Hyperthermic intraperitoneal chemotherapy in ovarian cancer: Qui Bono?

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Abstract: Ovarian cancer is a major cause of cancer related-death in women around the world. Recent statistics on the worldwide cancer burden by the International Agency for the research on Cancer revealed ovarian cancer being both the eighth most frequent malignancy in the west countries. Peritoneal metastasis from ovarian cancer is a major challenge in the clinical management. Despite the evidence of the benefit of Intraperitoneal Chemotherapy in ovarian cancer with peritoneal deposits it has not been widely adopted, mainly due to logistical difficulties and less to the logoregional morbidity as pain. The role of hyperthermic intraperitoneal chemotherapy (HIPEC) in patients during the end of cytoreductive surgery (CRS) is a more tolerable feasible method with potential advantages as drug distribution, combination with hyperthermia and application before tumor regrowth. The aim of this article is to investigate the potential benefits of HIPEC explains the rationale, data of major clinical trials meta-analyses and recent randomized trial are presented and explains the indications patient selection and the best time to applicate of this aggressive logo regional treatment.

Keywords: Cytoreductive surgery (CRS); hyperthermic intraperitoneal chemotherapy (HIPEC); ovarian cancer

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Introduction

Ovarian cancer remains a lethal condition among the women with gynecological tumors and the mortality rate will rise significantly by the year 2040 for different reasons (1). Cytoreductive surgery (CRS) and systemic chemotherapy by definition is the gold standard of treatment since the middle-90's (2).

Dissemination and implantation is the two most common routes of metastasis of peritoneum spread and the third route to lymph nodes or liver or lungs remains the hematogenous spread (3).

Intraperitoneal chemotherapy could reduce plasma toxicity compared with intravenous administration and increase the effect upon heating (4,5).

Investigators world wide have explored the role of HIPEC combined with aggressive CRS with controversial results and lack of well designed prospective randomized trials.

On the other hand in the era of new drugs targeted therapies and immunotherapy the method demands strict criteria for application. The aim of this article is to focuses in this field with base evidence indications.

Hyperthermic intraperitoneal chemotherapy (HIPEC)

HIPEC is the delivery of intraperitoneal chemotherapy under high temperature of the drugs solution after aggressive CRS. It is a well known procedure in the last 30 years with controversial results in different gastro intestinal tumors (6).

The main debate is the different approaches of HIPEC, from different groups are the drugs, the style (open *vs.* closed) and the different time period of intraperitoneal chemotherapy (60 *vs.* 90 *vs.* 120 min) and also the significantly more toxic effects concerning morbidity and mortality which are warning the academic community to

remain skepticism about the implementation of the method in the arsenal of therapeutic management (7,8).

Until the middle of recent decade the majority of ovarian cancer centers using the controversial systemic chemotherapy in the management of relapse or primary advance ovarian cancer (9). In 2015 a first randomized trial from Greece with some bias concerning the randomization approach investigating the role of HIPEC in "relapse" ovarian cancer with some excellent, a ray of hope, results concerning the OS (10).

Three years later van Driel *et al*. reported a benefit in survival with the use of HIPEC at interval debulking as upfront setting (11). At the same time a study from Korea, Lim *et al*. showed no benefit from HIPEC in the similar group of patients (12).

Many discussions are rising concerning the methodology of Driels study about patient selection, the role and the precision of cytoreduction in the 10 participating centers.

There was also an imbalance regarding the randomization, the toxicities and the adverse effects of neoadjuvant chemotherapy.

In conclusion in HIPEC group we observed more toxic effects and longer hospitalization and maybe worse quality of life (for example: stoma formation 72% in HIPEC group *vs*. 43% in non HIPEC group) (13).

As a result, the van Driel study should not drive changes in clinical practice in ovarian cancer and remains under investigation (14,15).

In late 80s a phase I trial study exams the pharmacological advantage of intraperitoneal normothermic chemotherapy (IP) by maintaining the drugs at higher concentration in the peritoneal spaced due to the lower peritoneal permeability (16,17). And this permeability increases from 3 to 5 mm when the temperature of the solution achieves the 42.5 to 43 grade of Celsius and also has been described that this pharmacokinetic advantage of i.p chemo is particularly evident in smaller lesions and avascular tumors (18,19).

All this data catching the attention of clinical oncologic society and in 2006 as a result of GOG172 a clinical alert was made available (20-22).

This study demonstrates that the combination of IP + IV chemotherapy versus only IV improves the progression free survival (PFS) by 5 months in the IP arm and the overall survival (OS) by nearly 16 months (22).

