Secondary cytoreductive surgery, hyperthermic intraperitoneal intraoperative chemotherapy, and chemotherapy alone: A retrospective comparison of alternative approaches in relapsed platinum sensitive ovarian cancer

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Secondary cytoreductive surgery ~~(SCR)~~, ~~hipec~~ hyperthermic intraperitoneal intraoperative chemotherapy, and chemotherapy alone: a retrospective comparison of alternative approaches in relapsed platinum sensitive ovarian cancer

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Summary

Introduction: The best treatment for relapsed platinum sensitive epithelial ovarian cancer (EOC) is controversial. The aim of the study was to compare progression-free survival (PFS) and overall survival (OS) in platinum-sensitive EOC patients treated with chemotherapy alone (CTA), secondary cytoreductive surgery (SCR) or SCR plus hyperthermic intraperitoneal intraoperative chemotherapy (HIPEC). *Materials and Methods:* Retrospective analysis of the clinical outcome of 46 EOC patients with at least 30 months of follow-up. *Results:* Median follow-up time was 32 months for the CTA group, 30 months for the SCR group, and 45 months for the SCR + HIPEC group. Fifteen recurrences were observed in the CTA group, seven in the SCR group, and 16 in the SCR + HIPEC group. The median time elapsed between first and second recurrence (PFI-2) was significantly higher among patients treated with SCR + HIPEC, in comparison with patients treated with CTA ($p = 0.012$ and $p = 0.017$, respectively). On the contrary, PFI-2 did not significantly differ between the SCR and SCR + HIPEC groups ($p = 0.877$). A statistically significant difference in OS favouring SCR + HIPEC in comparison with CTA ($p = 0.04$) was observed. *Conclusions:* SCR ± HIPEC compared with CTA improves PFI-2 in patients with platinum-sensitive EOC recurrence. SCR + HIPEC might also improve OS in comparison with CTA. No improvement in favor of SCR + HIPEC *vs* SCR was observed,. These results further support the need of a randomized trial comparing chemotherapy with SCR ± HIPEC in this setting.

Key words: Secondary cytoreduction; HIPEC; Platinum sensitive relapse; Ovarian cancer; Platinum based chemotherapy; Cytoreductive surgery.

Introduction

The optimal treatment of recurrent, platinum-sensitive epithelial ovarian cancer (EOC) is still controversial [1]. In fact, after a standard treatment at the time of diagnosis, consisting in optimal cytoreduction followed by adjuvant platinum-based chemotherapy, more than half of the patients will recur [2] and eventually die [3]. Although many of these relapses are platinum-sensitive, the best way to prolong the time to secondary progression and possibly to extend overall survival (OS) must still be defined.

Standard treatment of platinum-sensitive relapsed EOC is considered platinum-based chemotherapy [4]. However, starting from the front-line experience, which consolidates residual disease at the end of primary surgery as the principal prognostic factor in the treatment of ovarian cancer, during the last ten years secondary cytoreductive surgery [5] associated with perioperative intravenous chemotherapy obtained encouraging results with five-years OS from 37 to 66 months [6-10]. SCR associated with intraoperative administration of hyperthermic intraperitoneal intraoperative chemotherapy (HIPEC) has also been employed in EOC [11, 12], as well as in several other malignancies like pseudomyxoma peritonei, appendiceal, and colorectal cancer [13-17] with interesting results. Since the clinical evidence supporting SCR ± HIPEC in the setting of relapsed EOC is limited, these alternative therapeutic approaches have not still received worldwide consensus.

In this context, the authors conducted a retrospective analysis comparing progression-free survival (PFS) and OS in women with platinum-sensitive (progression-free interval or PFI > six months) EOC treated with either intravenous chemotherapy alone, SCR + intravenous chemotherapy or SCR + HIPEC and intravenous chemotherapy.

