being subjected to various chemotherapy trials without any consensus for standard of care. Secondary cytoreduction in patients who have had a long disease-free survival may be beneficial as suggested by Bristow et al. (1996) in a meta-analysis. Medically, patients with platinum sensitive disease are treated with carboplatin with or without paclitaxel. In platinum-resistant disease, patients are often subjected to non-platinum agents such as topotecan, pegylated liposomal doxorubicin, gemcitabine, and oral etoposide (Ozols 2002). The overall median survival of secondary cytoreduction in recurrent ovarian cancer is about 40 months (Matsumoto et al. 2006; Salani et al. 2007). With systemic chemotherapy, the median disease-free survival in patients with platinum-sensitive disease was 9 months when treated with gemcitabine plus carboplatin (Pfisterer et al. 2006), 14 months when treated with doxetaxol plus oxaliplatin (Ferrandina et al. 2007). In patients with platinum-resistant disease, doxetaxol plus vinorelbine can achieve a median disease-free survival of 13 months and overall survival was 9 months (Aravantinos et al. 2003).

Given that complete cytoreduction from the surgical procedure is a strong prognostic factor for the overall survival (Bristow et al. 2002; Winter et al. 2007) and that a recent

Table 3 Perioperative mortality and morbidity results of 16 studies comprising of 895 patients with peritoneal carcinomatosis from ovarian cancer

First author	Year	Patients, *n*	Median duration of procedure (h)	Median length of hospital stay (days)	Mortality (%)	Morbidity (%)				Common postoperative complications
						Grade 1	Grade 2	Grade 3	Grade 4	
Bereder et al.	2009	246	NR	17	0.4	NR	NR	12		Sepsis
Pavlov et al.	2009	56	5	14	2	5	11	0	2	Ileus
Fagotti et al.	2009	25	5	13	0	0	36	8	8	Bleeding
Guardiola et al.	2009	47	7.2	18	0	NR	NR	NR	13	Infections, postoperative pain, intraabdominal bleeding
Di Giorgio et al.	2008	47	9[a]	22[a]	4	NR	21	9	13	Pleural effusion, wound infection
Bae et al.	2007	67	NR	NR	0	14	13	0	0	Transient hepatitis, thrombocytopenia
Cotte et al.	2007	81	4[a]	17[a]	3	6	1	5	2	Anastomotic leakage, fistula
Helm et al.	2007	18	10[a]	12[a]	6	11	50	40	13	Infections, pleural effusion
Rufian et al.	2006	33	5	11	0	12	10	10	6	Pleural effusion
Raspagliesi et al.	2006	40	7[a]	21[a]	0	20	NR	NR	NR	Toxicity
Reichman et al.	2005	13	NR	8	NR	NR	NR	NR	NR	NR
Gori et al.	2005	29	NR	NR	NR	NR	NR	NR	NR	NR
Look et al.	2004	28	NR	NR	0	NR	NR	7	4	Bleeding
Ryu et al.	2004	57	NR	NR	4	14	5	NR	4	Ileus
Piso et al.	2004	19	9	25	5	10	10	10	15	Anastomotic leakage
Zanon et al.	2004	30	6	12	3	27	3	7	7	Ileus
Chatzigeorgiou et al.	2003	20	NR	12	10	70	20	0	0	Ileus
de Bree et al.	2003	19	NR	NR	10	10	20	0	10	Wound infection
Cavaliere et al.	2000	20	10[a]	NR	NR	NR	NR	NR	NR	Fistula

NR not reported

[a] Refers to results expressed as mean

Table 4 Survival results of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy of 895 patients with peritoneal carcinomatosis from ovarian cancer

