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CONTROVERSIES IN GYNECOLOGICAL CANCERS

Cytoreductive Surgery and HIPEC in the First-Line and Interval Time Points of Advanced Epithelial Ovarian Cancer

Shigeki Kusamura[1] · Snita Sinukumar[2] · Dario Baratti[1] · Marcello Guaglio[1] · Stefano Guadagni[3] · Marcello Deraco[1]

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Abstract The increasing popularity of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) for epithelial ovarian cancer (EOC) has been focus of a heated debate. The objectives of this review are to discuss: (1) the main concerns related to radical surgery and the importance of the quality of the CRS in the final outcome of the patient and (2) the rationale and current status to propose trials on CRS and HIPEC in the first-line and interval settings. Although the standard treatment of EOC is the combination of CRS and platinum-based adjuvant chemotherapy, the potential benefits of radical surgery have been under exploited due to unrealistic and exaggerated concern regarding the prognostic limit imposed by the initial tumor burden. Radical surgery at first-line or interval setting could: (1) enable the early treatment of chemoresistant clones that are likely to be already present at diagnosis; (2) not delay the initiation of subsequent chemotherapy at a point to jeopardize the prognosis; (3) enable, by means of HIPEC, the treatment of microscopic residuals that would otherwise grow after surgery, according to the tumor cell entrapment theory. Data from observational studies on first-line CRS and HIPEC did not demonstrate a striking prognostic advantage over CRS alone. However, a recent Dutch randomized trial on interval CRS and HIPEC versus interval CRS demonstrated a clear-cut improvement of overall and progression-free survivals. More prospective trials on HIPEC are ongoing, but the main question at stake, which is the advisable limits of radical surgery, will still remain open.

Keywords Cytoreductive surgery · HIPEC · Advanced ovarian cancer · First-line · Interval setting

✉ Marcello Deraco
marcello.deraco@istitutotumori.mi.it

[1] Peritoneal Surface Malignancy Unit, Fondazione IRCCS Istituto Nazionale dei Tumori Milano, Via Venezian 1, cap 20133 Milan, MI, Italy

[2] Jehangir Hospital, Sassoon Road, Pune, Maharashtra 411001, India

[3] General Surgery Sector, Dipartimento di Scienze cliniche applicate e biotecnologiche, Università degli Studi dell'Acquila, L'Aquila, Italy

Introduction

Epithelial ovarian cancer (EOC) is the main cause of gynecological cancer death in developed countries. Unfortunately, due in part to the inability to perform effective early detection [1], 75% of cases are diagnosed at advanced stage (FIGO stages III–IV) [2]. Standard management of EOC is the combination of cytoreductive surgery (CRS) and platinum- and taxane-based chemotherapy [3]. Despite very high initial chemosensitivity, the majority of patients with advanced EOC relapse after a mean period of 18 months and progressively develop resistance to the various chemotherapeutic options [2, 3]. The prognosis of these advanced stages thus remains poor, with the 5-year overall survival (OS) of no more than 25–35% [2].

The last two decades have witnessed the emergence of a new treatment option for EOC, resulting from the combination of CRS and hyperthermic intraperitoneal chemotherapy (HIPEC). Despite the limited evidence in its support, the combined procedure has attracted an enormous attention from the surgical field, with increasing number of centers offering CRS and HIPEC for EOC. However, it has represented a tremendously contentious issue, especially among surgically oriented and surgically non-oriented

segments of gynecologic oncology international community.

The objectives of this review are to discuss the:

(1) main concerns related to the maximal surgical effort and the importance of the quality of the CRS in the final outcome of the patient;
(2) rationale and current status to propose trials on CRS and HIPEC in the first-line and interval settings.

Defying the Limits Imposed by Tumor Biology with an Aggressive Surgery

Since the landmark study by Griffiths [4] demonstrating survival benefit of maximal tumor debulking, optimal cytoreduction was defined as residual disease (RD) of < 1–2 cm in the largest diameter. In 1994, Hoskins et al. [5] demonstrated a stepwise inverse correlation between residual disease diameter obtained after primary CRS and survival outcome. The cutoff point for optimal RD has evolved in the following years and in 2010, the Gynecologic Cancer InterGroup stated that the ultimate goal of cytoreductive surgery is to remove all macroscopic lesions and patients with microscopic RD should be defined as optimal cytoreduction [6].

