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Secondary cytoreductive surgery in platinum-sensitive recurrent ovarian cancer before olaparib maintenance: Still getting any benefit? A case-control study

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HIGHLIGHTS

- The role of SCS in PSROC is still controversial.
- BRCAmut patients who underwent SCS before platinum-based chemotherapy and olaparib maintenance had an increased TFST and PRS.
- Indication to SCS should be individualized.

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ABSTRACT

Objective: The role of secondary cytoreductive surgery (SCS) in platinum-sensitive recurrent ovarian cancer (PSROC) is still controversial. We investigated the role of SCS in PSROC patients with BRCA1/2 mutation (BRCAmut) who received platinum-based chemotherapy followed by olaparib maintenance.
Methods: This is a case-control study. Patients with first PSROC admitted to our Gynecologic Oncology Unit between 2014 and 2018 were identified. Main eligibility criteria: positive BRCA1/2 germline or somatic mutation status and olaparib maintenance at primary recurrence after response to platinum-based chemotherapy. Cases were those who received SCS followed by medical treatment (SCS-CT-OLA, group 1), controls were those who received medical treatment alone (CT-OLA, group 2).
Results: Overall, 46 patients were identified; 23 (50%) BRCAmut women undergoing SCS followed by platinum-based chemotherapy and olaparib maintenance were matched with 23 (50%) BRCAmut women who only received medical treatment. Groups were well balanced: no statistical differences were found with regard of age, mutational status, treatment's approach at diagnosis, timing and patterns of disease presentation at recurrence. Median time to first subsequent therapy (TFST) was significantly longer in the SCS-CT-OLA than in the CT-OLA group (42 months vs 16 months; $p = 0.05$). Also, SCS-CT-OLA patients had the best post-recurrence survival (PRS), with a 3-year PRS of 79% in SCS-CT-OLA group versus 42% in CT-OLA group ($p = 0.02$).
Conclusions: SCS increases TFST and PRS in PSROC patients with BRCAmut candidate for olaparib maintenance after platinum-based chemotherapy. Prospective studies are needed. In the era of personalized medicine, indication to SCS should be individualized.

1. Introduction

Despite initial maximal surgical effort and successful response to medical treatment, recurrence is a common event in high-grade serous ovarian cancer (HGSOC), with 75% of women experiencing relapse within 2 years from diagnosis [1].

Currently, second-line standard of care for patients with platinum sensitive recurrent ovarian cancer (PSROC) is retreatment with platinum-based chemotherapy [2]. Moreover, Parp inhibitor (PARPi) maintenance therapy after platinum retreatment has clearly shown to prolong secondary Progression Free Survival (sPFS) in BRCA1/2 mutated patients (BRCAmut) [3–5].

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Differently, the role of secondary cytoreductive surgery (SCS) is still unclear. Several observational studies had initially suggested that complete SCS was associated with a longer median overall survival compared with chemotherapy alone [6]. Conversely, more recent data coming from randomized controlled trials have raised some concerns that these improved survival outcomes may reflect selection biases of observational studies rather than the intrinsic value of SCS [7–9]. Moreover, none of the RCTs on SCS in PSROC patients have taken into account neither the correlation between SCS and BRCA mutation status, nor the impact of SCS in women receiving new emerging PARPi treatments.

Therefore, we performed this retrospective case-control study with the aim to evaluate the role of SCS in PSROC patients with BRCA ½ mutation who received platinum-based chemotherapy followed by olaparib maintenance.

2. Matherials and methods

2.1. Patients and study groups

Patients with recurrent platinum-sensitive high grade serous ovarian cancer admitted at the Gynecologic Oncology Unit (Fondazione Policlinico Universitario A. Gemelli, IRCCS; tertiary care referral center) between 2014 and 2018 were identified. Main eligibility criteria were primary platinum-sensitive recurrence, positive BRCA 1/2 germline or somatic mutation status and olaparib maintenance after response to platinum-based chemotherapy.

Cases were those who received SCS followed by medical treatment (SCS-CT-OLA, Group 1), controls were those who received medical treatment alone (CT-OLA, Group 2).

In order to avoid imbalance between the two Groups, Cases were matched with Controls according to tumor extension at recurrence, as well as other clinical characteristics at primary diagnosis.

All women gave a written informed consent for their data to be collected and analyzed for scientific purpose. The Institutional Review Board of our Institution approved the study, in agreement with local guidelines.

