ORIGINAL ARTICLES

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the treatment of ovarian cancer

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Received: June 28, 2015 **Accepted:** August 19, 2015 **Online Published:** September 22, 2015
DOI: 10.5430/css.v2n1p27 **URL:** http://dx.doi.org/10.5430/css.v2n1p27

ABSTRACT

The most common cause of primary ovarian malignancy is epithelial carcinoma, accounting for 95% of malignant ovarian neoplasia. The lifetime risk of epithelial ovarian cancer (EOC) is 1/70 females, representing the leading cause of gynecologic malignancy death. Due to its indolent clinical course, EOC tends to be diagnosed at an advanced stage, often resulting in unfavorable outcomes, since the stage at diagnosis is the most significant prognostic factor. So far the standard of care for ovarian cancer has been surgery followed by systemic chemotherapy. However, treatment with cytoreductive surgery, as described by Sugarbaker, and hyperthermic intraperitoneal chemotherapy (HIPEC) is another approach, showing promising results.

Key Words: Ovarian cancer, Cytoreductive surgery, Hyperthermic intraperitoneal chemotherapy

1. INTRODUCTION

The most common cause of primary ovarian malignancy is epithelial carcinoma, accounting for 95% of malignant ovarian neoplasia. Its exact cause has not yet been identified, however several pathophysiological mechanisms have been suggested, including the dedifferentiation of ovarian surface epithelium or the attachment of distal fallopian tube cells to the ovary.[1] Serous tubal intraepithelial carcinoma (STIC) closely resembles high grade serous carcinoma (HGSC) of the ovary, both in genetically predisposed patients and sporadic disease and it has been considered a precursor lesion. The identification of several genetic markers suggests a close clonal relationship between STIC and ovarian HGSC.[1]

The lifetime risk of epithelial ovarian cancer (EOC) is 1/70 females, representing the leading cause of gynecologic malignancy death.[2,3] Due to its indolent clinical course, EOC tends to be diagnosed at an advanced stage, often resulting in unfavorable outcomes, since the stage at diagnosis is the most significant prognostic factor.[4] EOC metastasizes locally or via blood vessels and lymphatics. Nonetheless, one of its most distinct features is the tendency to disseminate into the peritoneal cavity, causing peritoneal carcinomatosis, indicative of advanced stage disease. Moreover, 60% of advanced EOC patients will recur in the first three years following diagnosis and treatment.[5] So far the standard of care for ovarian cancer has been surgery followed by systemic chemotherapy.[6,7] However, treatment with cytoreductive surgery, as described by Sugarbaker,[8] and hyperthermic intraperitoneal chemotherapy (HIPEC) is another approach, showing promising results. Cytoreductive surgery consists

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of peritonectomy procedures and visceral resections aimed at the complete removal of tumor from the abdominal cavity. Most common chemotherapeutic agents used in HIPEC for EOC are cisplatin, doxorubicin and mitomycin C.

2. THE ROLE OF CYTOREDUCTIVE SURGERY

EOC follows a pattern of intraperitoneal dissemination and presents as a locoregional disease. The effort to minimize remnant disease aims to improve chemotherapeutic penetration in neoplastic tissue and also acts protectively against chemoresistance, given that less disease burden requires less cycles of systemic chemotherapy.[9]

Cytoreductive surgery is the initial step in the treatment of peritoneal carcinomatosis of ovarian origin. While debulking surgery is aimed to reduce disease burden, considered optimal when the largest residual tumor nodule is $\geq$ 1 cm,[10] cytoreductive surgery consists of a specific series of peritonectomy procedures and visceral resections, as described by Sugarbaker,[8] aiming at the complete removal of tumor from the peritoneal cavity. The importance of residual disease and its effect on overall survival is well summarized in the review article published by Schorge *et al*.[11] The Completeness of Cytoreduction Score (CCS) is used to approximate residual tumor after cytoreductive surgery, with CC-0 denoting no residual disease, CC-1 disease < 0.25 cm in diameter, CC-2 disease 0.25-2.5 cm and CC-3 disease > 2.5 cm.[12] Optimal cytoreduction requires residual disease to approximate 0, often requiring major splachnic resections in order to be achieved.[12] Splenectomy, for instance, has been evaluated as a safe practice at the time of primary cytoreductive surgery for ovarian cancer, offering better cytoreduction, with low perioperative complication rate.[13] Colon resection, most often rectosigmoidectomy followed by a primary anastomosis, has been found to have a positive impact on survival,[14] improving disease free and overall survival,[15] with an acceptable postoperative quality of life and without a delay on adjuvant systemic chemotherapy.[16] The significance of optimal cytoreduction can be demonstrated also on a microscopic level, since it has been found that intraperitoneal chemotherapy agents under hyperthermic conditions can penetrate tissue to a depth of only 2 to 3 milimeters,[17] therefore HIPEC administration can only be efficient given that meticulous resection has been performed, leaving residual tumor of less than 1 mm – 2 mm in thickness.

