AGO Score As a Predictor of Surgical Outcome at Secondary Cytoreduction in Patients with Ovarian Cancer

MUSTAFA ZELAL MUALLEM[1*], KHAYAL GASIMLI[1,2*], ROLF RICHTER[1], JUMANA ALMUHEIMID[1], SARA NASSER[1], ELENA IOANA BRAICU[1,2] and JALID SEHOULI[1]

[1]Department of Gynecology, and [2]Ovarian Cancer Tumor Bank, Virchow Campus Clinic, Charité Medical University, Berlin, Germany

Abstract. *Aim: The present study aimed to compare the outcome of secondary cytoreductive surgery retrospectively in patients with positive and negative Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) score that were operated on at the Department of Gynecology, Charité Comprehensive Cancer Center, Medical University, between 2006 and 2013. Patients and Methods: A total of 209 consecutive patients presenting a first recurrence of epithelial ovarian cancer were enrolled: 139 patients had a positive AGO score, and 70 patients had at least one negative criterion of the AGO score. All patients underwent secondary cytoreductive surgery and data were evaluated retrospectively. Results: Total macroscopic tumor resection was obtained during secondary cytoreductive surgery in 127 patients (61%), 93 (67%) in the AGO-positive group and 34 (48.5%) in the AGO-negative group. Overall (OS) and progression-free survival (PFS) were identical in both groups of patients when secondary cytoreductive surgery succeeded in achieving complete tumor resection. PFS was 22 months in AGO-positive patients who were tumor-free after secondary cytoreductive surgery and 21 months in AGO-negative patients with complete resection after secondary cytoreductive surgery. There were no significant differences in morbidity and mortality rates for both groups. Conclusion: AGO score is a useful predictor for operability in patients with a first recurrence of ovarian cancer. Patients with negative scores may still have a 50% chance of achieving optimal tumor resection after secondary cytoreductive surgery. This will be a pivotal factor when counseling patients with recurrent disease regarding further management options.*

Most patients with epithelial ovarian cancer (EOC) have advanced-stage disease at the time of diagnosis. At least 60% of patients with advanced EOC (The International Federation of Gynecology and Obstetrics (FIGO) stage III and IV) who achieve clinical complete remission after primary debulking and first-line platinum-based chemotherapy will ultimately experience relapse and require for further treatment (1). Secondary cytoreductive surgery (SCS) can be considered for patients who experience relapse after a long disease-free interval (6 months or more after the end of first-line chemotherapy) (2).

Surgical outcome after primary tumor debulking, together with platinum response, are the most important predictive and prognostic factors for EOC. This has been validated in several studies, and primary cytoreductive surgery followed by chemotherapy is considered to be a standard treatment procedure for patients with advanced ovarian cancer (3). Currently, there exist no data from prospective randomized clinical trials showing the benefit of Secondary cytoreductive surgery. Results from retrospective studies suggest that patients might benefit form this approach if maximal tumor debulking in terms of macroscopic clearance can be reached (4). The Descriptive Evaluation of preoperative Selection KriTeria for OPerability in recurrent OVARian cancer (DESKTOP OVAR) I study was an exploratory, retrospective study that analyzed the clinical records of 267 patients who underwent secondary cytoreduction for platinum-sensitive ovarian cancer. The results of the study showed that only complete resection was associated with prolonged survival in recurrent ovarian cancer (5). Since survival prolongation is mainly seen for patients with no residual disease, it is most important to identify predictors of complete resection in order to offer the best therapeutic chances to patients, but also to protect patients with limited life expectancy from additional surgical burden (6).

*These Authors contributed equally to this study.

Correspondence to: Dr. med. Dr. (syr.) Mustafa Zelal Muallem, Charité Universitätsmedizin Berlin, Campus Virchow-Klinikum, Augustenburger Platz 1, 13353 Berlin, Germany. Tel: +49 30450664373, Fax: +49 30450564900, e-mail: Mustafa-Zelal.Muallem@charite.de

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Table I. *Characteristics of 209 patients with relapse of ovarian cancer.*