First author	Year	Patients, *n*	Median follow-up (months)	Median disease free survival (months)	Median overall survival (months)	Median overall survival for optimal cytoreduction (months)	Overall 3-year survival (%)	Overall 5-year survival (%)
Bereder et al. (2009)	2009	246	NR	13	49	56	60	35
Pavlov et al. (2009)	2009	56	60	26	38	NR	NR	NR
Fagotti et al. (2009)	2009	25	18	10	NR	NR	NR	NR
Guardiola et al. (2009)	2009	47	23	14	NR	NR	63[a]	NR
Di Giorgio et al. (2008)	2008	47	NR	20	24	26	NR	17
Bae et al. (2007)	2007	67	NR	NR	NR	NR	NR	66
Cotte et al. (2007)	2007	81	47	19	28	55	NR	NR
Helm et al. (2007)	2007	18	16[b]	10	31	31	NR	NR
Rufian et al. (2006)	2006	33	NR	NR	48	66	46	37
Raspagliesi et al. (2006)	2006	40	26	11	32	NR	NR	15
Reichman et al. (2005)	2005	13	14	15	NR	NR	55	NR
Gori et al. (2005)	2005	29	64[b]	57[b]	64	NR	NR	NR
Look et al. (2004)	2004	28	27	17	46	56	NR	NR
Ryu et al. (2004)	2004	57	47	26	NR	41	NR	54
Piso et al. (2004)	2004	19	24	18	33[b]	44[b]	NR	15
Zanon et al. (2004)	2004	30	19[b]	17	28	38	35	12
Chatzigeorgiou et al. (2003)	2003	20	NR	21	NR	29	NR	NR
de Bree et al. (2003)	2003	19	30[b]	26	54	NR	63	42
Cavaliere et al. (2000)	2000	20	20	NR	25	NR	50[a]	NR

NR not reported

[a] 2-year survival result

[b] Refers to results expressed as mean

meta-analysis by Bristow and Chi (2006) has demonstrated that there is no role for neoadjuvant platinum-based chemotherapy. Management of ovarian cancer should primarily involve a maximal surgical effort for complete cytoreduction. In situations whereby extensive disease burden have rendered limitations to achievement of a complete resection, neoadjuvant chemotherapy may be considered. The EORTC-GCG/NCIC-CTG randomized trial comparing primary debulking surgery with neoadjuvant chemotherapy in advanced ovarian, fallopian tube, and peritoneal cancer have shown that similar overall survival and progression-free survival outcomes may be achieved compared to standard primary debulking and with a lower morbidity rate (Vergote et al. 2008). However, emphasis must be made that neoadjuvant chemotherapy should not form the basis of selecting a favorable prognostic group of patients who are chemo-responsive to undergo aggressive surgical cytoreduction.

CRS using limited peritonectomy procedures to resect peritoneal implants and HIPEC aims to allow both macroscopic cytoreduction through surgery and cytotoxic cytoreduction through loco-regional administration of heated chemotherapy. Tabulation of the results from these studies show that CRS and HIPEC are associated with significant severe morbidity rates of up to 40% and a mortality rate of 0–10%. However, we would point out that contemporary mortality and morbidity figures from institutions who routinely perform this procedure are low. The treatment related complications is considered acceptable and further large volume peritonectomy units have low morality rates that range from 0 to 2% (Bereder et al. 2009; Look et al. 2004; Raspagliesi et al. 2006). The complication rate of this treatment has been recently compiled through a systematic review by Chua et al. who reviewed the morbidity and mortality results of 24 treatment centres, of which ten centers that were regarded as high volume specialized centres based on the number of procedures performed, showed a major morbidity rate ranging from 12 to 52% and a mortality rate ranging from 0.9 to 5.8% (Chua et al. 2009b). Majority of these procedures in these institutions were performed in patients with high-volume carcinomatosis with surgical morbidity being attributed specifically to the extent of disease rather than the HIPEC procedure.

Notwithstanding the limitations of inferring treatment efficacy through large case series, we demonstrate a long median disease-free survival in patients with ovarian

cancer peritoneal carcinomatosis with a range of 10 to 57 months and an overall median survival of 22 to 64 months in a heterogeneous cohort of patients. Although specific conclusion of outcomes for primary advanced ovarian cancer or recurrent ovarian cancer cannot be accurately elucidated from the published reports, a significant proportion of patients have undergone multiple treatments with a proportion of patients who have failed treatment (time point 5). Hence, this review suggests that CRS and HIPEC in patients with recurrent ovarian cancer may be beneficial when compared with results of conventional secondary cytoreduction or systemic chemotherapy reported in the literature. Rufian et al. (2006) in their study reported 19 patients with advanced ovarian cancer and 14 patients who have relapsed for the first time following primary treatment that involved surgery and systemic chemotherapy. The long median survival of 66 months in the patients that had an optimal cytoreduction may further suggest that intervening early with CRS and HIPEC may be useful. The largest experience to date was reported by Bereder et al. (2009), who reported a median overall survival of 46 months in patients with first relapsed ovarian cancer of which a proportion are chemoresistant. In their institutions, the mortality rate was under 1% and the morbidity rates were about 10%.