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Materials and Methods

Patients

The authors conducted a retrospective analysis of 46 patients with first recurrence of platinum-sensitive EOC treated in two Italian Institutions (Institute of Candiolo, IRCCS and Ospedale S. Giuseppe Empoli) between 1995 and 2012 with one of the following treatments: 1) intravenous platinum-based chemotherapy alone, 2) intravenous platinum-based chemotherapy associated with SCR or 3) intravenous platinum-based chemotherapy associated with SCR and HIPEC (SCR + HIPEC)

The main inclusion criteria were: age ≥ 18 years, performance status ECOG ≤ 1, patients with histologically documented first platinum-sensitive recurrence of EOC (low grade and borderline tumours were excluded), recurrence occurred at least six months after completion of first-line treatment (PFI ≥ six months), and lesions confined to the abdominal cavity. All included patients had normal cardiac, hepatic, respiratory, and bone marrow functions (e.g. absolute neutrophils count > 1,500/μL, haemoglobin > 9 mg/dL, platelets count > 150,000/μL, total bilirubin, and creatinine levels < 1.5 times the upper range). Patients affected by non-epithelial tumors, low grade and borderline tumours, EOC relapses with extra-abdominal, and/or intra parenchymal spread and those not submitted to frontline optimal cytoreduction were excluded from the study population.

Personal history, age, and ECOG performance status of the patients, as well as relevant data on diagnosis, treatment, and follow were prospectively collected in an electronic database. Recurrence diagnosis was determined by Ca125 serum level exponential rise (increase to twice the upper limit of normal concentration) associated with PET-TC and/or total body TC-scan evidence of neoplasia: relapse extension and localization data were also collected.

SCR treatment

Gynecologists and general surgeons constituted the medical team. All patients underwent surgical laparotomic exploration with subsequent maximum attempt to completely remove all sites of disease. SCR, as well as primary cytoreductive surgery, demands a xifo-pubic laparotomic access to the abdominal cavity: in order to achieve complete cytoreduction, several procedures may be required, such as hysterectomy and or bilateral salpingo-oophorectomy, if not previously performed, removal of bulky lymphadenopathy or radicalization of previous lymphadenectomy, radicalization of omentectomy, parietal and diaphragmatic peritoneal removal, splenectomy, single or multiple ileal, colic or rectal resections, and subsequent anastomosis or cutaneous stoma, and partial or complete cystectomy. At the end of surgery, the completeness of cytoreduction was evaluated by the following "Cytoreduction Completeness" (CC) score [18]: CC 0: no residual tumor; CC 1: lesions < 0.25 cm; CC-2: lesions between 0.25 and 2.5 cm; CC-3: lesions > 2.5 c. "Optimal" SCR was intended as CC0.

SCR plus HIPEC treatment

General surgeons and gynaecologic oncologists constituted the medical team. Cytoreductive surgery attempted to remove all macroscopic disease by visceral resections and peritonectomy procedures as described by Sugarbaker [19]. Peritonectomy extension was recorded as the sum of peritonectomy sites, classified in five areas. As for SCR alone, the completeness of cytoreduction was classified according to the CC score [18]. All HIPEC procedures were carried out intraoperatively following cytoreductive surgery, with an original semi-closed technique [20). HIPEC was performed for 60 minutes at a temperature of 41.5°C. The drugs used were cisplatin (CDDP) 100 mg/m^2 plus doxorubicin 15.2 mg/l. Patients were treated postoperatively in the intensive care unit for at least 24 hours (range 24–96 hours).

Intravenous chemotherapy treatment

All patients were treated with platinum-based chemotherapy. The most common doublet used was carboplatin AUC 6 and paclitaxel 175 mg/m^2 for six cycles. One patient was treated with carboplatin AUC 5 and pegylated liposomal doxorubicin ~~(Caelyx)~~ and other two patients received the doublet carboplatin and cyclophosphamide or gemcitabine. Three patients received carboplatin or cisplatin as single agents. At the end of secondary treatment all groups were submitted to an identical follow up regimen: periodical visits occurred every three months during the first year and every six months in the following years, and included physical and gynaecological examinations, pelvic ultrasound examination, quality of life assessment, and a CA125 essay. PET-TC and/or total body TC-scan were just performed at Ca125 exponential rise, on clinical indication or in symptomatic disorders. At the end of secondary treatment, all groups were submitted to an identical follow up regimen: periodical visits occurred every three months during the first year and every six months in the following years and included physical and gynaecological examinations, pelvic ultrasound examination, quality of life assessment, and a CA125 essay. PET-TC and/or total body TC-scan were just performed at Ca125 exponential rise, on clinical indication or in symptomatic disorders.

