Is There a Role for Tertiary (TCR) and Quaternary (QCR) Cytoreduction in Recurrent Ovarian Cancer?

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Abstract. *Background: The aim of the present study was to evaluate the efficacy of tertiary and quaternary cytoreduction in recurrent ovarian cancer patients. Patients and Methods: Between January 1997 and December 2014, 53 patients were submitted to cytoreductive surgery for second and third ovarian cancer recurrence at our Unit. Results: Median age at first diagnosis was 48 years (range=20-69). Forty-six patients (86.8%) underwent tertiary cytoreduction. At the time of surgery, isolated and diffuse disease was observed in 48 (90.6%) and 5 (9.4%) patients, respectively. Complete and optimal cytoreduction was obtained in 41 (77.5%) and in 1 (1.9%) patients, respectively. We did not observe any statistically significant survival differences according to residual tumor. Patients with TFI >12 months showed longer PFS (38 vs. 7 months, p<0.002) than those with TFI <12 months. In 18 of these patients a third recurrence was observed. In 12 patients (66.7%) a complete quaternary cytoreduction was performed. Longer PFS (16 vs. 21 months; p=0.032) and OS (152 vs. 116 months; p=0.015) in patients submitted to cytoreduction with respect to those treated with chemotherapy were observed. Conclusion: Our data suggest that selected ovarian cancer patients who develop a secondary and tertiary recurrence may benefit from additional cytoreductive attempts. The benefit seems to be greater in patients with TFI >12 months showing a single-site recurrence disease, in which complete cytoreduction is achievable. Further studies are required to better-define the role of tertiary and quaternary cytoreduction in recurrent ovarian cancer patients.*

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Ovarian cancer is the fifth cause of cancer-related death in women (1), and worldwide 200,000 new cases are estimated per year (2). Epithelial ovarian cancer accounts for approximately 3% of cancers women, and is the most lethal gynecological malignancy presenting at an advanced stage in 75% of patients (3, 4). Despite a complete clinical remission after cytoreduction and platinum-based chemotherapy is achieved in almost 80-90% of these patients, in 25-75% of patients a recurrence occurs (5, 6).

The goals of treatment of recurrent ovarian cancer are to prolong survival, delay time to progression, control disease-related symptoms, minimize treatment-related symptoms, and to maintain or improve the quality of life. The value of surgical approach in the management of platinum-sensitive recurrence represents one of the most debated issues in the gynecological cancer community. In these patients standard therapy consists of re-induction chemotherapy with platinum-based combination; otherwise in the last decade great attention has been focused on the role of secondary cytoreduction (6-10). Currently, 2 randomized clinical trials are ongoing to demonstrate the prognostic role of secondary cytoreduction (SCR) in recurrent EOC patients: AGO DESKTOP III trial (NCT01166737) and GOG 213 (NCT00565851). Different retrospective studies have shown that the maximal survival benefit of surgery for primary recurrent ovarian cancer might be limited to patients in whom a complete cytoreduction can be achieved (10-14).

The role of tertiary (TCR) and quaternary (QCR) cytoreductive surgery in patients with second and third ovarian cancer recurrence is not established. Usually, preferred treatment depends on a several factors such as: performance of the patient, pattern of recurrence, the disease-free interval and the platinum-based agent's sensitivity. Many retrospective studies demonstrated a benefit in patients who have undergone to second or third surgery (15-19), and few studies evaluated the fourth surgery in the third relapse (20-21).

The aims of the present study were: (i) to evaluate the efficacy of TCR and QCR in terms of survival outcomes, (ii) to describe the pattern of recurrence, and (iii) to assess the type of main surgical procedures performed.

Materials and Methods

Between January 1997 and December 2014, 53 patients were submitted to cytoreductive surgery for second and third platinum-sensitive ovarian cancer recurrence at the Division of Gynecologic Oncology of Catholic University of the Sacred Heart of Rome. Institutional Review Board for retrospective analysis was obtained. Clinical data regarding the population study were anonymously collected in an electronic database.