Perioperative use of IP chemotherapy as HIPEC or early postoperative IP chemotherapy (EPIC) overcomes the limitations of the IP/IV treatment regime that has been shown to be efficacious in the randomized trials of IP chemotherapy in ovarian cancer which, however, is associated with high rates of IP catheter complications. Administration of IP chemotherapy intraoperatively and during the early postoperative period allows free circulation of the chemoperfusate and hence an improved drug distribution without the compromise of any adhesions; heating of the chemoperfusate enhances the synergistic effect of the cytotoxic agent and most importantly, it avoids the need to implant any peritoneal access device and hence, full compliance (Sugarbaker 2007).

Despite the lack of quality (level I evidence) data, the consistent and reproducible results demonstrated in this review suggest that there is an overall survival advantage associated with CRS and HIPEC in this group of patients that are at various stages of their disease process, who have been heavily treated with both surgeries and chemotherapy and with issues of chemoresistance. For this treatment to become generally accepted, the oncology community must commit to a randomized trial (Chua et al. 2009a). Specifically, trials should be set in the context of HIPEC use according to the various time-points as previously proposed (Helm et al. 2008).

Conflict of interest All authors have no conflict of interest to declare.

References

Abu-Hijleh MF, Habbal OA, Moqattash ST (1995) The role of the diaphragm in lymphatic absorption from the peritoneal cavity. J Anat 186:453–467

Aravantinos G, Bafaloukos D, Fountzilas G, Christodoulou C, Papadimitriou C, Pavlidis N et al (2003) Phase II study of docetaxel–vinorelbine in platinum-resistant, paclitaxel-pretreated ovarian cancer. Ann Oncol 14(7):1094–1099

Armstrong DK, Bundy B, Wenzel L, Huang HQ, Baergen R, Lele S et al (2006) Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N Engl J Med 354(1):34–43

Bae JH, Lee JM, Ryu KS, Lee YS, Park YG, Hur SY et al (2007) Treatment of ovarian cancer with paclitaxel- or carboplatin-based intraperitoneal hyperthermic chemotherapy during secondary surgery. Gynecol Oncol 106(1):193–200

Bereder J, Glehen O, Habre J, Desantis M, Cotte E, Mounier N et al (2009) Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from ovarian cancer: a multiinstitutional study of 246 patients. J Clin Oncol 27(15s):abstr 5542

Bristow RE, Chi DS (2006) Platinum-based neoadjuvant chemotherapy and interval surgical cytoreduction for advanced ovarian cancer: a meta-analysis. Gynecol Oncol 103(3):1070–1076

Bristow RE, Lagasse LD, Karlan BY (1996) Secondary surgical cytoreduction for advanced epithelial ovarian cancer. Patient selection and review of the literature. Cancer 78(10):2049–2062

Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ (2002) Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. J Clin Oncol 20(5):1248–1259

Carmignani CP, Sugarbaker TA, Bromley CM, Sugarbaker PH (2003) Intraperitoneal cancer dissemination: mechanisms of the patterns of spread. Cancer Metast Rev 22:465–472

Cavaliere F, Perri P, Di Filippo F, Giannarelli D, Botti C, Cosimelli M et al (2000) Treatment of peritoneal carcinomatosis with intent to cure. J Surg Oncol 74(1):41–44

Chatzigeorgiou K, Economou S, Chrysafis G, Dimasis A, Zafiriou G, Setzis K et al (2003) Treatment of recurrent epithelial ovarian cancer with secondary cytoreduction and continuous intraoperative intraperitoneal hyperthermic chemoperfusion (CIIPHCP). Z Gynäkol 125(10):424–429

Chua TC, Liauw W, Robertson G, Chia WK, Soo KC, Alobaid A et al (2009a) Towards randomized trials of peritonectomy and hyperthermic intraperitoneal chemotherapy for ovarian cancer peritoneal carcinomatosis. Gynecol Oncol, Epub

Chua TC, Yan TD, Saxena A, Morris DL (2009b) Should the treatment of peritoneal carcinomatosis by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy still be regarded as a highly morbid procedure? A systematic review of morbidity and mortality. Ann Surg, Epub

Cotte E, Glehen O, Mohamed F, Lamy F, Falandry C, Golfier F et al (2007) Cytoreductive surgery and intraperitoneal chemo-hyperthermia for chemo-resistant and recurrent advanced epithelial ovarian cancer: prospective study of 81 patients. World J Surg 31(9):1813–1820

de Bree E, Romanos J, Michalakis J, Relakis K, Georgoulias V, Melissas J et al (2003) Intraoperative hyperthermic intraperitoneal chemotherapy with docetaxel as second-line treatment for peritoneal carcinomatosis of gynaecological origin. Anticancer Res 23(3c):3019–3027