2.1 Cytoreduction technique

The operations performed during cytoreductive surgery were initially described by Sugarbaker,[8] followed by several modifications and attempts to standardize the technique.[18] The operations can be summarized as follows:[19]

- Upper Right Peritonectomy: right diaphragmatic peritonectomy with Glisson's capsule dissection; lesser omentectomy, stripping of the omental bursa $\pm$ cholecystectomy $\pm$ gastric antrectomy or total gastrectomy.
- Upper Left Peritonectomy: left diaphragmatic and parietal peritonectomy with splenectomy and greater omentectomy.
- Pelvic Peritonectomy: pelvic parietal peritonectomy $\pm$ sigmoidectomy $\pm$ hysterectomy and salpingooophorectomy.
- Right Parietal Peritonectomy $\pm$ right/total colectomy.
- Mesenteric Peritonectomy implants on visceral surfaces could be alternatively removed by electrosurgical local dissection.

Since cytoreductive surgery is a major abdominal operation, with possible morbidity, good preoperative patient selection is of crucial importance, so as to identify which patients will benefit more from such an extensive procedure. While so far age over than 65 years was considered a major contraindication for cytoreductive surgery and HIPEC,[20] two recent studies by Votanopoulos *et al*.[21] and Spiliotis *et al*.[22] demonstrated that HIPEC can be safely performed in patients older than 70 years, with acceptable postoperative morbidity and mortality.

Prognostic and predictive factors for optimal cytoreductive surgery in EOC are age < 65, performance status > 80, interval from initial diagnosis > 12 months, Peritoneal Cancer Index (PCI) < 20, absence of retroperitoneal lymph nodes and platinum – sensitive disease.[23] A recent phase I trial was conducted in the attempt to evaluate the use of aminolevulinic acid – mediated photodynamic diagnosis (ALA-PDD) during cytoreductive surgery in detecting peritoneal metastasis in ovarian cancer patients, thus improving cytoreductive technique and reported that it is a safe and feasible method of high sensitivity and specificity.[24] Another approach to cytoreductive surgery is minimally invasive cytoreduction, as described recently by Fagotti *et al*. in ovarian carcinomatosis patients with platinum sensitive isolated relapse, which proved to be a safe alternative in selected patients.[25]

The importance of optimal cytoreduction in the management of ovarian carcinomatosis has been validated in multiple studies, including a meta-analysis of 6885 stage III/IV patients, which identified maximal cytoreduction as one of the most significant determinants of survival. Many series have reported a relationship between survival and surgical outcome, indicating completeness of cytoreduction as the strongest predictor of survival.[23] improving it significantly, in all disease stages, when HIPEC follows a complete cytoreduction (CCSs of 0 and 1).[11] The HYPER-O registry also reported

similar results, with complete cytoreduction (CC-0 or CC-1) being a significant factor affecting survival after multivariate analysis.[26] In a recent phase III study in recurrent ovarian cancer, published by our team, we also demonstrated that the effect of HIPEC is maximized when a complete cytoreduction is achieved, leading to statistically significant prolonged survival.[27]