Characteristic	All patients n=209	AGO Score positive n=139	AGO Score negative n=70	*p*-Value
Median age at first diagnosis (range), years	53 (21-81)	51 (21-72)	55 (25-81)	*p*=0.029
Median age at recurrence (range), years	55 (22-84)	54 (22-78)	57.5 (27-84)	*p*=0.125
Median preoperative serum CA125 (range), U/ml	156.5 (0-19208)	149.5 (0-19208)	202.0 (10-14284)	*p*=0.339
ECOG status, n (%)				*p*<0.001
0	49 (23.4)	44 (31.7)	5 (7.1)	
1	133 (63.6)	95 (68.3)	38 (54.3)	
2	23 (11.0)	0	23 (32.9)	
3	4 (1.9)	0	4 (5.7)	
Initial FIGO stage, n (%)				*p*<0.001
IA	10 (4,8)	9 (6.5)	1 (1.4)	
IC	13 (6,2)	10 (7.2)	3 (4.3)	
IIA	3 (1,4)	3 (2.2)	0	
IIB	6 (2.9)	4 (2.9)	2 (2.9)	
IIC	7 (3.3)	6 (4.3)	1 (1.4)	
IIIA	9 (4.3)	8 (5.8)	1 (1.4)	
IIIB	18 (8.6)	13 (9.4)	5 (7.1)	
IIIC	120 (57.4)	78 (56.1)	42 (60.0)	
IV	23 (11.0)	8 (5.8)	15 (21.4)	
Histology at first diagnosis, n (%)				*p*=0.383
Serous	167 (79.9)	116 (83.5)	51 (72.9)	
Endometrioid	8 (3.8)	4 (2.9)	4 (5.7)	
Clear cell	6 (2.9)	3 (2.2)	3 (4.3)	
Mucinous	4 (1.9)	2 (1.4)	2 (2.9)	
Mixed	2 (1.0)	2 (1.4)	0	
Unknown	22 (10.5)	12 (8.6)	10 (14.3)	
Grading at first diagnosis, n (%)				*p*=0.534
I	12 (5.7)	10 (7.2)	2 (2.9)	
II	66 (31.6)	41 (29.5)	25 (35.7)	
III	120 (57.4)	81 (58.3)	39 (55.7)	
Unknown	11 (5.3)	7 (5.0)	4 (5.7)	
Intraoperative ascites, n (%)				*p*<0.001
No ascites	152 (72.7)	111 (79.9)	41 (58.6)	
<500 ml	41 (19.6)	28 (21.1)	13 (18.5)	
>500 ml	16 (7.7)	-	16 (22.9)	
Postoperative tumor residual, n (%)				*p*=0.003
No visible burden	127 (61.0)	93 (67.0)	34 (48.5)	
<0.5 cm	17 (8.1)	13 (9.4)	4 (5.7)	
<1 cm	20 (9.4)	11 (8.0)	9 (12.9)	
<2 cm	12 (5.7)	5 (3.6)	7 (10.0)	
>2 cm	31 (14.9)	15 (10.6)	16 (22.9)	
Unknown	2 (0.9)	2 (1.4)	-	
Median duration of surgery (range), minutes	200 (16-631)	207 (16-631)	185 (20-490)	*p*=0.715
Relapse period (months), n (%)				*p*=0.002
6-12	53 (25.4)	29 (20.9)	24 (34.3)	
12-24	68 (32.5)	42 (30.2)	26 (47.1)	
24-36	45 (21.5)	33 (23.7)	12 (17.1)	
36-60	28 (13.4)	24 (17.3)	4 (5.7)	
>60	15 (7.2)	11 (7.9)	4 (5.7)	

AGO: Arbeitsgemeinschaft Gynäkologische Onkologie. CA125: Cancer-Antigen 125. ECOG: Eastern Cooperative Oncology Group. FIGO: International Federation of Gynecology and Obstetrics.