In practice the GOG 172 remains limited due to problems of intraperitoneal administration every week (day 2 and day 8 of the cycle) and the locally adverse effects (abdominal pain, mobilization of intraabdominal catheter, adhesion formation) and the evidence that after 2 or 3 cycles the fluid distribution is not impeded by different causes (23).

Another question which arises in GOG 172 study is the completeness of cytoreductive, which in this study remains optimal debulking <1 cm. This residual disease is huge as it is compared with CC0 cytoreduction with no evidence of residual disease or CC, that means less 0.25 mm (16,24-26).

The conclusion is that IP chemo therapy, either with local difficulties, improves OS and PFS in well selected patients after meticulous cytoreduction in order to eliminate all the visible disease (16,26).

The most important thing is to standardize exactly the drugs and the dose and also the use of targeted therapies at the same time (27,28). The main benefit and biological advantage remain the less toxicities less than iv chemotherapy and also the main logoregional effect in the peritoneal metastasis especially from ovarian tumors. Remains under question the consensus acceptance and demands main efforts from medical oncologist to accept this procedure.

CRS

The principles of CRS is to eliminate of all visible disease by surgical resection and includes peritonectomy procedures and organ sparing resections (29).

The most ideal procedure is to perform through a large midline laparotomy incision, but recently some groups especially in low peritoneal cancer index patients (PCI) are performed laparoscopically.

Diaphragmatic areas, liver Glisson capsule and falciform ligament is taken.

The PCI standardizes the initial tumor volume separating the abdominal cavity into 13 regions (*Figure 1*) (30). Maximal cytoreduction is a critical point of view especially in ovarian cancer patients concerning the OS and the residual disease after the initial operation remains the most important prognostic factor, together with tumor biology for the final outcome (6).

After the initial exploration to rule out the solid organ metastasis we procced with peritonectomies and resection of all sites of diseases. Most important think is to advocate the standard resection of the great omentum nearly to the splenic hilum and the lesser omentum. Cholecystectomy, appendicectomy and total hysterectomy with bilateral salpingo-oophorectomy are also the next steps concerning

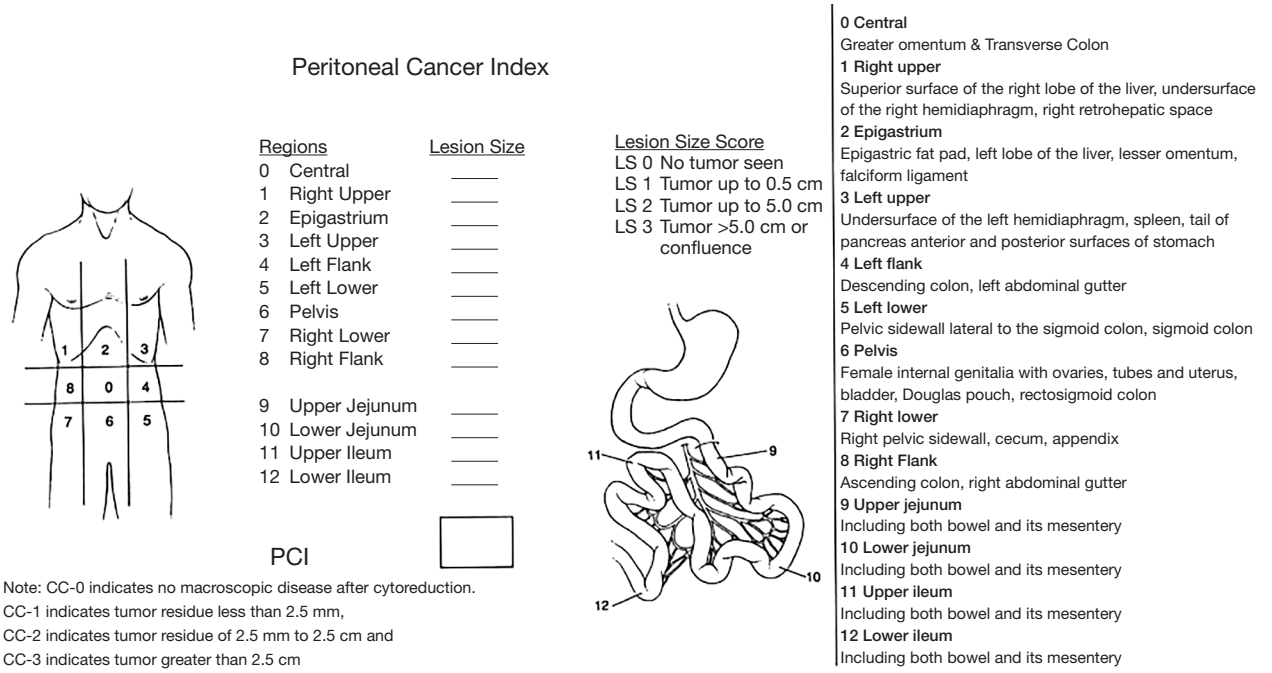

Figure 1 Peritoneal cancer index.