3. Intraperitoneal chemotherapy: from the Armstrong trial to HIPEC

The rationale for intraperitoneal chemotherapy in the treatment of ovarian cancer can be better understood taking into account the specific features of the disease. Regarding the biologic behavior of the tumor, it has been found that it tends to infiltrate adjacent structures, such as the urinary bladder and the large intestine, with hematogenous dissemination being less frequent. Moreover, exfoliated neoplastic cells are detached from the primary tumor and are disseminated inside the peritoneal cavity via the intraperitoneal circulation and mechanisms involving metalloproteinases, E-cadherin, integrins and fibronectin.[23] Another significant feature of the EOC is its tendency to chemoresistance, which, as described above, seems possible to overcome with the application of cytoreductive surgery and HIPEC. Chemoresistance can be either a de novo feature of the neoplastic cell line or be acquired. De novo chemoresistance is attributed to the presence of neoplastic blastic cells in the primary tumor, which are insusceptible to chemotherapeutic agents, while acquired chemoresistance happens due to the disturbance of tumor suppressive genes or oncogenes as a result of epigenetic alterations after chemotherapy.[28]

HIPEC also has several benefits as opposed to simple intraperitoneal chemotherapy, since it is performed immediately after surgery, in an abdomen free of adhesions, at the moment when the tumor burden is at its lowest.[29] The efficacy of intraperitoneal chemotherapy in the treatment of EOC has been demonstrated in three large randomized trials, by Alberts, Armstrong and Markman.[30–32] Regarding the choice of the intraperitoneal chemotherapeutic drug used in ovarian cancer, there has been no consensus.[26,33–35] The features taken into consideration for the choice of a drug to be administered intraperitoneally are its clinical efficacy and its pharmacokinetic properties in the abdominal cavity. The ideal drug has to have a high molecular weight in order not to be absorbed by systemic circulation, a high level of plasma clearance and a mechanism of action which is enhanced by hyperthermia.[36] Cisplatin is the most widely used antineoplastic agent to be delivered intraperitoneally, while other options include oxaliplatin, paclitaxel, doxorubicin, carboplatin, irinotecan and gemcitabine. At our institution, cisplatin and paclitaxel are used in platinum sensitive disease, and doxorubicin and paclitaxel or mitomycin in platinum resistant disease.[27]

As for the HIPEC parameters, most regimens suggest the administration of the chemoperfusate for 60 to 120 minutes, at 42°C, while the patient is still under general anaesthesia. This temperature represents an optimal therapeutic window, since at a higher temperature continuous exposure may damage normal tissue, while at a lower temperature a longer exposure may be required for the cytotoxic effect. The options for HIPEC administration are either with the open or the closed technique. In the open technique, the abdominal wall is elevated to create a funnel in which the chemoperfusate circulates through inflow and outflow lines attached to a pump and heating unit. On the other hand, in the closed technique, the inflow and outflow lines are placed through separate incisions and afterwards the abdominal wall is closed before the delivery of HIPEC. Both techniques can be applied safely, with similar perioperative morbidity and similar long term results, with complications ranging from nausea, vomiting, metabolic acidosis, neutropenia, blood product transfusion, pneumonia and reintubation to reoperation and ICU admission.[37] In a recent series of 638 patients treated with HIPEC, ovarian origin of carcinomatosis was reported as a predictor of higher perioperative morbidity but not perioperative mortality after multivariate analysis. Other predictors of perioperative morbidity were older age, presence of ascites, the implementation of the closed technique and longer operative time. This demonstrates that the process of preoperative patient selection is of utmost importance before the application of cytoreductive surgery (CRS) & HIPEC.[38] Another recent study reporting on morbidity and mortality, which included 32 patients with carcinomatosis of ovarian origin (including fallopian tube and primary peritoneal cancer), found CRS & HIPEC to be a feasible therapeutic approach, with major morbidity (Grade III and IV complications) occurring in 65.6% of patients and without perioperative mortality.[39]

As for the subsequent systemic therapy, single agent therapy seems to be a significant option in the therapeutic plan of platinum resistant patients, taking into consideration the cumulative toxicity from previous treatment. Numerous agents are available, such as gemcitabine, PLD, topotecan, paclitaxel, docetaxel, oral etoposide and hormonal agents.[23]

4. Timing to HIPEC

Cytoreductive surgery and HIPEC has been implemented at several time points in the course of the disease,[40,41] making the timing of HIPEC in the disease course a most important issue (see Table 1). CRS & HIPEC have shown maximum

efficacy when applied either after neoadjuvant chemotherapy without previous resection (interval HIPEC) or after initial cytoreductive surgery and a full course of adjuvant chemotherapy in patients with a clinically complete response (consolidation HIPEC).[26]