In 2011, the Cochrane Review by Elattar et al. [7] proposed that all surgical attempts should be made to resect all visible tumors. More recently a meta-analysis conducted by Chang et al. [8]. that included six retrospective studies and 12 randomized controlled trials for adjuvant chemotherapy, concluded, after multiple linear regression, that patients left with microscopic RD was an important independent predictor of survival and each 10% increase in complete cytoreduction rate resulted in an increment of 2.3 months in median survival.

In spite of consensus reached about the goal of primary cytoreduction as the complete resection of macroscopic disease [9], the unfolding of such theoretical definition in the everyday clinical practice of average gynecologic oncology surgeon has resulted in heterogeneous scenario in terms of surgical outcomes. Take the example of EORTC-55971 clinical trial which represents the one of the largest randomized surgical study ever conducted in EOC [10]. Six hundred and seventy patients affected by EOC were randomized between primary CRS or neoadjuvant systemic chemotherapy. An alarming variability in the rate of optimal and complete cytoreduction was observed. Complete cytoreduction rates at primary surgery ranged from 3.9 to 62.9%. The overall rate of complete cytoreduction was 19.4%. The rate of complete cytoreduction at primary laparotomy was less than 12% in six of the seven participating countries. The widespread surgical competence insufficiency across the centers that participated in the study is apparent and might be related to different interpretations of the principle of complete cytoreduction.

In those patients with less extensive peritoneal disease tumor, it is undisputed that complete cytoreduction is easily achievable with less surgical effort. Most of EOC patients present with advanced disease typically characterized by peritoneal metastasis, omental cake, and lymph node metastasis. When the tumor extensively involves diaphragm, liver, spleen, pancreas, stomach, or bowel, complex multi-visceral resections are required for a complete cytoreduction.

However, there is no consensus on the optimal extent of surgical resection that the surgeon should pursue to achieve complete cytoreduction. In contrast to proponents of maximal surgical effort [11–14], most gynecologic oncologists adopt a non-surgically oriented policy and are skeptical regarding the benefits of radical surgery, claiming that ultra-radical surgical maneuvers could never offset the biological aggressiveness of the tumor dictated by the initial disease burden. According to these gynecologists it is the inherent tumor biology that determines the resectability of the tumor, not surgical aggressiveness.

The three most important studies that have addressed this issue presented conflicting results. Crawford et al. [15] retrospectively reviewed the SCOTROC-1 trial data. The study included 889 patients with FIGO stage IC–IV EOC. A prognostic score system was coined by means of a multivariate model using patient' s preoperative biologic characteristics based on FIGO stage, tumor histology, baseline CA-125, and omental cake. The authors concluded that the benefit in terms of PFS associated with optimal surgery is limited to patients with less aggressive disease and tumor biology is a major determinant of survival.

Horowitz et al. [16] retrospectively reviewed the GOG 182 trial data on 2655 patients with FIGO stage III or IV EOC. PFS and OS were analyzed based on three scores: preoperative disease score (DS), surgical complexity score (CS), and RD. The DS was defined as follows: DS low, with pelvic and retroperitoneal spread; DS moderate, with additional spread to the abdomen but sparing the upper abdomen; or DS high, with the presence of upper abdominal disease affecting the diaphragm, spleen, liver, or pancreas. PFS and OS were decreasing with increasing DS, and patients with high DS had the worst PFS and OS. In patients with complete cytoreduction, the high DS still had a worse influence on PFS and OS than those with low-to-moderate DS. After adjusting for RD and DS, CS was not an independent predictor of survival. They concluded that, although complete cytoreduction is achieved, initial tumor burden is an important prognostic factor and aggressive surgery alone does not seem to have a positive impact.

Du Bois et al. [17] conducted an exploratory analysis of three prospective randomized trials (AGO-OVAR 3, 5, and 7) aiming at a better understanding of the impact of surgery

alongside with other prognostic factors in advanced EOC. A total of 3126 patients were included. Multivariate analysis showed improved PFS and OS for group with complete resection compared with groups with small RD of 1–10 mm or RD of more than 10 mm ($p < 0.0001$). A stratified analysis of RD considering patients with FIGO IIB-IIIB, FIGO IIIC, or FIGO IV separately, revealed a similar relative impact of complete resection for all groups with different preoperative tumor burden. The corresponding hazard reductions for PFS and OS in these 3 groups were 63/63% in FIGO IIB-IIIB, 61/64% in FIGO IIIC, and 47/51% in FIGO IV, respectively. Moreover, the adjusted hazard ratio associated with incomplete cytoreduction was fairly larger than those associated with other prognostic variables related to the biology of the tumor (grade, stage, histological subtype). Taken together, these analyses indicate that complete surgical resection improves prognosis in any FIGO substage in advanced EOC but, anyway, cannot completely compensate the prognostic impact of preoperative tumor burden.