Statistical analysis

The authors named primary platinum-free interval (PFI-1) the time elapsed between the end of primary treatment and the first recurrence. The duration of second response or secondary platinum-free interval (PFI-2) was defined as the time elapsed between the first recurrence and the second recurrence or date of last follow-up. They defined OS as the time elapsed from the second recurrence to the date of death or the date of last follow-up. All patients reached at least 24 months of follow-up. The response to treatments and progression was estimated according to the Gynecological Cancer Intergroup (GCIG) response criteria [21], using both serological and radiological criteria. In brief, complete response (CR) consisted in the disappearance of all known disease on CT scan and return of serum CA-125 levels to normal values (35 IU/ml) for at least four weeks. Partial response (PR) was considered to be a 30% decrease in the sum of the longest diameter of target lesions (evaluated by CT scan) in measurable disease or a 50% decrease in serum levels of CA-125 (confirmed with repeat serum CA-125 level assessments in no less than four weeks). Progressive disease (PD) was considered to be appearance of new lesions or more than 30% increase in the sum of the longest diameter of target lesions (evaluated by CT scan) in measurable disease or increase in serum levels of CA-125 more than two-fold the nadir value in non-measurable disease. At the end of secondary treatment, all groups were submitted to an identical follow up regimen: periodical visits occurred every three months during the first two years and every six months during the following years, and included physical and gynaecological examinations, pelvic ultrasound examination and CA125 dosing. PET-TC and/or total body TC-scan were just performed when CA 125 exponentially increased, or at the onset of symptoms.

Comparisons between categorical variables were evaluated by the Chi Square or the Fisher's exact test. Survival curves were compared by the log-rank test. Statistical significance was set at $p < 0.05$. All the analyses were conducted with the SPSS 20.0 statistical package.

Ethical approval statement

In Italy, the National Regulation established that retrospective studies require a notification to the local ethical committee with the tacit consent formula. The authors therefore notified to the Candiolo Cancer Center ethical committee of the conduction of the study on January 17, 2015. All patients included in this retrospective study were treated according to the ethical standards of the local committee on

Table 1. — *Patient characteristics.*

	SCR N= 11 (%)	SCR +HIPEC N= 19 (%)	CTA N= 16 (%)	*p* value
Age, years (mean)	56.27	51.26	57.69	0.139
Histology				0.843
Serous	7 (63.6)	11 (57.9)	9 (56.3)	
Endometrioid	1 (9.1)	3 (15.8)	1 (6.3)	
Clear cell	0 (0)	0 (0)	1 (6.3)	
Mucinous	0 (0)	1 (5.3)	0 (0)	
Undifferentiated	2 (18.2)	3 (15.8)	3 (18.8)	
Unknown	1	1 (5.3)	2 (12.5)	
Grade				0.074
2	3 (27.2)	0 (0)	1 (6.2)	
3	6 (54.5)	12 (63.1)	9 (56.2)	
Unknown	2 (18.1)	7 (36.8)	6 (37.5)	
Stage				0.121
1	2 (18.1)	1 (5.3)	0 (0)	
2	2 (18.1)	1 (5.3)	2 (12.5)	
3	6 (54.5)	11 (57.9)	11 (68.7)	
4	0 (0)	2 (10.5)	0 (0)	
Unknown	2 (18.1)	3 (15.7)	0 (0)	
Ca125 at diagnosis (mean)	1204	529	1101	0.699
Ca125 at relapse (mean)	82	59	201	0.331
Ascites (ml)				0.522
< 500	10 (91)	3 (15.7)	12 (75)	
> 500	1 (9)	1 (5.3)	2 (12.5)	
Unknown	0 (0)	15 (79)	2 (12.5)	
Residual tumor after first surgery				0.309
R0	9 (82)	14 (74)	7 (44)	
R1	0 (0)	3 (16)	3 (19)	
R2	0 (0)	2 (10)	2 (12.5)	
Unknown	2 (18)	0 (0)	4 (25)	
ECOG at relapse				0.04
0	8 (73)	11 (58)	12 (75)	
1	1 (9)	0 (0)	4 (25)	
Unknown	2 (18)	8 (42)	0	
Tumor locations				
Pelvis	2 (18.2)	4 (23.5)	1 (6.7)	–
Retroperitoneal	4 (36.4)	0 (0)	2 (13.3)	–
Peritoneum	5 (45.5)	13 (76.5)	11 (73.3)	–
Liver	0 (0)	0 (0)	1 (6.7)	–

Legend: *SCR:* secondary cytoreductive surgery*; CTA:* chemotherapy alone*; HIPEC:* hyperthermic intraperitoneal chemotherapy*;*
PFI-1 primary progression-free interval.

human experimentation and with the Helsinki Declaration.