Table 1. Recent ovarian cancer patient series

In combination with cytoreductive surgery	
Upfront CRS & HIPEC	As first treatment for newly diagnosed ovarian cancer
Interval CRS & HIPEC	After neoadjuvant chemotherapy without previous resection except for biopsies
Consolidation CRS & HIPEC	After upfront (near) complete CRS and a full course of chemotherapy in patients with a clinically complete response
Secondary CRS & HIPEC	After upfront incomplete CRS followed by chemotherapy in patients with a partial response or stable disease
Salvage CRS & HIPEC	For recurrent ovarian cancer after initial complete response to CRS & chemotherapy
Without cytoreductive surgery	
Palliative HIPEC without CRS	For unresectable ovarian cancer with refractory ascites

Note. CRS: Cytoreductive surgery; HIPEC: Hyperthermic intraperitoneal chemotherapy

4.1 Upfront CRS & HIPEC

A recent study of 42 patients suggested that CRS & HIPEC is most effective when applied as upfront and first recurrence treatment, however it is recognized that these results warrant further evaluation in the context of a clinical trial.[40]

4.2 Interval CRS & HIPEC

Two phase III trials have attempted to determine whether interval cytoreductive surgery after adjuvant chemotherapy adds a survival benefit, with conflicting results. The European Organisation for Research and Treatment of Cancer (EORTC) trial identified a 6 month survival advantage in patients re-explored after three cycles of chemotherapy,[42] while the Gynecologic Oncology Group (GOG) reported no such benefit,[43] pointing out the importance of initial cytoreduction. Vergote *et al*. demonstrated in a randomized trial including stage IIIc and IV EOC patients that neoadjuvant chemotherapy followed by interval debulking surgery and primary debulking followed by chemotherapy have similar outcomes in terms of survival, indicating complete resection of macroscopic disease as the most important prognostic factor, whenever surgery is performed.[44]

4.3 Consolidation & Secondary CRS & HIPEC

A recent case control study by Fagotti *et al*. compared survival data in 30 platinum sensitive EOC patients undergoing secondary CRS & HIPEC versus 37 patients who did not undergo HIPEC. Statistically significant results were reported in favor of the HIPEC group regarding the rates of secondary recurrence, the duration of secondary response and mortality, with a DFS of 26 months in the HIPEC group *vs*. 15 months in the non-HIPEC group.[45]

4.4 Recurrent ovarian cancer

Several recent studies have been attempting to identify the role of cytoreductive surgery & HIPEC in recurrent EOC. The CHIPOR study is a phase III randomized trial in progress, evaluating the efficacy of HIPEC with cisplatin in patients with a first EOC recurrence, six months after first – line treatment.[2]

In a recent review of recurrent EOC patient series, median overall survival (OS) and median disease free survival (DFS) after CRS & HIPEC and subsequent adjuvant chemotherapy were 15-57 months and 3-48 months respectively, while 5 year OS and 5 year DFS were 18%-57% and 0-12.5% respectively. When a complete cytoreduction was achieved, median OS was 97.4 months and 5 year OS was 63%-67%.[41] Our recently reported results of 26.7 months OS come in accordance with previous experience.[27] Bakrin *et al*. have reported similar results.[33,46] In this multicenter French study including 474 recurrent epithelial ovarian cancer (REOC) patients, patients with platinum resistant and platinum sensitive disease treated with optimal cytoreduction had a similar survival of 51.6 and 47.2 months respectively (non statistically significant, NSS).[46] In our team's recent study accordingly, survival was 26.6 months in platinum sensitive and 26.8 months in platinum resistant disease (non statistically significant, NSS).[27]

In a recent patient series of patients with platinum sensitive recurrence treated with CRS & HIPEC (with paclitaxel), it was reported that the presence of tumors with undifferentiated histology was the only independent factor associated with a reduced DFS, with a 1-year DFS of 77% and a 3-year DFS of 45%, denoting a tendency versus patients who did not undergo HIPEC.[47] Tumor differentiation and HIPEC

treatment also proved to be independent prognostic factors in a series of advanced ovarian cancer patients.[48] Another recent study correlated response to HIPEC in the treatment of recurrent ovarian cancer to their BRCA status, demonstrating that the benefit from HIPEC is greater in BRCA mutation carriers.[49] In a recent series of 70 EOC patients, divided in two groups (first recurrence after surgery and adjuvant chemotherapy, six months after chemotherapy versus multiple relapses), survival was similar in the two groups after CRS & HIPEC.[50]