All women had previously received six cycles of carboplatin 5 AUC/paclitaxel 175 mg/m2 of body surface area, with or without bevacizumab, according to institutional local policy. After chemotherapy administration, patients entered into a routine follow-up program, including gynecological examination, CA125 assessment, and computed tomography (CT) scan or positron emission tomography (PET)/CT scan every 6 months. Once clinical or radiological ROC was diagnosed, patients were selected for surgery or chemotherapy according to disease spread, general health condition, physician's and patient's choice.

Relapse was classified according to site (intra/retroperitoneal and parenchymal) and number of nodules (localized, up to three nodules at one or more sites, and diffuse abdominal carcinomatosis) evaluated at standard imaging (CT scan, FGG-PET-CT scan) [10–12].

Patients deemed suitable for secondary cytoreductive surgery (SCS) after radiological evaluation underwent staging laparoscopy to assess the chance of complete SCS. Laparotomy or minimally invasive surgery (MIS) was performed in patients susceptible to SCS, according to extent and site of disease.

All women received platinum-based chemotherapy followed by olaparib 400 mg taken twice daily (8 × 50 mg capsules twice a day) in case of partial or complete response. Dose interruptions and reductions to 200 mg twice a day or 100 mg twice a day were permitted for toxicity.

2.2. Clinical data

Data regarding disease presentation at recurrence, and timing of relapse from the end of first-line chemotherapy were prospectively recorded and retrospectively analyzed for study purposes.

Maximal surgical effort was attempted in all patients selected for SCS, and residual tumor was recorded. Follow up time was calculated as the interval between diagnosis of recurrence and the last follow-up contact. The primary PFI was defined as the time between the end of primary treatment and the first recurrence, while post-recurrence survival (PRS) was defined as the time between diagnosis of recurrence and the date of death or the date of the last follow-up visit. Time to first subsequent treatment (TFST) was defined as the time between diagnosis of recurrence to the time the patient starts her following line of treatment for subsequent recurrence.

2.3. Data collection and statistical analysis

Data (medical, surgical, biological) were retrieved on the platform REDCap (Research Electronic Data Capture) [13] which is prospectively filled out and updated for all ovarian cancer patients treated at our Institution, who have agreed with a signed consent form. Initially, we identified cases (SCS-CT-OLA) and then matched them with Controls (CHT + OLA), in a 1:1 ratio. Differences between groups in terms of clinicopathological features at diagnosis, and treatment, were analyzed using the Pearson Chi square exact test and Kruskal– Wallis test, as appropriate. Medians and life tables were computed using the product limit estimate by the Kaplan–Meier method, and the log-rank test was used to assess statistical significance. Statistical analysis was performed using GraphPad Prism version 6.0 (GraphPad Software, San Diego, CA, USA) and IBM-Microsoft SPSS version 25.0 for Mac (IBM Corporation, Armonk, NY, USA).

3. Results

Overall, 46 patients were identified; 23 (50%) BRCAmut women undergoing SCS followed by platinum-based chemotherapy and olaparib maintenance were matched with 23 (50%) BRCAmut women who received medical treatment alone. Patients in Group 2 did not receive SCS for the following reasons: I) referred from other hospitals at time of maintenance (10 women, 44%); II) patient's decision (9 women, 39%); III) physician's decision (4 women, 17%) (Supplemental Figure 1).

No differences were observed between Cases and Controls in term of patients' clinico-pathological characteristics at primary diagnosis (Table 1). As per inclusion criteria, all patients had a BRCA 1 or 2 somatic (18, 39%) or germline mutation (28, 61%); in detail, 36 (78%) patients presented with BRCA1 mutation and 10 (22%) presented with BRCA2, without statistically significant differences between study Groups. Median age at recurrence for those undergoing SCS before medical treatment was 54 years (range 36–71), which appears non significantly higher compared with Controls (median 55 years, range 42–74; p-value = 0.62). No differences were observed between SCS-CT-OLA and CT-OLA alone groups in terms of International Federation of Gynecology and Obstetrics (FIGO) stage at diagnosis, primary surgical approach (interval debulking surgery vs. primary debulking surgery), and residual tumor at first surgery (Table 1). With regard of bevacizumab, more than half of the overall population (29 of 46, 63%) had received bevacizumab maintenance at first medical treatment, with no differences between the Groups (p-value = 0.27)

The distribution of relapse according to treatment Group is reported in Table 2. There was no statistically significant difference in the rates of partially and fully platinum-sensitive recurrence.