Results

Patients' characteristics

The authors included 46 patients: 16 patients were treated with intravenous chemotherapy alone (CTA group), 11 patients were treated with secondary cytoreductive surgery and perioperative intravenous platinum-based chemotherapy (SCR group), and 19 patients with secondary cytoreductive surgery in association with hyperthermic intraperitoneal chemotherapy and perioperative intravenous platinum-based chemotherapy (SCR + HIPEC group). Patients' baseline characteristics are summarized in Table 1. Baseline characteristics were similar for all variables considered. The median age at diagnosis was 57.7, 56.3, and 51.3 years for the CTA, SCR, and SCR + HIPEC groups, respectively. Most patients had high-grade (G3), Stage III, serous epithelial carcinoma at diagnosis. CA 125 levels at diagnosis were similar in all groups. At relapse, most patients had elevated CA 125, with no differences of the means among groups. The median PFI-1 was similar for all groups (18.1, 25.9 and 22.0 months for CTA, SCR, and SCR + HIPEC groups, respectively). Surgical details, including cytoreductive procedures and mean hospital stay are shown in Table 2.

Table 2. — *Characteristics of surgery.*

	SCR (N 11)	SCR+HIPEC (N19)
SURGICAL DETAILS, mean (range)		
Duration of surgery, minutes	233 (90-460)	461 (48-720)
Blood loss, ml	362 (100-1200)	NA
Mean hospital stay, days	8.4 (3-25)	.25 (16-36)
SURGICAL PROCEDURES		
Hysterectomy (%)	0 (0)	1 (5.3)
Ovariectomy	0 (0)	1 (5.3)
Omentectomy	3(27.3)	18 (94.7)
Pelvic lymphadenectomy	4 (36)	8 (42)
Para-aortic lymphadenectomy	6 (54)	7 (36.8)
Other lymphadenectomy	3 (27)	0 (0)
Pelvic peritonectomy	6 (54)	12 (63)
Paracolic peritonectomiy	3 (27.3)	9 (47.4)
Diaphragmatic peritonectomy	2 (18.2)	8 (42)
Colon resection	4 (36)	7 (36.8)
Intestinal resection	0 (0)	3 (15.8)
Splenectomy	0 (0)	5 (26.3)
Liver resection	1 (9.1)	3 (15.8)

Legend: *SCR:* secondary cytoreductive surgery*;*
HIPEC: hyperthermic intraperitoneal chemotherapy*;*

Outcome of second-line treatment

Complete cytoreduction, defined as the absence of macroscopic disease, was obtained in all patients who underwent surgery (SCR and SCR + HIPEC groups). No patients submitted to CTA, had a complete remission defined as absence of detectable disease at computed tomography (CT scan) and Ca 125 levels < 35 ml/UI.

Survival analysis

Survival data following second line treatment are shown in Figures 1A and 1B. The median follow-up time was 32.9 months for the CTA group, 30.4 months for the SCR group, and 45.4 months for SCR + HIPEC group. During this period, 15, 7, and 16 recurrences were observed in the CTA,

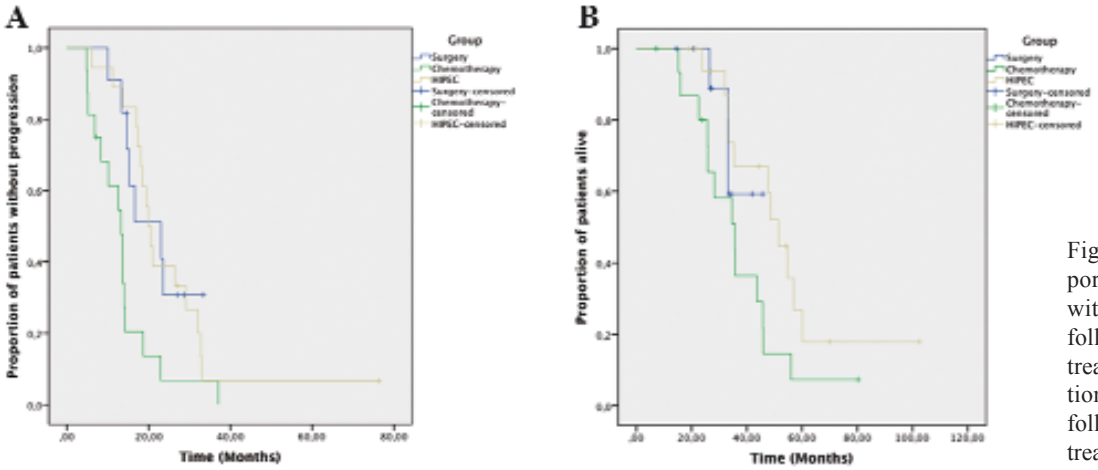

Figure 1. — A: Proportion of patients without progression following second-line treatment. B: Proportion of patients alive following second-line treatment.