The actual role of aggressive ultra-radical cytoreduction has never been addressed thus far by a prospective randomized trial, so that the relative influence of tumor and maximal surgical effort on oncologic outcome is not yet completely cleared. The Cochrane initiative attempted to provide an answer to this issue evaluating, by means of a systematic review, the effectiveness and morbidity associated with ultra-radical/extensive surgery in the management of advanced stage EOC [18]. One non-randomized study met the inclusion criteria. It analyzed retrospectively the data of 194 women with stage IIIC advanced EOC who underwent either ultra-radical (extensive) or standard surgery. Multivariate analysis identified better disease-specific survival among women receiving ultra-radical surgery, although this was not statistically significant (Hazard ratio [HR] = 0.64, 95% confidence interval 0.40–1.04). In a subset of 144 women with peritoneal metastasis, those who underwent ultra-radical surgery had significantly better disease-specific survival than women who underwent standard surgery (adjusted HR = 0.64, 95% CI 0.41–0.98). The authors concluded that ultra-radical surgery may result in better survival. Other indicators such as quality of life, morbidity, and the cost-effectiveness of this intervention have to be investigated and randomized data warranted.

New Combined Treatment Option for Advanced EOC

In the early 1990s, a new treatment modality emerged resultant from the combination of CRS and hyperthermic intraperitoneal chemotherapy (HIPEC) for the management of various types of peritoneal surface malignancies [19]. Promising results have been obtained when this combined treatment has been applied to treat pseudomyxoma peritonei [20], peritoneal mesothelioma [21, 22], and peritoneal metastasis from colorectal cancer [23, 24]. The CRS is performed according to Sugarbaker's technique and comprises the so-called ultra-radical surgical maneuvers such as parietal peritonectomy, omentectomy, and multi-visceral resections, according to the disease extent [19] to achieve the goal of a RD of measuring less than 2.5 mm. The macroscopic cytoreduction is then complemented with the addition of a single shot intraperitoneal chemotherapy instillation under hyperthermic condition (HIPEC), aiming at eliminating microscopic residuals left behind by the surgical phase of the combined procedure.

Owing to the proclivity of ovarian cancers to present with peritoneal spread and the inherent responsiveness to platinum-based chemotherapy, researchers have explored the prospect of administering adjuvant chemotherapy directly into the peritoneal cavity after surgical cytoreduction. The addition of postoperative normothermic intraperitoneal chemotherapy (IP) following CRS has been studied in several large, randomized studies. These trials and a Cochrane meta-analysis have shown a survival benefit with IP chemotherapy [25]. Despite the improvement in survival, the improvement in progression-free survival has remained modest. In addition, IP therapy has not been widely adopted by oncologists owing to the toxicity of the IP chemotherapy and the morbidity and problems associated with delivery using catheters [26]. The association of hyperthermia with locoregional chemotherapy delivery offers the advantage of lower side effects as compared to normothermic bidirectional conventional chemotherapy, keeping, at the same time, the goal of increased dose intensity.

It is known that hyperthermia by itself is tumoricidal. Apart from the direct cytotoxic effects, hyperthermia also enhances the cytotoxic efficacy of chemotherapy agents. It facilitates chemotherapy uptake by malignant cells, increases drug tissue penetration and inhibits cellular repair mechanisms [27].

The application of the combined procedure for advanced EOC has been done in all time points of the natural history of the disease [28–30]. Here we will present the rational of why such an aggressive approach should be tested preferably in earlier phases of the disease evolution, in particular, as first-line and after neoadjuvant systemic chemotherapy (interval setting).