Stage of disease was assigned according to the International Federation of Gynecology and Obstetrics staging system (22). The tumor histology and grade were achieved by analyzing the pathology reports. All patients were treated with platinum-based adjuvant chemotherapy and were regularly evaluated at the end of treatment for evidence of a disease recurrence. Clinical examinations, trans-vaginal and trans-abdominal ultrasound, and CA-125 assays (if the preoperative value was elevated) were performed every 3 months. A computed tomography (CT) scan and/or positron emission computed tomography (PET/CT) was performed if the above examinations revealed any pathology. Isolated CA-125 increase was not regarded as a recurrence. An expert gynecologic oncology team performed all surgical procedures. Patients requiring palliative surgery for bowel obstruction were excluded from the analysis. Cytoreductive surgery was defined as complete if there was no visible residual tumor (RT), optimal if the largest dimension of the RT was <1 cm, and suboptimal if the dimension was ≥1 cm.

Statistical analysis. Statistical analysis was performed using SPSS statistical software, version 17 (SPSS Inc., Chicago, IL). Continuous variables were expressed as median whereas percentages and frequencies were used for categorical variables. The Fisher exact test and chi-square test were used for the univariate analysis, where appropriate. Estimates of treatment-free survival after TCR were calculated using the Kaplan–Meier method.

Treatment-free interval (TFI) was defined as the time, in months, from the date of the last paclitaxel/platinum cycle to the date of treatment (surgery or chemotherapy) start for recurrence or censoring of the patient. Progression free (PFS) and overall survival (OS) was defined as the time, in months, from the date of diagnosis to the date of recurrence and death or last follow-up, respectively. p-Values ≤0.05 in two-sided tests were regarded significant.

Results

During the study period, 53 patients with secondary platinum-sensitive ovarian cancer recurrence were enrolled in the study. Baseline characteristics, primary and secondary treatments of the study populations are summarized in Table I. The median age at first diagnosis was 48 years (range=20-69). The vast majority of patients had a FIGO III tumor stage (56.7%) and grade 3 (62.2%). At the time of diagnosis and primary recurrence almost 80% of them was submitted to complete primary and secondary cytoreduction (Table I). Median TFI after the end of second-line chemotherapy was 22 months (range 7-120). All patients were submitted to explorative surgery: 46 (86.8%) underwent to TCR, and the remaining 7 (13.2%), deemed as unresectable at surgical exploration, started third-line chemotherapy. At the time of surgery, isolated and diffuse disease was observed in 48 (90.6%) and 5 (9.4%), respectively. Complete and optimal cytoreduction was achieved in 41 (77.5%) and in one 1 (1.9%) patients, respectively. In the remaining 4 patients (7.6%), a sub-optimal RT was obtained.

Median TFI after the end of third-line chemotherapy was 20 months (range 6-120). During the follow-up period, in 18 patients (33.9%) of the study population a third platinum-sensitive recurrence was observed. In 12 patients (66.7%) a successful QCR was performed. In the remaining 6 patients (33.3%), deemed as unresectable a fourth-line chemotherapy was started. At the time of surgery isolated and diffuse relapse was observed in 13 (72.2%) and in 5 (27.8%) patients, respectively. In all patients submitted to QCR a complete RT was obtained.

Surgical procedures performed at the time of TCR and QCR are summarized as follows: Pelvic and/or aortic node dissection was performed in 22 (47.8%) and 6 (49.9%) patients at TCR and QCR, respectively. Bowel resection was required in 14 patients (30.5%) at TCR and in 6 patients (49.9%) at QCR. Peritonectomy was performed in 10 (21.7%) and 2 (16.6%) patients at TCR and QCR, respectively. Splenectomy was performed in 9 patients (17.4%) at TCR and 1 (8.3%) at QCR. Gastro-colic omental recurrence was resected in 3 (6.5%) and 2 (16.6%) patients at TCR and QCR, respectively. We registered 5 atypical liver resections (10.9%) during TCR, whereas distal pancreasectomy was performed in 2 cases, 1 (2.2%) at TCR and 1 (8.3%) at QCR. Other procedures included 4 partial colpectomies, 2 partial bladder resections, 2 ureteral resections, and 1 craniotomy for brain metastasis. Median follow-up period of the study population was 99 months (range=30-203 months).