Di Giorgio A, Naticchioni E, Biacchi D, Sibio S, Accarpio F, Rocco M et al (2008) Cytoreductive surgery (peritonectomy procedures) combined with hyperthermic intraperitoneal chemotherapy

(HIPEC) in the treatment of diffuse peritoneal carcinomatosis from ovarian cancer. Cancer 113(2):315–325
Fagotti A, Paris I, Grimolizzi F, Fanfani F, Vizzielli G, Naldini A et al (2009) Secondary cytoreduction plus oxaliplatin-based HIPEC in platinum-sensitive recurrent ovarian cancer patients: a pilot study. Gynecol Oncol 113(3):335–340
Ferrandina G, Ludovisi M, De Vincenzo R, Salutari V, Lorusso D, Colangelo M et al (2007) Docetaxel and oxaliplatin in the second-line treatment of platinum-sensitive recurrent ovarian cancer: a phase II study. Ann Oncol 18(8):1348–1353
Goff BA, Mandel L, Muntz HG, Melancon CH (2000) Ovarian carcinoma diagnosis. Cancer 89(10):2068–2075
Gori J, Castano R, Toziano M, Habich D, Staringer J, De Quiros DGB et al (2005) Intraperitoneal hyperthermic chemotherapy in ovarian cancer. Int J Gynecol Cancer 15(2):233–239
Guardiola E, Delroeux D, Heyd B, Combe M, Lorgis V, Demarchi M et al (2009) Intra-operative intra-peritoneal chemotherapy with cisplatin in patients with peritoneal carcinomatosis of ovarian cancer. World J Surg Oncol 9(7):14
Helm CW, Randall-Whitis L, Martin RS III, Metzinger DS, Gordinier ME, Parker LP et al (2007) Hyperthermic intraperitoneal chemotherapy in conjunction with surgery for the treatment of recurrent ovarian carcinoma. Gynecol Oncol 105(1):90–96
Helm CW, Bristow RE, Kusamura S, Baratti D, Deraco M (2008) Hyperthermic intraperitoneal chemotherapy with and without cytoreductive surgery for epithelial ovarian cancer. J Surg Oncol 98:283–290
Jacquet P, Sugarbaker PH (1996) Current methodologies for clinical assessment of patients with peritoneal carcinomatosis. J Exp Clin Cancer Res 15:49–58
Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ (2007) Cancer statistics, 2007. CA Cancer J Clin 57(1):43–66
Look M, Chang D, Sugarbaker PH (2004) Long-term results of cytoreductive surgery for advanced and recurrent epithelial ovarian cancers and papillary serous carcinoma of the peritoneum. Int J Gynecol Cancer 14:35–41
Matsumoto A, Higuchi T, Yura S, Mandai M, Kariya M, Takakura K et al (2006) Role of salvage cytoreductive surgery in the treatment of patients with recurrent ovarian cancer after platinum-based chemotherapy. J Obstet Gynaecol Res 32(6):580–587
Ozols RF (2002) Recurrent ovarian cancer: evidence-based treatment. J Clin Oncol 20(5):1161–1163
Ozols RF (2005) Treatment goals in ovarian cancer. Int J Gynecol Cancer 15(suppl 1):3–11
Pavlov MJ, Kovacevic PA, Ceranic MS, Stamenkovic AB, Ivanovic AM, Kecmanovic DM (2009) Cytoreductive surgery and modified heated intraoperative intraperitoneal chemotherapy (HIPEC) for advanced and recurrent ovarian cancer—12-year single center experience. Eur J Surg Oncol (in press)
Pfisterer J, Plante M, Vergote I, du Bois A, Hirte H, Lacave AJ et al (2006) Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. J Clin Oncol 24(29):4699–4707
Piso P, Dahlke MH, Loss M, Schlitt HJ (2004) Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in peritoneal carcinomatosis from ovarian cancer. World J Surg Oncol 2(21)
Raspagliesi F, Kusamura S, Campos Torres JC, de Souza GA, Ditto A, Zanaboni F et al (2006) Cytoreduction combined with intraperitoneal hyperthermic perfusion chemotherapy in advanced/recurrent ovarian cancer patients: the experience of National Cancer Institute of Milan. Eur J Surg Oncol 32(6):671–675