How to Deal with Platinum Resistance as Early as Possible

Opponents of radical CRS have also claimed that maximal surgical effort is useless in EOC due to its high initial chemosensitivity. In effect, up to 80% of advanced EOC

present at least partial response to first-line platinum-based systemic chemotherapy [2]. This could challenge the rationale of submitting a patient to a surgical treatment characterized by a higher risk of side effects as compared to medical approach. However, the reverse interpretation of this data could also support the reasoning of proponents of maximal surgical effort. About half of the patients present disease relapse after 18 months from the initial treatment and progressively develop chemotherapy resistance [2]. Platinum-resistant recurrence portends a very dismal prognosis of no more than 12 months of median OS, whatever the chemotherapy option.

Moreover, up to 15% of advanced EOC is platinum refractory disease at outset. These cases are represented by histotypes like clear cell or mucinous or by tumors with intrinsic chemoresistance disease that progress during the course of platinum-based first-line therapy. Another 30% turned out to be or develops resistance during the subsequent 6 months from the initial surgery [31].

The mechanisms of platinum resistance might, under the effects of consecutive chemotherapy cycles, recall the "Darwinian" type of selection of a resistant clone, which was already present at diagnosis [32]. Mathematically, it is more likely that such mutations, which are responsible for restoration of the effective DNA repair pathways, occurred randomly before the clinical diagnosis. Such hypothesis of intratumor heterogeneity would confirm the principles of radical and early surgery in the therapeutic pathway of advanced EOC. In fact, an inverse correlation between increasing number of chemotherapy cycles prior to surgery and survival has been suggested in a meta-analysis of EOC patients [12]. Maximal surgery performed as early as possible would thus enable chemoresistant clones to be maximally removed through complete macroscopic resection, with the resistant populations dispersed in the initial lesions [31].

The performance of HIPEC following radical surgery is an attempt to overcome intrinsic resistance of tumor by fully exploiting the concepts of dose intensity and thermal enhancement of drug cytotoxicity. For platinum compounds, pharmacokinetic advantages, represented by the area under curve ratio of peritoneal cavity and plasma compartments, of up to 10 have been reported, during the perfusion [33]. Therefore, tumor residuals left after surgery are expected to be bathed by chemotherapies at concentrations fairly higher than those obtained via the systemic route of administration. Moreover, it was observed in experimental model that the mechanisms of platinum cytotoxicity enhancement by hyperthermia, (measured by platinum intracellular accumulation and adduct formation, and cell log kill effect), are far more pronounced in platinum-resistant cell lines, as compared to platinum-sensitive cell lines [34].

Another overlooked theory that could partially explain the phenomenon of chemotherapy resistance during the therapeutic pathway of EOC is that of tumor cell entrapment that was first described by Sugarbaker [35]. This hypothesis explains the rapid peritoneal disease progression in patients who have undergone surgery as sole treatment. The malignant cells could be disseminated when the tumor is inadvertently ruptured, opened, or cut into [36, 37]. The transection lymphatics and blood vessels could also lead to intraoperative seeding of malignant tumor cells. The traumatized surfaces and areas where the peritoneal barrier is disrupted during the course of cytoreduction might provide a favorable environment for neoplastic cell implantation and proliferation [38]. The tumor cells become entrapped in the local fibrin deposition, where they can progress in the presence of growth factors involved in inflammatory response and wound healing [39, 40]. Moreover, entrapped neoplastic cells are likely to be in a protected environment against subsequent systemic treatments as postoperative adherences and intra abdominal fibrous tissue scar would reduce the bioavailability of chemotherapeutic agents in the nearby of regrowing tumor foci. Lee et al. [41] investigated using a murine model and observed that wound-associated inflammation enhances pro-MMP-9 expression. This in turn plays a key role in the growth and progression of tumor cells associated with peritoneal metastasis [42]. The performance of HIPEC right after the complete cytoreduction is a strategy to minimize that residual tumor cells could regrowth under the effect of local inflammatory response to surgical trauma.

Time to Chemotherapy (TTC)

Opponents of radical surgery have claimed had extensive surgeries could delay the beginning of systemic treatment(s) due to higher rates of perioperative complications and longer in-hospital stays. Such delay could jeopardize the final prognostic outcome of advanced EOC. The issue has been recently cleared by Usón Junior et al. [43]. These investigators conducted a meta-analysis of randomized and observational data, to evaluate the impact of TTC on disease recurrence and survival 3 years after the original surgery. The cutoffs used for TTC were between 20 and 40 days. All 12 eligible studies used a platinum-based chemotherapy, and the rates of patients with suboptimal cytoreduction varied from 33 to 70%. A longer TTC was not associated with higher rates of disease recurrence (odds ratio 0.89; 95% CI 0.63–1.24) or death at 3 years (odds ratio 1.06; 95% CI 0.9–1.24). There was no evidence of significant publication bias (Egger test $p = 0.472$), but data were heterogeneous ($I = 64.3\%$).