Table 1 Trials in upfront setting

Study	Cohorts	Drugs	Results
Ansaloni 2012 (33)	Open prospective	Cisplatin 100 mgr/m^2	No different survival
	Randomized II	Paclitaxel 175 mgr/m^2	
	Primary versus recurrent	Doxorubicine 25 mgr/m^2 90 min 41.5 ℃	
Lim 2017 (12)	Randomized III	Cisplatin 75 mgr/m2 90 min 41.5 ℃	5-year survival, HIPEC 51%, control 49.4% NS
	CRS + HIPEC + Syst. Chemotherapy		
	CRS + Syst. Chemotherapy		
van Driel 2018 (11)	Neoadjchem 3 cycles + CRS + Hipec + Syst. Chem versus Neoadjchem 3 cycles + CRS + Syst. Chem	Cisplatin 100 mgr/m2 90 min 40 ℃	Median survival, HIPEC 45.7 m, control 33.9 m

CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy.

the cytoreduction.

Meticulous resection is important in the large implants in the smell bowel mesentery which sometimes demands small bowel resection. The diaphragmatic stripping is an important surgical route and the main reason of inappropriate cytoreductional the initial operation. It demands experience, surgical team and sometimes the place during or the end of the operation thoracic tubes to eliminate postoperative pleural infussions (31,32).

HIPEC as upfront treatment in primary ovarian cancer

Multiple studies mainly retrospective and case control studies are published in the upfront setting. *Table 1* summarized the most recent data.

In 2012, an Italian phase II prospective trial demonstrates improved outcome in well CRS patients with HIPEC and delayed recurrent time in 14.4 m (33).

In 2013, a French multicenter study evaluated 566

patients, which includes 92 women in the upfront line setting a HIPEC. The median OS in this group was 35.4 m and in complete cytoreduction (CC0) the median survival was 41.5 m (34). In Spain at tertiary centers 52 patients received HIPEC in the upfront setting after CC0 in cytoreduction. Disease free survival was improved at 3 years (66% *vs.* 18%) P<0.01 (35). Finally, Huo *et al.* in a recent meta-analysis showed an improvement in OS in the HIPEC arm when it compares with no-HIPEC arm (36).

The first more specifically, randomized, open-label phase III multicenter trial by van Driel *et al.* evaluated the role of HIPEC as a part of interval CRS in patients with stage III EOC (11).

The groups of patients are from 10 centers randomized, open-label was designed to assess the efficacy and safety of interval CRS + HIPEC. The 245 participants received neoadjuvant chemotherapy and had to have at least stable disease after 3 cycles of carboplatin and paclitaxel intravenously.

After surgery all patients received adjuvant chemotherapy with same regimen.

At a median follow-up of nearly 5 years, 50% of HIPEC group died versus 62% in no HIPEC group. The median OS was 45.7 versus 33.9 m (37-39).

Interesting data from Shimokawa *et al.* demonstrates the important role of first line chemotherapy in PFS and OS in advanced ovarian cancer (40).

Some cautions in the bias of this study concerning randomization, heterogeneity of the groups especially between the different centers, subgroups analyses and interactions of statistical tests produce a lack of consistency on the basis of different treatment effects (41,42).

On the contrary in a study from Korea presented preliminary results of a randomized trial, neither median OS nor median RFS were different (54 *vs.* 51 m P=0.4 and 20 *vs.* 19 m P=0.1) and among the patients from the neoadjuvant subgroup who were randomized to receive either surgery plus HIPEC or no HIPEC for the management of EOC of stage III and IV (43).

Interestingly the neoadjuvant group showed a trend of improved survival in favour of HIPEC group after 30 m of OS and 20 m of RFS which necessitates further long term observation.

Concerning complications, the HIPEC group was found with significantly increases rates of anemia and creatinine elevation compared to control group and the dose of the IP cisplatin was de-escaled to 75 mgr which was administered for 90 min at 41.5 ℃.