Our team has previously reported a series of 28 recurrent EOC patients, on 14 of whom CRS was followed by HIPEC and systemic chemotherapy while on the remaining 14 CRS was followed only by systemic chemotherapy. The results were significantly better in the HIPEC group, with a 1 year and 3 year overall survival of 90% and 30% respectively.[51] So far the management of REOC is based upon systemic chemotherapy. However, the need for an alternative treatment modality has been pointed out by a recent study by Stathopoulos *et al*., stating that multiple chemotherapy lines[3–9] do not offer a survival benefit versus 1 or 2 lines.[52] The need for appropriate surgical management of recurrent EOC has been shown in a study by Fotopoulou *et al*., describing tertiary cytoreductive surgery in the course of treatment of patients with multiple relapses.[53]

4.5 Palliative HIPEC without cytoreductive surgery

HIPEC has been used in the management of patients with chemoresistant or chemorefractory ovarian cancer for the purposes of palliation from malignant ascites.[59] Ascites frequently diminished after a single HIPEC treatment and vanished within less than 3-5 administrations, improving patients' quality of life.

Recent patient series are presented in Table 2.

Table 2. Recent ovarian cancer patient series

Author, Year	# of pts (Management)	Stage	Optimal CR	OS	Median DFS	Morbidity	Mortality
Furet, 2013 [54]	17 (CRS & HIPEC)	Recurrent	94%	Median: 8.9 y	Median: 11.9 m	58.8%	0%
Chan, 2012 (review) [55]	1,167 (CRS & HIPEC)	Advanced		Median: 14-64 m 5-yr: 35%-70%	Median: 13-56 m	0-40% major	0-5%
		Recurrent		Median: 23-49 m 5-yr: 12%-54%	Median: 13-24 m	0-49% major	0-10%
Bakrin, 2012 [33]	246 (CRS & HIPEC)	Recurrent, Persistent	92.2%	Median: 48.9 m		11.6%	0.37%
Deraco, 2012 [56]	56 (CRS & HIPEC)	Recurrent	96.4%	Median: 25.7 m 5-yr: 23%	Median: 10.8 m 5-yr: 7%	26.3%	5.3%
Tentes, 2012 [57]	43 (CRS & HIPEC)	Advanced	69.8%	5-yr: 54%		51.2%	4.7%
Spiliotis, 2011 [51]	24 (CRS & HIPEC) *vs*. 24 (CRS)	Recurrent	83% *vs*. 66%	Median: 19.4 m *vs*. 11.2 m (SS) 3-yr: 50% *vs*. 18%		40% *vs*. 20%	0% *vs*. 0%
Spiliotis, 2014 [58]	60 (CRS & HIPEC) *vs*. 60 (CRS)	Recurrent		Median: 26.7m *vs*. 13.4m (SS) 3-yr: 75% *vs*. 18% (SS)			

Note. CR: Cytoreduction, CRS: Cytoreductive surgery, HIPEC: Hyperthermic intraperitoneal chemotherapy, OS: Overall survival, DFS: Disease free survival, SS: Statistically significant

5. CONCLUSION

Cytoreductive surgery and HIPEC holds a significant role in the management of peritoneal carcinomatosis of ovarian origin. Good patient selection, regarding the timepoint of the disease and patient performance status, is of crucial importance in order to identify which patients will benefit most from its application. Cisplatin is the most widely used antineoplastic agent to be delivered intraperitoneally in the treatment of ovarian peritoneal carcinomatosis. In the course of management of EOC, CRS & HIPEC have shown maximum efficacy when applied either after neoadjuvant chemotherapy without previous resection (interval HIPEC)

or after initial cytoreductive surgery and a full course of adjuvant chemotherapy in patients with a clinically complete response (consolidation HIPEC). It should be stressed, finally, that HIPEC administration can only be efficient given that optimal cytoreduction has been performed, leaving behind minimum residual tumor.

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