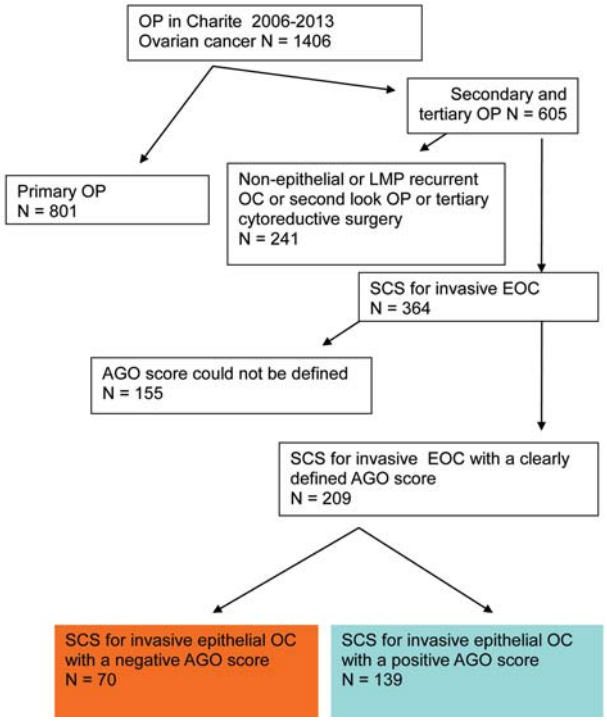

Figure 1. *Inclusion and exclusion criteria for the study population.*

In the DESKTOP I study, clinical prognostic factors were identified. The Arbeitsgemeinschaft Gynäkologische Onkologie (AGO)- score [a score for the prediction of complete cytoreduction in recurrent ovarian cancer. Resectability was assumed if 3 factors were present: (i) complete resection at first surgery (or alternatively FIGO I/II), (ii) good performance status, and (iii) absence of ascites >500 ml that was then validated prospectively in the DESKTOP II study, with 516 patients with ovarian cancer. The results of the study showed that using this score could predict 76% of patients who would benefit from secondary cytoreduction (7). Unfortunately, no data from randomized prospective studies were available at the time.

In 2000, a randomized study was initiated randomizing between second-line chemotherapy with secondary surgery and second-line chemotherapy alone in patients with a disease-free interval of more than 12 months after the end of first-line treatment (EORTC55963). Unfortunately, this study was prematurely closed due to sub-optimal patient enrolment (only 32 patients were included over 30 months). A Cochrane Review found no evidence from randomized clinical trials to inform decisions on secondary surgical cytoreduction and chemotherapy compared to chemotherapy alone for women with recurrent EOC. The author concluded that ideally, a large randomized controlled trial or, at the very least, well-designed non-randomized studies that use multivariate analysis to adjust for baseline imbalances are needed to compare these two treatment modalities (8).

The AGO group started the DESKTOP III trial in 2011. This study is a randomized phase III trial comparing cytoreductive surgery followed by platinum-based chemotherapy *versus* chemotherapy alone in a population of 408 patients with recurrent platinum-sensitive ovarian cancer with positive AGO score at the first event of disease recurrence (9).

Herein we aimed to compare the outcome of secondary cytoreductive surgery retrospectively in patients with positive and negative AGO score who were operated on at the Department of Gynecology, Charité Comprehensive Cancer Center, between 2006 and 2013.

Patients and Methods

209 consecutive patients presenting a first recurrence of EOC were enrolled. In the study period, 1,406 operations for ovarian cancer were performed at our Institution: 801 operations as primary cytoreductive surgery and 605 operations for recurrent disease. We determined the AGO score after reviewing all AGO three criterions in our Tumor Bank database in only 209 patients who underwent SCS in this period. A total of 139 patients had a positive AGO score (a good general condition=ECOG 0-1, no residual disease after surgery for primary ovarian cancer and absence of ascites in presurgical diagnostics), and the 70 patients had at least one negative criterion of the DESKTOP AGO score. Detailed inclusion and exclusion criteria for the entire cohort are presented in Figure 1.

All patients underwent secondary cytoreductive surgery between 2006 and 2013. All operations were performed by one of the experienced Gynecological Oncology surgeons. Data were obtained from the Ovarian Cancer Tumor Bank database. This database is a prospective documentation tool, which includes clinical data, disease history, tumor spread, presence of ascites, and presence and location of residual tumor mass intraoperatively. These parameters are obtained through an interview with the surgeon immediately after the surgical procedure.

Recurrence was proven by clinical examination and imaging. Cancer Antigen-125 (CA-125) was determined in most of the patients, but an isolated increase in this tumor marker was not considered as recurrence. All patients provided their written informed consent before clinical data were collected. Approval from Charite local Ethics Committee was provided for this study (EK207/2003). All patients included in the study had platinum-sensitive disease and received a re-indicated platinum-based chemotherapy 6-8 weeks after SCS. FIGO classification stages mentioned in this study depended on the old classification before the modification from 2013.

At the end of treatment, patients were regularly evaluated for evidence of a new recurrence by clinical examination, transvaginal and transabdominal sonography, and CA-125 values (if elevated preoperative values applied). A Computerized Tomography (CT scan)/ Magnetic resonance imaging (MRI) examination was performed if the examinations mentioned above revealed pathological findings. No treatment decisions were taken based only on raised CA-125 levels.