Reichman TW, Cracchiolo B, Sama J, Bryan M, Harrison J, Pliner L et al (2005) Cytoreductive surgery and intraoperative hyperthermic chemoperfusion for advanced ovarian carcinoma. J Surg Oncol 90(2):51–56 (discussion 56–58)
Rowan K (2009) Intraperitoneal therapy for ovarian cancer: why has it not become standard? J Natl Cancer Inst, Epub
Rufian S, Munoz-Casares FC, Briceno J, Diaz CJ, Rubio MJ, Ortega R et al (2006) Radical surgery–peritonectomy and intraoperative intraperitoneal chemotherapy for the treatment of peritoneal carcinomatosis in recurrent or primary ovarian cancer. J Surg Oncol 94(4):316–324
Ryu KS, Kim JH, Ko HS, Kim JW, Ahn WS, Park YG et al (2004) Effects of intraperitoneal hyperthermic chemotherapy in ovarian cancer. Gynecol Oncol 94(2):325–332
Salani R, Santillan A, Zahurak ML, Giuntoli RL II, Gardner GJ, Armstrong DK et al (2007) Secondary cytoreductive surgery for localized, recurrent epithelial ovarian cancer: analysis of prognostic factors and survival outcome. Cancer 109(4):685–691
Spratt JS, Adcock RA, Muskovin M, Sherrill W, McKeown J (1980) Clinical delivery system for intraperitoneal hyperthermic chemotherapy. Cancer Res 40(2):256–260
Sugarbaker PH (1995) Peritonectomy procedures. Ann Surg 221(1):29–42
Sugarbaker PH (1996) Observations concerning cancer spread within the peritoneal cavity and concepts supporting an ordered pathophysiology. In: Sugarbaker PH (ed) Peritoneal carcinomatosis: principles of management. Kluwer, Boston
Sugarbaker PH (2007) Laboratory and clinical basis for hyperthermia as a component of intracavitary chemotherapy. Int J Hyperth 23(5):431–442
Trimble EL, Christian MC (2008) National Cancer Institute—United States strategy regarding intraperitoneal chemotherapy for ovarian cancer. Int J Gynecol Cancer 18(suppl 1):26–28
Vergote I, Tropé CG, Amant F, Kristensen GB, Sardi JE, Ehlen T et al (2008) EORTC-GCG/NCIC-CTG randomised trial comparing primary debulking surgery with neoadjuvant chemotherapy in stage IIIC–IV ovarian, fallopian tube and peritoneal cancer (OVCA). Paper presented at the 12th Biennial Meeting International Gynecologic Cancer Society—IGCS, Bangkok, Thailand
Walker JL (2009) Intraperitoneal chemotherapy for ovarian cancer: 2009 goals. Gynecol Oncol 112(3):439–440
Walker JL, Armstrong DK, Huang HQ, Fowler JM, Webster K, Burger RA et al (2006) Intraperitoneal catheter outcomes in a phase III trial of intravenous versus intraperitoneal chemotherapy in optimal stage III ovarian and primary peritoneal cancer: a Gynecologic Oncology Group study. J Clin Oncol 100:27–32
Winter WE 3rd, Maxwell GL, Tian C, Carlson JW, Ozols RF, Rose PG et al (2007) Prognostic factors for stage III epithelial ovarian cancer: a Gynecologic Oncology Group Study. J Clin Oncol 25(24):3621–3627
Witkamp AJ, De Bree E, Van Goethem AR, Zoetmulder FAN (2001) Rationale and techniques of intra-operative hyperthermic intraperitoneal chemotherapy. Cancer Treat Rev 27:365–374
Yan TD, Black D, Savady R, Sugarbaker PH (2006) Systematic review on the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal carcinoma. J Clin Oncol 24(24):4011–4019
Yan TD, Black D, Savady R, Sugarbaker PH (2007a) A systematic review on the efficacy of cytoreductive surgery and perioperative intraperitoneal chemotherapy for pseudomyxoma peritonei. Ann Surg Oncol 14(2):484–492
Yan TD, Welch L, Black D, Sugarbaker PH (2007b) A systematic review on the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for diffuse malignancy peritoneal mesothelioma. Ann Oncol 18(5):827–834
Zanon C, Clara R, Chiappino I, Bortolini M, Cornaglia S, Simone P et al (2004) Cytoreductive surgery and intraperitoneal chemohyperthermia for recurrent peritoneal carcinomatosis from ovarian cancer. World J Surg 28:1040–1045