Table 3. — *Comparison of secondary progression-free interval (PFI-2) among groups*

Variable	SSCR (months)	SCR + HIPEC (months)	CTA (months)	*p* value
PFI-2	23,031	19,877	13,207	0.009
	23,031	.	13,207	0.012
	23,031	19,877	.	0.877
	.	19,877	13,207	0.017
OS	.	51,483	35,647	
	.	.	35,647	
	.	51,483	.	
	.	51,483	35,647	0.040
FU	30,423	45,357	32,868	0.044

Legend: *SCR: secondary cytoreductive surgery; CTA: chemotherapy alone; HIPEC: hyperthermic intraperitoneal chemotherapy; PFI progression-free interval;* OS: median overall survival, not reached for SCR group FU: median follow up.

Table 4. — *Comparison of duration of primary (PFI-1) and secondary (PFI-2) disease-free interval among groups.*

	PFI-1 (months)	PFI-2 (months)	*p* value
SCR	22.14	23.03	0.499
SCR + HIPEC	21.98	19.88	0.903
CTA	20.01	13.21	0.013

Legend: *CTA:* chemotherapy alone*; SCR:* secondary cytoreductive surgery*; HIPEC:* hyperthermic intraperitoneal chemotherapy*; PFI:* progression-free interval.

SCR and SCR + HIPEC groups, respectively.

The median PFI-2 was significantly different in the CTA, SCR, and SCR + HIPEC groups (13.2 months, 23.0 and 19.9 months, respectively; $p = 0.009$). PFI-2 was significantly higher among patients treated with SCR and SCR + HIPEC as compared to patients treated with CTA ($p = 0.012$ and $p = 0.017$, respectively). On the contrary, PFI-2 did not significantly differ between the SCR and SCR + HIPEC groups ($p = 0.877$) (Table 3).

Table 5. — *Treatment-related complications.*

Adverse events (%)	CTA (N =16)		SCR (N = 11)		SCR + HIPEC (N=19)	
	Any G3	Above G3	Any G	Above G3	Any G	Above G3
Re-laparotomy	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)	1 (5)
Pleural effusion	0 (0)	0 (0)	0 (0)	0 (0)	2 (11)	2 (11)
Bleeding	0 (0)	0 (0)	1 (9)	0 (0)	0 (0)	0 (0)
Pulmonary embolism	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)	0 (0)
Infection	0 (0)	0 (0)	1 (9)	0 (0)	1 (5)	0 (0)
Leukopenia	0 (0)	0 (0)	1 (9)	0 (0)	1 (5)	0 (0)
Paralytic ileus	0 (0)	0 (0)	1 (9)	0 (0)	0 (0)	0 (0)

Surgical complications were scored following the Clavien-Dindo [28] classification; medical complications were scored using the CTCAE v3 criteria. *CTA:* chemotherapy alone*; SCR:* secondary cytoreductive surgery*; HIPEC:* hyperthermic intraperitoneal chemotherapy.

During the follow-up period, a total of 27 deaths were observed: 13 belonged to the CTA group, three to the SCR group, and 11 to the SCR + HIPEC group. The median survival has not yet been reached in the SCR group. Patients in the SCR + HIPEC group survived significantly longer than patients in the CTA group, with a median OS of 51.5 versus 35.6 months, respectively ($p = 0.040$) (Figure 1B).

Interestingly, when the authors compared PFI-2 with PFI-1 for each treatment group, they observed a statistically significant reduction of PFI-2 *vs* PFI-1 only in the CTA group ($p = 0.012$) (Table 4).

Toxicities

As expected, chemotherapy alone was the less toxic treatment with only few cases of febrile neutropenia and no serious adverse effects (Table 5); interestingly, however, no treatment related deaths were observed in the SCR and SCS + HIPEC groups [22].

Discussion

At present, the optimal treatment of platinum-sensitive recurrent EOC remains controversial. For patients who experience platinum-sensitive relapse, platinum-based chemotherapy has long been considered the standard treatment. In these patients, the combination of platinum with taxanes, gemcitabine, or pegylated liposomal doxorubicin is associated with a median survival of 29, 18, and 31.5 months respectively [23, 24].