Cytoreductive Surgery and HIPEC as First-Line Treatment Option

Ten studies have reported the results of CRS and HIPEC as first-line treatment for stage III/IV ovarian cancer (Table 1) [14, 29, 44–51]. The results were compared with studies conducted on broadly similar cohorts of patients who underwent CRS without HIPEC as first treatment for newly diagnosed stage III/IV ovarian cancer (Table 2) [10, 13, 52–57]. No studies attempted a comparison between first-line CRS and HIPEC with CRS alone.

In the CRS and HIPEC group the mortality rates ranged from 2.5 to 3.8%. Median and 5-year overall survival (OS) ranged from 27.0 to 57.2 months and 28.0 to 60.7%, respectively, Median and 5-year PFS ranged from 24.8 to 37.0 months and 15.2 to 19.7%, respectively.

In the sole CRS group, mortality rates ranged from 0.7 to 2.7%. Median and 5-year OS ranged from 29.0 to 58.2 months and 19.5 to 49.0% for the whole group and 45 to 78 months and 31.3% in case of complete resection (CC0). Median and 5-year PFS range from 12.0 to 33.2 months and 31.0%, respectively. Although it is impossible to draw clear-cut conclusions from this comparison, there does not seem to be a striking survival advantage by adding HIPEC to first-line CRS.

Cytoreductive Surgery and HIPEC in the Interval Setting

Seven studies have reported the results of CRS and HIPEC in the interval setting for stage III/IV ovarian cancer, after the performance of neoadjuvant systemic chemotherapy (Table 3) [29, 47, 48, 58–61].

The results were compared with eight studies conducted on broadly similar cohorts of patients who underwent CRS without HIPEC in the same setting of interval surgery (Table 4) [10, 55, 56, 60–64].

In the CRS and HIPEC group, the mortality rates, when provided, were 0% excepting to a very small study ($n = 9$) that reported 11%. Median and 5-year overall survival (OS) ranged from 44.9 to 68.6 months and 47.9 to 62.0%, respectively. Median and 5-year PFS were 15.0–23.6 months and 9.6%, respectively.

In the sole CRS group, mortality rates ranged from 0.7 to 2.7%. Median and 5-year OS ranged from 26.0 to 53.0 months and 21.1 to 27.7%. Median PFS ranges from 11.0 to 19.0 months.

The eagerly awaited results of the Phase III randomized trial on CRS and HIPEC after neoadjuvant systemic chemotherapy conducted by Dr. van Driel et al. was finally presented at the last ASCO meeting in 2017 [60]. Two-hundred and forty-five patients affected by FIGO stage III EOC, initially deemed as unresectable/inoperable, were

Table 1 Surgical and oncological outcomes after CRS and HIPEC as first-line treatment in advanced EOC

Authors	*n*	FIGO stage	Follow-up (months)	CC0 (%)	Morbidity (%)	Mortality (%)	Median OS (months)	5-year OS (%)	Median PFS (months)	5-year PFS (%)
Piso 2004 [44]	08				37		29.0			
Rufian 2006 [45]	19	III		47	36	0	38.0	37.0	25.0	
Di Giorgio 2008[a] [46]	22	IIIc–IV					27.0		25.5	
Pavlov 2009 [47]	31	IIIc–IV			17.8	0	34.1			
Helm 2010 [48]	26						41.7	33.3	24.8	19.7
Roviello 2010 [49]	14	III		79	23	0		55.0		
Deraco 2011 [14]	26	IIIc–IV	25	58	15	3.8		60.7	30.0	15.2
Parson 2011 [50]	51		98	40			28.5	28.0		
Bakrin 2013 [51]	12						52.7	33.8		
Di Giorgio 2017[b] [29]	53	III–IV			19	2.5	57.2		37.0	

[a]Author' center experience

[b]Italian experience

Table 2 Surgical and oncological outcomes after cytoreduction as sole treatment first-line in advanced EOC