The questions remain unanswered when using HIPEC in primary treatment ovarian cancer. It is obvious that further well-designed prospective randomized trials are warranted to describe the role of HIPEC application in the management of primary EOC. It appears that using it at interval cytoreduction holds the most promise and the latest NCCN guidelines supports this approach. The NCCN recommends that all women undergoing surgery for ovarian cancer should be counseled for combined iv and ip chemotherapy administration preoperatively. Finally, the fact that elderly and medically infirm patients experience problematic tolerance to ip chemotherapy is reiterated (44,45).

Further questions regarding the most appropriate drug, dosing, time and temperature also exist. For instance, the CHORINE study the interim analysis of the other ongoing protocols demonstrates promising results.

HIPEC in relapse disease

Residual ovarian cancer remains a difficult problem in the management of EOC, with the recurrence rates arises to 50–70% 3 years after initial treatment.

Among other factors completeness of primary/internal debulking is also affecting the patient risk of "relapse".

Recent study from our group demonstrates the incidence of residual disease in 70% of cases (46). By definition in our study, the main sites of residual disease are, if we observed deposits in remain great omentum, liver rounge ligament, gallbladder and vaginal stump and recurrent disease included small bowel, mesenterium, pelvic floor, diaphragm (31).

The most important finding is the survival rates between residual and recurrent disease. Median survival rates in residual disease HIPEC group was 38 versus 26 m in recurrent HIPEC group (46).

HIPEC in recurrent disease

The use of HIPEC for the secondary management of relapse due to advanced EOC has been more extensively investigated. The majority of studies are retrospective small trials, evaluating small number of patients (*Table 2*).

A phase I trial from Zivanovic *et al.* evaluated the dose of cisplatin (maximum tolerated) for HIPEC and a phase II trial is currently under investigation (47).

Another paper from France in recurrent chemosensitive and chemoresistant EOC patients demonstrates improves of survival in lower PCI <8 and CC0 score. The results also

Table 2 HIPEC in relapse ovarian cancer

Author	Study type	Drugs	PFS	OS
Zivanovic *et al.* (47)	Prospective phase I, n=12 pts	Cisplatin	13.6 m	N/A
Gonzalez Bayon *et al.* (48)	Prospective n=27 pts	Cisplatin + doxorubicin	N/A	62.8 m, 1st recurrence
Bakrin *et al.* (34)	Retrospective n=470 pts	Cisplatin 76% other drugs 24%	N/A	CC0 51.5 m
Fagotti *et al.* (49)	Case control n=30 pts	Oxaliplatin	26 m	5 years =42.7%
Spiliotis *et al.* (26)	Prospective phase III trial, n=120 pts	Chemosensitive cisplatin + paclitaxel, chemoresistant doxorubicin + paclitaxel or mitomycin	N/A	HIPEC 26.7 m versus control 13.4 m
Cascales-Campos *et al.* (50)	Case control n=39 pts	Paclitaxel	24 m	N/A

Last decade studies on role of HIPEC in recurrent disease. HIPEC, hyperthermic intraperitoneal chemotherapy; PFS, progression free survival; OS, overall survival.

demonstrate not significant difference between platinum sensitive or resistant tumors (34). The last observation demands and need more available data (51).

A Spain study evaluates the role of HIPEC in primary and secondary recurrent disease from EOC and demonstrates an improvement of OS in both groups and also in both CC0 and CC1 cytoreduction groups (48). The main question concerning the role of HIPEC in this study is that the survival is similar with other studies without HIPEC but treated with secondary cytoreduction only (52,53).

Cascales-Campos *et al*. (50) in 2015 evaluate the CRS solely versus CRS plus HIPEC in platinum-sensitive EOC. The results demonstrate same PFS (22 *vs.* 21 m) in favor of CRS alone. The only explication for this result is that in the 39 patients of HIPEC group the mean PCI score is significantly higher. Some investigators suggest also a bias in the choice of paxcitaxel as HIPEC regimen which it may not be effective for use (50).

Fagotti *et al*. (49) in a case control study with 3 arms CRS + IV chemo, (13 pts) IV chemotherapy alone (24 pts) and CRS + HIPEC (30 pts). The results demonstrate similar RFS and only a minimal pattern of recurrence with HIPEC group to achieve a longer secondary PFS after initial treatment (49).

The first RTC in the field was published by Spiliotis *et al*. (26) evaluated the role of HIPEC at first recurrence and was highly criticized due to methodological issue.