Table 1
Distribution of patients' clinico-pathological characteristics at diagnosis, according with treatment received.

Parameters	All pts	SCS-CT-OLA (Group 1) *n* (%)	CT-OLA (Group 2) *n* (%)	*p value*[a]
All cases	46	23 (50)	23 (50)	
Median age at diagnosis (range, years)	52 (33–72)	51 (33–68)	53 (41–72)	0.49
Type of BRCA mutation				0.14
BRCA 1	36 (78)	20 (87)	16 (70)	
BRCA 2	10 (22)	3 (13)	7 (30)	
FIGO Stage at diagnosis				0.25
II	1 (2)	1 (4)	0	
III	44 (96)	22 (96)	22 (96)	
IV	1 (2)	0	1 (4)	
Bevacizumab at primary diagnosis				
No	17 (37)	10 (44)	7 (30)	0.27
Yes	29 (63)	13 (56)	16 (70)	
Primary treatment strategy				
PDS	31 (67)	16 (70)	15 (65)	0.50
NACT	15 (33)	7 (30)	8 (35)	
RT at primary surgery (mm)[b]				
0	27 (87)	14 (88)	13 (87)	0.94
1-10	4 (13)	2 (12)	2 (13)	

SCS: secondary cytoreductive surgery; CT chemotherapy; RT residual tumor.
[a] Calculated by Chi-square test.
[b] Calculated only in women treated with PDS.

Table 2
Patients characteristic and pattern of disease at recurrence, according with treatment received.

Parameters	All pts	SCS AND OLA (Group 1) *n* (%)	CT AND OLA (Group 2) *n* (%)	*p value*[b]
All cases	46	23 (50)	23 (50)	
Median age at recurrence (range, years)	54 (36–74)	54 (36–71)	55 (42–74)	0.62
Median PFI (range, months)	24 (8–56)	27 (8–56)	24 (13–54)	0.22
Timing of 1st relapse (months)				
6 < PFI ≤ 12	14 (30)	8 (35)	6 (26)	0.37
>12	32 (70)	15 (65)	17 (74)	
Performance status ECOG				
0	40 (89)	21 (91)	20 (87)	0.47
1	5 (11)	2 (9)	3 (13)	
Ascites at recurrence				
No	43 (94)	22 (96)	21 (91)	0.50
Yes	3 (6)	1 (4)	2 (9)	
Site of recurrence[a]				
Lymph nodal	32 (69)	16 (70)	16 (70)	0.62
Parenchimal (lung, liver, spleen)	10 (22)	6 (26)	4 (17)	0.36
Peritoneum	33 (72)	17 (74)	16 (70)	0.50
Extension of peritoneal disease				
Localized (up to 3 nodules)	10 (21)	7 (29)	3 (13)	0.35
Diffused (more than 3 nodules)	23 (51)	10 (48)	13 (56)	
RT at secondary surgery (mm)				
0	NA	22 (96)	NA	
1-10		1 (4)		

SCS: secondary cytoreductive surgery; CT chemotherapy; RT residual tumor.
[a] Some patients may have different sites of recurrence; percentages are expressed on the total number of patients according to treatment group.
[b] Calculated by Chi-square test.

Median PFI was also similar between Groups: 27 months in SCS-CT-OLA patients (range 8–56) compared with 24 months (range 13–54) in the CT-OLA counterpart (p value = 0.22).

Focusing on the pattern of disease presentation, no differences were found between those who underwent SCS or not, in term of both peritoneal involvement (p value = 0.50) and parenchimal recurrences (p value = 0.36), with 1 (4%) patient requiring right lung lobectomy, 2 (8%) women requiring splenectomy and 3 (12%) requiring segmental liver resection. Moreover, no differences in number of peritoneal nodules were found among Groups (p value = 0.35) (Table 2). Of the 23 patients who underwent SCS, complete cytoreduction was achieved in 22 (96%) patients.

Groups were similar with regard of platinum treatment received (Table 3), with the majority of patients (34 women, 74%) receiving 6 cycles of platinum-based therapy before olaparib maintenance. In those patients not undergoing SCS, response to platinum was as follows: 9 patients (39%) and 14 (61%) achieved complete and partial response, respectively.

All patients were PARP inhibitors naïve. Olaparib was well tolerated among both Groups; dose reduction was necessary in 8 (35%) (Group 1) compared with 4 (17%) (Group 2), without significant differences (p value = 0.15). Only 1 patient discontinued Olaparib administration due to unacceptable toxicity. At the time of final analysis, 16 patients (60%) compared with 12 (52%) are still under treatment in the SCS-CT-OLA and CT-OLA groups, respectively (p value = 0.18).