Authors	*N*	FIGO stage	Follow-up	CC0 (%)	Morbidity (%)	Mortality (%)	Median OS (months)	5-year OS (%)	Median PFS (months)	5-year PFS (%)
Alberts 1996 [52]	279	III		26.0		0	41.0			
Yen 2001 [53]	55	III	74	–		0	48.0			
Markman 2001 [54]	227	III		36.0		0.9	52.2		22.2	
Eisenkop 2003 [13]	408	IIIc	33	86.0		2.5	58.2	49		
Sehouli 2010 [55]	332	III–IV	23	60.0		2.7	51.3		33.2	
Kumar 2010 [56]	68	III	42	–			39.0		15.0	
Vergote 2010 [10]	336	IIIc–IV	56	20.0	7.4	2.6	29.0	20	12.0	
Sioulas 2017 [57]	496	IIIc	53	37%	17.0	0.4	54.7		18.6	

Table 3 Surgical and oncological outcomes after CRS and HIPEC in the interval setting in advanced EOC

Authors	*n*	Stage	Follow-up	CC0 (%)	Morbidity (%)	Mortality (%)	5-year OS (%)	Median OS (months)	5-year PFS (%)	Median PFS (months)
Helm 2010 [48]	19					0	50.2	68.6	9.6	16.8
Roviello 2010 [49]	31	III		65.0	23.0	0	58.0			
Carrabin 2010 [58]	10	III		80.0		0				16.9
Muñoz-Casares 2011 [59]	9	III	39	78.0		1/9	62.0			
Angelo Di Giorgio 2016[a] [29]	111[a]	III/IV		74.8	9.0			48		20
	45[b]			57.8	20.0			25		15
	17[c]			100.0	17.6			77		73
	173[d]			72.9	12.7			44.9		23.9
van Driel WJ 2017 (NCT00426257) [60]	122	III	56.4	68.0	28			48		15
Myong Cheol Lim 2017 (NCT01091636) [61]	33	III/IV	32.6			0	47.9	54		20

* Patients were further sub-classified according to the response to neoadjvant systemic chemotherapy in non-responders (a), partial responders (b), and complete responders (c), total calculated by weighted average

treated with neoadjuvant systemic chemotherapy. After CRS they were randomized between CRS-HIPEC and CRS alone. HIPEC was conducted using cisplatin 100 mg/m^2. Stratification was done according to the number of involved peritoneal regions, center, and prior surgery. The investigators had to face the daunting task of slow pace patient enrollment that was finally closed after more than 9 years. Interval CRS with HIPEC was associated with longer recurrence-free survival than interval CRS alone (15 vs. 11 months, respectively; hazard ratio [HR] 0.65; 95% confidence interval [CI] 0.49–0.86; $p = 0.003$). Although the primary endpoint of the study was recurrence-free interval, a significant improvement in OS favoring HIPEC (48 vs. 34 months; HR 0.64; 95% CI 0.45–0.91, $p = 0.01$) was also observed. Grade 3–4 adverse events was similar in both treatment arms (28 vs. 24%, $p = 0.61$) as well as the median TTC (33 vs. 30 days).

These results are in line with previous studies that have addressed CRS and HIPEC in interval setting (Table 3). Further details regarding the distribution of main prognostic factors between the randomized groups are not available as the study has not been published yet.

Table 4 Surgical and oncological outcomes after cytoreduction as sole treatment in the interval setting in advanced EOC

Author	*n*	Stage	Follow-up	CC0 (%)	Morbidity (%)	Mortality (%)	5-year OS (%)	Median OS	5-year PFS (%)	Median PFS
Morice 2003 [62]	34	III/IV	> 24.0			0.0		26.0		
Lee 2006 [63]	18	III/IV	20.0					53.0		15.0
Onda 2009 [64]	53	III/IV	39.0					45.0		14.0
Vergote 2010 [10]	334	III/IV	56.0			0.7	21.1	30.0		12.0
Sehouli 2010 [55]	40	III/IV	23.0					36.5		14.6
Kumar 2010 [56]	71	III	42.0					41.0		15.0
van Driel WJ 2017 (NCT00426257) [60]	123	III	56.4	67.0	24.0			34.0		11.0
Myong Cheol Lim 2017 (NCT01091636) [61]	39	III/IV	31.5			0.0	27.7	51.0		19.0