A large body of data from non-randomized studies has accumulated over the years, suggesting that also SCR may have a role and could significantly prolong survival in selected patients with relapsed EOC. A recent meta-analysis, conducted in forty cohorts of patients with recurrent ovarian cancer (2,019 patients) submitted to SCR, demonstrated that the only clinical parameter significantly associated with post-recurrence survival was the achievement of complete cytoreduction (i.e. absence of any macroscopic residual disease) [25]. Indeed, complete SCR may be associated with prolonged survival, with some studies reporting median survival times ranging between 45 and 61 months [26, 27]. However, in these patients for whom complete cytoreduction cannot be achieved, surgery may have a potentially detrimental effect due to its associated morbidity and to the delay of more effective approaches.

Over the least 20 years, cytoreductive surgery has been also associated with HIPEC in the treatment of various peritoneal malignant diseases with contradictory results [12, 13, 20]. In a recent systematic review, it was reported that HIPEC after cytoreductive surgery in EOC was associated with a median DFS ranging from 10 to 57 months and a median OS ranging from 22 to 64 months, suggesting that it may be a feasible option for patients with advanced or recurrent ovarian cancer [11]. In the setting of recurrent EOC, three case-control studies have been published comparing SCR plus chemotherapy versus the same treatment plus HIPEC and they all show significantly higher five-year OS rates for SCR + HIPEC (50-68%) as compared to SCR alone (17-42%) [12, 28, 29].

In the present study the authors attempted to add further information on the subject by also including in the analysis a group of patients with comparable baseline characteristic who received platinum-based chemotherapy without any surgery, in order to compare the three currently available options in platinum sensitive recurrent ovarian cancer.

Since the duration of response after first recurrence becomes progressively shorter, the ability of a treatment to pair the time of the primary response is a crucial test for any experimental approach [12]. Harrison *et al.* in their retrospective analysis of 35 patients with relapsed EOC submitted to second-line platinum-based chemotherapy found that the median duration of PFI-2 was shorter as compared to PFI-1 (10.8 *vs* 17.8 months, respectively), with only three patients (9%) showing a PFI-2 longer than PFI-1 [30]. Accordingly, in the present series the authors observed a significant reduction in PFI-2 *vs* PFI-1 in the CTA group. Conversely, the medians of PFI-2 and PFI-1 both in the SCR (25 months *vs* 23 months) and SCR plus HIPEC (21 months *vs* 19 months) groups were comparable. Moreover, they observed a significantly longer PFI-2 both for the SCR and the SCR + HIPEC groups *vs* the CTA group.

The present data are consistent with a possible inferiority of the "chemo-alone" approach in platinum-sensitive relapsed EOC in comparison with the "surgery + chemo" approaches. On the contrary, the present authors were not able to demonstrate any significant difference from the addition of HIPEC to SCR, perhaps due the limited number of patients compared. Therefore, both SCR and SCR + HIPEC appear superior to CTA in terms of PFS-2, at least in patients with good performance status and without extra-abdominal diffusion of the disease.

Although a detailed treatment-related morbidity and mortality analysis was out of the aim of this study, the authors substantially confirmed that SCR and SCR plus HIPEC are feasible procedures thanks to recent progresses in more accurate perioperative care, increased surgical expertise, and safer administration of chemotherapy with very low risk of severe morbidities

The strength of the present results is the homogeneity of the analyzed groups, with no significant differences between them in terms of PFI-1, histotype, grading, stage at diagnosis, CA125 at diagnosis and at relapse, residual disease after primary surgery, and amount of ascites at relapse. The weakness of the study is, obviously, its retrospective design and the small number of patients in each group.

In conclusion, this retrospective study comparing the effect of different treatments in platinum-sensitive recurrent ovarian cancer patients adds further evidence on the role of SCR in relapsed platinum sensitive ovarian cancer. On the contrary, the absence of a significantly statistically difference between SCR and SCR ± HIPEC in terms of PF-2 and OS does not support the use of SCR + HIPEC in this setting.

Results from phase-III studies comparing survival rates in women submitted to SCR plus HIPEC *vs* SCR alone (NCT01539785) and results of the DESKTOP III trial (NCT01166737) comparing survival rates in women submitted to chemotherapy alone (control) or cytoreductive surgery followed by chemotherapy are being awaited with interest.

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