After a median follow-up of 22 months (range 6–46), 20 (87%) patients in the SCS-CT-OLA group were alive, compared with 17 (74%) patients in the CT-OLA group (p = 0.23).

At Kaplan–Meier analysis median time to first subsequent therapy (TFST) was significantly longer in the SCS-CT-OLA than in the CT-OLA group (42 months vs 16 months; p = 0.05; Fig. 1).

Table 3
Details of medical treatment at recurrence.

Parameters	All pts	SCS AND OLA (Group 2) *n* (%)	CT AND OLA (Group 2) *n* (%)	*p value*[a]
All cases	46	23 (50)	23 (50)	
Chemotherapy at I recurrence				
• Carboplatin-Paclitaxel	7 (15)	2 (9)	5 (22)	0.20
• Carboplatin- PLD	20 (44)	12 (52)	8(35)	
• Carboplatin-Gemcitabine	17 (37)	7 (30)	10 (43)	
• Carboplatin alone	2 (4)	2 (9)	0 (0)	
Nr of Platinum cycles before Olaparib maintenance				
• 4 cycles	6 (13)	3 (13)	3 (13)	0.39
• 5 cycles	2 (4)	0	2(9)	
• 6 cycles	34 (74)	17 (74)	17 (74)	
• > 6 cycles	4 (9)	3 (13)	1 (4)	
Response to Platinum				
• Complete Response	NA	NA	9 (39)	
• Partial Response			14 (61)	
Dose Reduction of Olaparib				
No	34 (74)	15 (65)	19 (83)	0.15
Yes	12 (26)	8 (35)	4 (17)	
Olaparib interruption due to inacceptable toxicity				
No	45 (98)	23 (100)	22 (96)	
Yes	1 (2)	0 (0)	1 (4)	0.50
Olaparib still ongoing				
No	18 (39)	7 (30)	11 (48)	0.18
Yes	28 (61)	16 (70)	12 (52)	

PLD: peghilated liposomal doxorubicin.
[a] Calculated by Chi-square test.

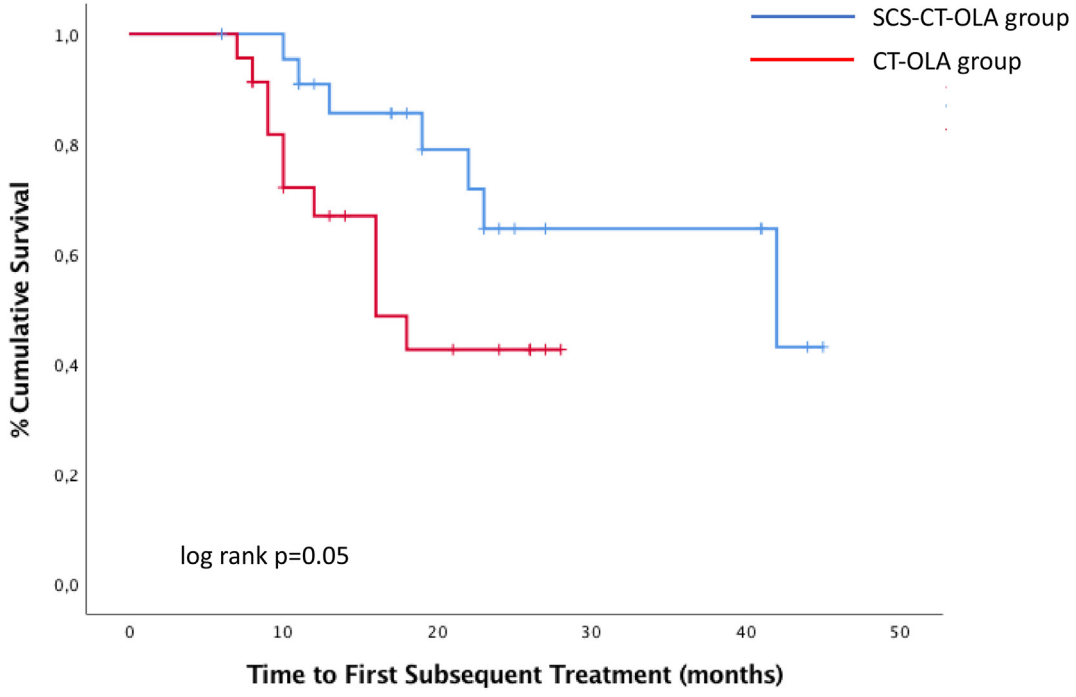

Fig. 1. Median Time to First Subsequent Therapy according to treatment received: SCS-CT-OLA (23 patients) compared with CT-OLA (23 patients): 42 months vs 16 months (p-value = 0.05).