Median OS and TFI in patients with second recurrence were 96 months (range 30-203 months) and 22 months (range=7-120 months), respectively. Univariate analysis of PFS and OS according to clinicopathological characteristics of patients with second recurrence is shown in Table II. In this

group we did not observe any statistically significant survival differences according to different RT (RT=0 *vs*. RT≠0) at the end of surgery (PFS 22 *vs*. 10 months, p=0.155; OS 99 *vs*. 79 months, p=0.709). Patients with single recurrence showed longer but not statistically significant PFS (22 *vs*. 7 months, p=0.525) and OS (99 *vs*. 64 months, p=0.157) with respect to those with diffuse recurrence. In the group of patients with TFI >12 months we observed a significant longer PFS (38 *vs*. 7 months, p<0.002) compared to those with TFI <12 months. In the same sub-groups no significant differences in terms of OS were detected (133 *vs*. 64 months, p=0.382) (Table II).

Median OS and TFI in patients with third recurrence were 135 months (range=50-206 months) and 20 months (range=6-120 months), respectively. In this group a better PFS (16 *vs*. 21 months; p=0.032) and OS (152 *vs*. 116 months; p=0.015) in patients submitted to QCR, compared to those treated with chemotherapy, were observed.

Discussion

Improvement in ovarian cancer medical and surgical treatments increases the number of patients developing second and third ovarian cancer recurrence. In these patients, the role of cytoreduction is controversial and the impact of surgery on the prognosis remains unclear because of lack of data from prospective randomized trials (6, 19, 23).

In the present study we analyzed the effect of TCR and QCR in platinum-sensitive recurrent ovarian cancer patients. Furthermore, we described the intraoperative tumor dissemination pattern and the surgical procedures performed. We observed that even in TCR and QCR a 77.5% and 66.7% of complete cytoreduction rate was obtained. This cytoreduction rate is higher to that reported in other studies where a 40% of complete cytoreduction has been reported (17, 20). This difference could be partially justified by the difference in terms of pattern of recurrence between our population and the others; in the vast majority of our patients an isolate recurrence both at TCR and QCR was observed, whereas in other studies the intraoperative tumor dissemination pattern revealed that during tertiary setting tumor does not tend to recur in a solitary site but rather in a diffuse manner (10, 17, 20, 24).

The question whether a patient would be an optimal candidate for TCR and QCR remains definitely to be cleared, though, in future prospective randomized trials with the primary objective being the identification of risk factors for a higher operative morbidity and mortality. In that way, a better patient selection for surgery could be obtained, since the associated complications are not acceptable for all patients undergoing surgery. Similar to what has been reported in other studies (17, 20, 24), in our study retroperitoneal and upper-abdominal debulking represents the vast majority of surgical procedures performed at TCR and QCR. In the present literature the morbidity rate reported is between 15% and 30% (19) with a 30-day mortality of 8% (17, 19). It is reliable that patients with multiple intestinal resections in prior surgeries, massive ascites, and main tumor dissemination pattern in upper abdomen such as in the

Table I. *Patients' characteristics*.

	Number (%)
Total	53
Median (range) age at the time of first diagnosis (years)	48 (20- 69)
FIGO stage	
I	7 (13.2%)
II	6 (11.3%)
III	30 (56.7%)
IV	1 (1.9%)
NA	9 (16.9%)
Histotype	
Serous-papillary	40 (75.5%)
Endometriod	4 (7.5%)
Mucinous	1 (1.9%)
Clear cell	2 (3.8%)
Mixed	5 (9.4%)
Transitional cell	1 (1.9%)
Grading:	
G1	2 (3.8%)
G2	10 (18.9%)
G3	33 (62.2%)
NA	8 (15.1%)
RT at primary debulking (N=53)	
RT=0	46 (86.8%)
RT <1 cm	3 (5.7%)
RT >1 cm	0 (0.0%)
NA	4 (7.5%)
Time to first recurrence (N=53)	
Patients with PFI 6-12 months	10 (18.9%)
Patients with PFI 12-24 months	16 (30.2%)
Patients with PFI >24 months	27 (50.9%)
Sites of recurrence: first recurrence (N=53)	
Single	48 (90.6%)
Multiple	5 (9.4%)
RT at secondary cytoredcution (N=46):	
RT=0	41 (77.5%)
RT <1 cm	1 (1.9%)
RT >1 cm	4 (7.6%)
Time to third recurrence (N= 18)	
No. patients with PFI 6-12 months	6 (33.3%)
No. patients with PFI 12-24 months	4 (22.2%)
No. patients with PFI >24 months	8 (44.5%)
Sites of recurrence: third recurrence (N=18)	
Single	13 (72.2%)
Diffuse	5 (27.8%)
RT at quaternary cyotreduction (12 patients)	
RT=0	12 (100%)
RT≠0	0 (0%)

NA, Data not available.