The preliminary results of another important trial were presented during the same ASCO meeting by Korean group of investigators [61]. One hundred and eighty-four patients staged III and IV, submitted to surgical cytoreduction down to 1 cm, in first-line setting or after neoadjuvant chemotherapy, were randomized between HIPEC using cisplatin 75 mg/m^2 and no HIPEC. No postoperative mortality was identified in both groups. The HIPEC group had higher rates of anemia and elevation of creatinine. Five-year PFS was 20.9 and 16.0% in HIPEC and control group, respectively ($p = 0.569$). Five-year OS was 51.0 and 49.4% in HIPEC and control group, respectively ($p = 0.574$). In women who received NAC, the median PFS for HIPEC and control group were 20 and 19 months, respectively (log-rank test, $p = 0.137$) and the median OS for HIPEC and control group were 54 and 51 months, respectively (log-rank test, $p = 0.407$). After 20 months in PFS and 30 months in OS, two survival curves in women who received NAC showed the trend of gradual distinction, favoring HIPEC group. The authors concluded that, in this preliminary analysis, the survival curves did not show the statistical superiority of the HIPEC arm. More follow-up is necessary to confirm the impact of HIPEC on long-term survival outcome in ovarian cancer.

A more careful evaluation of these data allows us to raise some criticisms. Two different time points, namely first-line and interval setting were mixed without stratification. Although previous randomized studies have not demonstrated a clear outcome difference between these subsets, they should be addressed separately as they present biologically different profile in the routine clinical practice. Patients submitted to cytoreduction after neoadjuvant chemotherapy usually have unresectable or more aggressive disease at outset. The authors claimed that both groups were well-balanced in terms of histological characteristics but the HIPEC arm was characterized by a higher rate of grade 3 tumors (64.1 vs. 50%, *p* value 0.05). The authors adopted the cutoff point of 1 cm of RD, far larger than what is advocated by peritoneal surface oncological surgeons. Experimental data have shown that cisplatin is not able to penetrate inside tumor residuals is deeper than 3 mm [65]. Therefore, for patients in the trial that had RD more than 2.5 mm, HIPEC procedure might have not exerted a positive effect. Anyway, the analysis was interim, and at least 180 more cases are expected to be recruited until December 2017, according to the study protocol [66].

Final Remarks

The application of CRS and HIPEC in the treatment of advanced EOC has generated a heated debate regarding its actual effectiveness. There has been much confusion surrounding the issue, and no progress in this controversy is expected to be achieved unless some misconceptions and wrong attitudes are corrected. Firstly, the combined procedure should absolutely be performed within a clinical trial. Many PSM centers have offered the treatment outside research protocols, and this kind of practice has hampered the enrollment of patients in clinical trials testing CRS and HIPEC in advanced EOC [67]. The only way to prove the beneficial effect of CRS and HIPEC is pursuing the increment in the level of evidence.

The second point is the erroneous focus that has been given on the topic. The major question at stake in the treatment of advanced EOC is not whether HIPEC works or not. This question was answered brilliantly by Dr. van Driel et al., in the interval setting, with a well-designed randomized study. More level I data will be hopefully provided in the near future by current ongoing clinical trials testing HIPEC in advanced EOC [68–71]. But all these studies unfortunately do and will not clear the issue of how much the maximal surgical effort should be pursued to overcome the prognostic limits imposed by the tumor

biology. It is the surgical component of the binomium CRS and HIPEC, the element that contributes most to the final outcome of the patient. The success of HIPEC is a natural consequence of a cytoreduction of good quality. Optimal surgical aggressiveness could be mean different possible surgical outcomes, according to a gynecologic oncologist, depending on his own interpretation of the concept of complete cytoreduction.

The biology of the tumor, dictated by the initial tumor burden and other molecular characteristics, is likely to impose limits on the prognostic impact of radical surgery. However, in the current scenario of gynecologic oncology international community that is dominated by non-surgically oriented professionals, the potential benefits of a radical cytoreduction are deliberately underexploited due to a skeptical and nihilistic attitude against the principle of maximal surgical effort.

The most desirable question to be posed by a future clinical trial is to compare the radical surgical cytoreduction versus conventional gynecologic surgical approach in advanced EOC. As long as there is no standardization of surgical practice, discussions about the role of HIPEC per se in EOC will be insufficient to promote an actual advance in the treatment of this deadly condition.

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Compliance with Ethical Standards

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