Furthermore, SCS-CT-OLA patients had the best post-recurrence survival (PRS), with a 3-year PRS of 79% in SCS-CT-OLA group versus 42% in CT-OLA group (p = 0.02; Fig. 2). (Median PRS not reached in the Group of SCS-CT-OLA).

Among those who did not undergo for surgery, those who achieved a partial response after platinum combination showed a shorter median TFST compared those with a complete response after platinum (12 months vs. not reached; p = 0.001)

4. Discussion

In this retrospective case-control study we found that patients candidate for olaparib maintenance after platinum-based chemotherapy undergoing SCS achieve a significant increase of both TFST and PRS, compared with those who received CT only, followed by Olaparib maintenance.

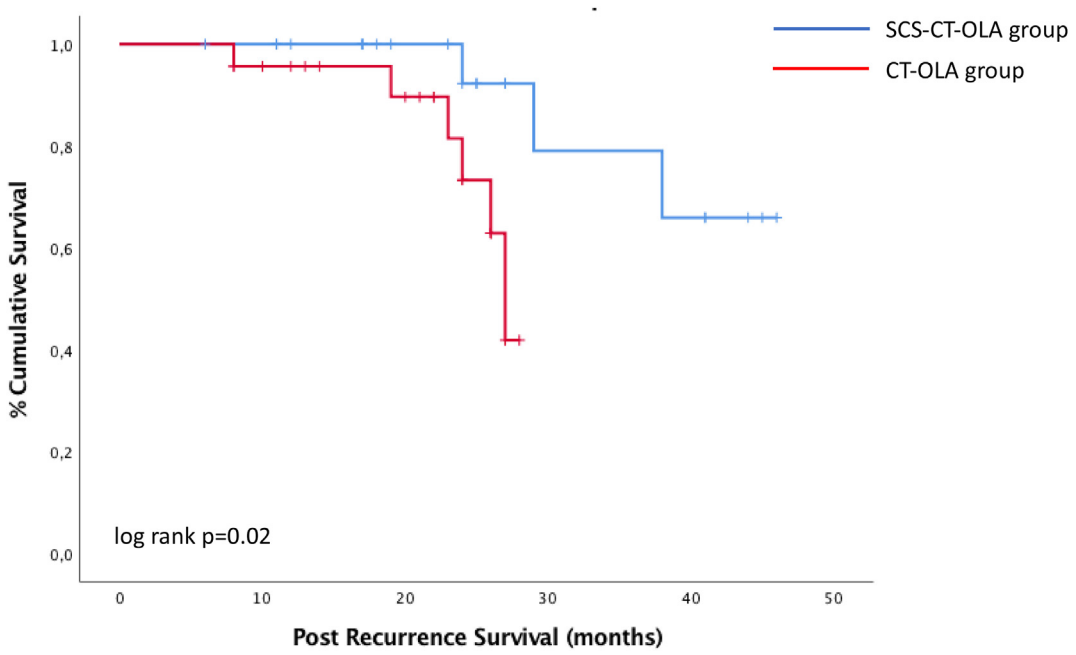

Fig. 2. Post Recurrence Survival according to treatment received: 3-years PRS of SCS-CT-OLA (23 patients) compared with CT-OLA (23 patients): 79% vs 42% (p-value = 0.02).

It is now well established that PARPi maintenance is an effective and survival-prolonging treatment option for patients with BRCA-mut recurrent ovarian cancer [3–5]. Nonetheless, the extent of benefit is still uninvestigated in those patients who are exposed to SCS before medical treatment.

In some PARPi trials this subgroup of patients has been included, but data are still pending [3,4]. In clinical practice, some physicians are reluctant to propose maintenance with a PARPi when the patient is tumor-free, as it happens after complete SCS, suggesting that maintenance with PARPi should be postponed in later lines of chemotherapy.

However, recent data from a post-hoc analysis of the SOLO-1 trial presented at ASCO this year [14] have shown a significantly increasing beneficial effect of olaparib in patients achieving absent residual tumor at primary surgery.