Table II. *Univariate analysis of PFS and OS according to clinicopathological characteristics at tertiary cytoreduction.*

	Univariate			
	N (%)	Median PFS (range)	Median OS (range)	*p*-Value
Residual tumor				
0	41	22 (5-120)	99 (30-203)	0.155 (PFS)
≠0	12	10 (5-36)	79 (50-206)	0.709 (OS)
Pattern of of recurrence				
Single	48	22 (4-120)	99 (30-206)	0.525 (PFS)
Diffused	5	7 (5-19)	64 (36-192)	0.157 (OS)
Treatment free interval (TFI)				
TFI <12 months	23	7 (5-12)	64 (30-194)	0.002 (PFS)
TFI >12 months	30	38 (14-120)	133 (36-206)	0.382 (OS)

omental bursa, with tumor infiltration of duodenum and pancreas, could possibly signify negative predictors of operative outcome in terms of a higher morbidity (17).

The majority of retrospective reviews on surgical cytoreduction in the secondary setting have demonstrated that the amount of residual disease after surgical cytoreduction is the strongest predictor of outcome showing a significant advantage in patients submitted to complete secondary cytoreduction (6, 10). Additionally, optimal surgical outcomes were obtained from patients with solitary lesions and survival assessments confirmed a statistically significant advantage for patients who had a solitary site of relapse (13, 14). Probably the 2 randomized trials (AGO DESKTOP III trial (NCT01166737) and GOG 213 (NCT00565851)) comparing surgery plus chemotherapy *vs.* chemotherapy alone in platinum-sensitive ovarian cancer recurrence, will definitively solve this question. Moreover, the proposed survival benefits of complete secondary cytoreduction have induced many authors towards the definition of clinical and clinic-surgical scores able to predict complete secondary cytoreduction (25).

The value of TCR and QCR is less clear than that of secondary cytoreduction due to a lack of large randomized trials. Leitao *et al.* (16) firstly reported a series of 26 patients who had undergone TCR for recurrent epithelial ovarian cancer at a single Institution. At multivariate analysis, TFI >12 months and residual disease retained prognostic significance. The postoperative tumor residual disease was confirmed as the strongest predictor of survival in other subsequent retrospective studies (10, 17, 24). In this study, we observed longer but not statistically significant better PFS and OS in the groups of patients with absence of RT compared to those with RT≠0, patients with single *vs.* diffuse recurrence, and patients with TFI >12 months with respect to those with TFI <12 months. Our study has several limitations inherent to its retrospective design, small sample size and bias due to selection of patients. These biases could partially justify why we were unable to find any statistical significant difference except for PFS and TFI >12 months. Despite these limits the absolute values of PFS and OS observed might suggest a positive role of complete cytoreduction especially in patients with isolate secondary platinum-sensitive cancer and a TFI of al least 12 months.

These findings are congruent to the well-established experiences already reported for primary and secondary cytoreduction in advanced and recurrent ovarian cancer patients, where maximal surgical effort, reflected in minimal or absent postoperative residual disease, was translated in a significant survival benefit. This criterion could probably be also adopted in subsequent recurrence as firstly reported by Fotopoulou *et al.* (17). In this study, we confirmed that even in patients submitted to quaternary cytoreduction postoperative residual tumor was associated with a significant prolongation of survival.

Despite the fact that we did not include in our analysis a control group of patients treated with chemotherapy alone, results from this study provide new insight into this specialized group of patients with recurrent epithelial ovarian cancer. Our data suggest that selected patients who develop a secondary and tertiary platinum-sensitive recurrence may benefit from additional attempts at surgical cytoreduction. The benefit seems to be greater in patients with TFI >12 months showing a single-site recurrence disease in which a complete cytoreduction is achievable.

It is understandable that it is not logical to treat all patients using a single approach and that these patients should be selected carefully weighing the potential survival benefit against potential surgical risks. Designing a prospective randomized trial on these patients could be problematic and assemble prospective series from tertiary centers might overcome the limits of small volume analysis in order to better define the role of TCR and QCR.

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