The authors included 120 patients with advanced stage EOC (> IIIc) who had disease recurrence and were randomized to either receive CRS plus HIPEC followed by systemic chemotherapy or CRS with systemic chemotherapy alone.

The regimens used for IP administration were as follows: 100 mgr/m^2 cisplatin and 175 mgr/m^2 paxcitaxel for platinum sensitive disease and whereas for platinum resistant disease 35 mgr/m^2 doxorubicin and 175 mgr/m^2 paxcitaxel or 15 mgr/m^2 mitomycin for 60 min at 42.5 ℃ in both groups. A significant improved in the mean OS in the 3 year overall was noted in favour of HIPEC group in both platinum sensitive or platinum resistant women (26).

Additionally in another study by Spiliotis *et al*. (46) the authors tried to clarify whether there is difference in survival who received CRS plus HIPEC as secondary management of residual or recurrent disease after primary surgery in favour of residual disease (38 *vs.* 26 m) (46).

The aforementioned outcomes indicate the significance of the complete cytoreduction in the primary management of advanced EOC, which was further enhanced by the addition of HIPEC.

Future directions

The most important issue at this moment is what is the role of HIPEC and the timing of administration in the management of EOC.

In our group recently we exam the data from our data base in 230 women with advance ovarian cancer. There are 30 upfront procedures with a median survival of 32 m, 60 women with Neo-adjuvant chemotherapy with intermined cytoreduction with 30 m median survival and 140 cases with “relapse disease” (recurrent or residual) with median survival of 38 m far residual disease compared to 23.8 m for recurrent disease.

Another question is what is the role of systemic chemotherapy in relapse disease.

There is some evidence that the use of second line systemic chemotherapy in relapse ovarian cancer before the CRS + HIPEC may offers a survival benefit in PFS and OS as compare with CRS + HIPEC alone (46 versus 31 m P=0.013) (46).

The main debate especially in multidisciplinary tumor conferences is what kind of IP chemotherapy would be recommended for a woman if she was diagnosed with advanced ovarian cancer. There are two attitudes: one with normothermic IP based on the results of GOG172 with a median global survival of 65.2 m but with possibilities of successfully finish the treatment schedule very low 42%. On the other hand, the choice of HIPEC which with acceptable morbidity and mortality rates with acceptable risk the 5 years survival rates higher that 60% (54). The fact that although GOG 172 showed worse toxicity in the ip group, the most recent GOG 252 study demonstrated that the overall rates of toxicities and discontinuation among iv and ip chemotherapy arms were comparable (28).

A recent article from Fotopoulou *et al*. (55) arises the question concerning HIPEC: is a hope of hype in the fight against advanced ovarian cancer? The response from the authors of this article is that: Publicly available evidence addressing the value of HIPEC in EOC is rather inconclusive, revealing contradictory and inconsistent results while some studies even report harm to the patients from a higher morbidity. On this ground we cannot recommend the implementation and use of HIPEC outside of a randomized clinical trial setting (55).

So the question concerning our review is: is the right time to include HIPEC as a standard of care in ovarian cancer management? Although there is as strong rationale for the implementation of HIPEC in ovarian cancer treatment scientifically sound data from randomized clinical trial are coming. Recently DESKTOP III confirmed the role of optimal cytoreduction in the recurrent disease. We reached the same conclusion by the HIPEC trials as well (56). Another important observation is that the result of HIPEC is related to PCI, therefore the possibility to achieve optimal cytoreduction (57). The results from the Japanese iPocc trial are eagerly expected (NCT01506856; Intraperitoneal Therapy For Ovarian Cancer With Carboplatin Trial). This is a randomized phase II/III trial of iv weekly paclitaxel plus iv carboplatin once every 3 weeks versus iv weekly paclitaxel plus ip carboplatin once every 3 weeks in patients with epithelial ovarian cancer. The study attempts to isolate the effects of ip carboplatin; nevertheless, it enrolls few Caucasians, which would raise serious concerns.

The two main questions emerge for further research is when is the best setting to perform HIPEC and is it high time for inclusion of HIPEC in standard clinical practice. The rationale for HIPEC as a part of a multi-model treatment in women with advanced ovarian cancer is strong. In combination with CRS this type of aggressive loco-regional therapy has the potential to cure patients given that hyperthermia enhances tumor penetration and the cytotoxic effects of chemotherapy. HIPEC does not increase the mortality and morbidity compared to CRS alone. This type of treatment should be offered at experienced centers by well-trained multidisciplinary groups after meticulous patient selection (58).

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