Therefore, we investigated whether the larger efficacy of PARPi in absent macroscopic disease at primary diagnosis can be translated into the recurrent setting. In other words, we tried to understand whether SCS before olaparib treatment in BRCAmut patients might be inconvenient or beneficial. We found that when complete SCS is performed, patients experience a significantly 2-times longer TFST, compared with those with similar tumor spread and health conditions but who did not receive surgery (42 months vs 16 months; p = 0.05; Fig. 1).

It should be noticed that the population of our series is comparable with others presented in previous experiences, with regard of both clinical characteristics and outcomes at primary diagnosis; accordingly, the TFST we found in the CT-OLA group resembles the one already proposed in the current literature, showing a TFST 19-months long for PSROC on olaparib [4].

Contrariwise, the 42-months of TFST we described in those receiving olaparib after SCS has never been shown in the literature, as well as the 80% 3-year PRS. Moreover, an increase of PRS has never been shown in BRCA women receiving PARPi maintenance versus placebo [3–5]. Some explanations might be proposed for this finding.

First of all, the rationale of tumor surgical removal is supported by the mathematical model of Goldie and Coldman [15] suggesting that the likelihood of chemotherapy being curable is related to the number of tumor cells present (chemotherapy is able to kill 10^5 tumor cells, but each 1 cm tumor nodule contains 10^6–10^7 cells). Consequently, the more the tumor burden, the higher the risks of developing chemo-resistance to treatments, advocating that the removal of a great amount of disease might delay olaparib's resistance development.

Accordingly with this hypothesis, data form the SOLO 1 study have demonstrated that, albeit the overall population benefit form olaparib maintenance after first line chemotherapy, those who have been completed debulked are those who unequivocally benefit the most, compared with those with residual disease after surgery (median PFS not reached versus 15.3 months) [14].

Secondly, it could be assumed that patients submitted to surgery have been accurately selected, due to the particularly high rate of optimal cytoreduction we reported. With this regard, it should be underlined that 2 randomized control trials about SCS in ROC have recently come up with unsettled results about the role of SCS [7–9]; in both of them radicality was slightly lower and only in the AGO-DESKTOP III trial patients have been preselected before surgery. Nevertheless, none of the RCTs focused on the role of SCS in relation to the BRCA status as well as the use of PARPi.

In a previous experience we reported that SCS is extremely beneficial for wild type BRCA PSROC patients amenable for SCS, meanwhile for BRCA ½ mutated patients prognosis seemed to be related with molecular tumor characteristics more than tumor resectability. Nonetheless in that original series the use of PARPi wasn't as wide as it is in the present study, follow up of women under olaparib was too short for being evaluated [16].

Of course, despite the exact matching in term of disease extension, residual tumor at first surgery, and recurrence's presentation, the retrospective nature and the small sample size certainly represent relevant study limitations and these data need to be prospectively validated in larger series. A randomized control trial would be useful to clarify this issue but extremely challenging to be designed. Indeed, the role of SCS is still debated, waiting for definitive OS results of the DESKTOP III trial [7]. In this context, an exploratory analysis of subgroup of patients according to BRCA status is desirable. Finally, population landscape is quickly changing as the majority of BRCA mut patients are now supposed to receive

OLA maintenance after first line chemotherapy. Type and diffusion of recurrence after PARPi is also unknown, and we are waiting for clinical trials results to clarify the role of a PARPi schedule after a previous PARPi treatment [17].

Nonetheless, this is the first and larger series investigating the correlation, if any, between PARPi maintenance and SCS. Furthermore, survival outcomes of those undergoing SCS-CT-OLA considered out of comparison, are among the longest proposed in the setting of PSROC receiving a PARPi and are notable for themselves.

In conclusions, we found that SCS before platinum-based chemotherapy and olaparib maintenance is a promising approach that allows to increase outstandingly survival expectations and deserves to be further investigated. Disease's chronicity also means that we should concentrate our surgical effort when the greatest results can be achieved, such as in patients for which PARPi might be an option. Overall, our experiences suggest that SCS is not for all, but not even for none and in the era of personalized medicine, we believe that the indication to SCS should be individualized.

Author contribution

AF,CM:writing and data interpretation.
CM,AR:data analisys
GS,AR,EP,AF,CM:study design and literature search.
AR,MA,RE:data collection.
GS,AF:reviewing of the final manuscript.

Declaration of Competing Interest

CM, AR, GS, MA, RE, EP, GS, AF report no potential conflict of interest. AP worked until December 2018 at the Astrazeneca Medical Department.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.09.020.

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