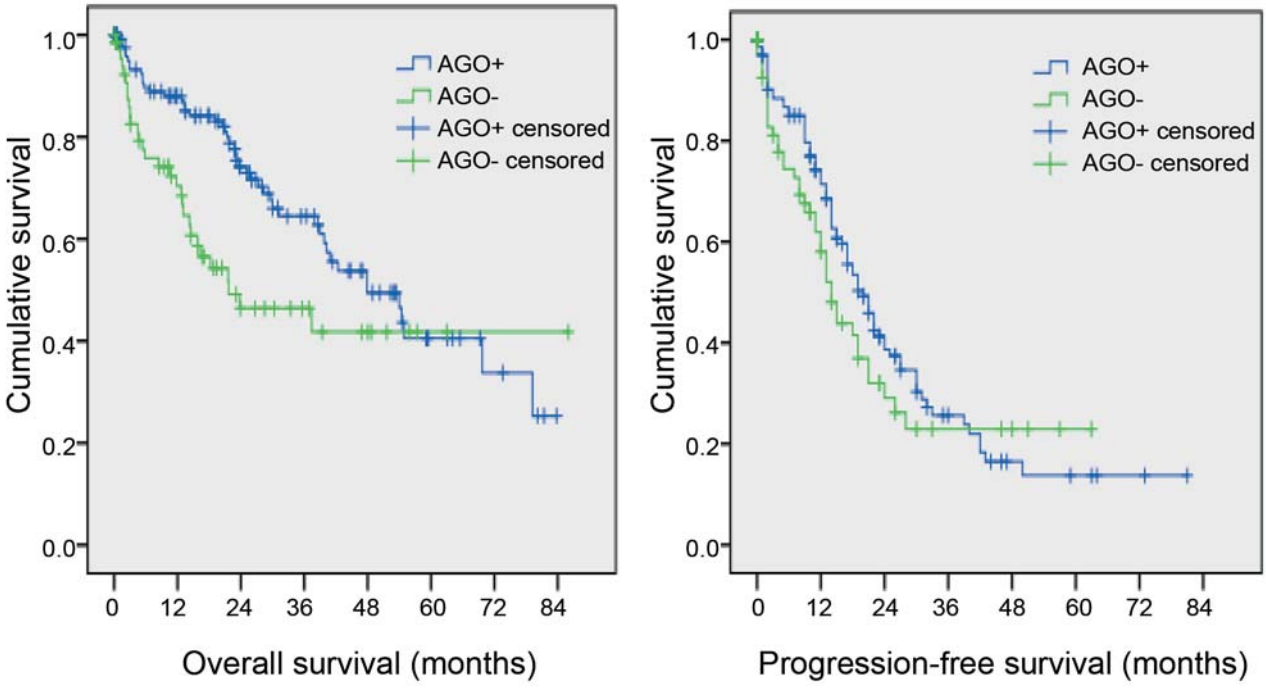

Figure 2. *The overall and progression free survival for positive and negative AGO-score patients.*

The statistical analysis was performed at the Charite Medical University, Berlin. All analyses were performed using PASW 18.0 software (SPSS, Chicago, IL, USA). Data were analyzed by descriptive statistics. Frequency counts and percentages were used to describe categorical variables, and mean and ranges were used for continuous variables. Associations between AGO score and other variables were evaluated by the chi-square test, Fisher's exact test, Kendall's tau b, and Mann–Whitney *U*-test when appropriate. Overall (OS), progression-free survival (PFS) and 95% confidence intervals (CIs) were estimated according to Kaplan–Meier curves. PFS was defined as the length of time between the end of the last chemotherapy cycle to the occurrence of the relapse. OS was determined as the length of time between the surgical treatment for the first relapse and the date of death or end of follow-up. Log-rank test statistics for analysis of the equality of survival distribution were performed. 95% CIs were calculated where appropriate. Statistical significance was defined by a value of $p<0.05$ and two-sided tests were applied.

Results

Patients' characteristics. We included all 209 patients with EOC who underwent secondary cytoreductive surgery in the study period and had full documentation in our data bank. Patients and tumor-related characteristics are presented in Table I.

Two-thirds of patients were AGO-positive, and one-third AGO-negative. The median age (range) at first diagnosis of ovarian cancer was 51 (21-72) years in the AGO-positive group and 55 (25-81) years in the AGO-negative group. Serous histological tumor subtype was diagnosed in 167 patients (79.9%) [116 (83.5%) *versus* 51 (72.9%) for AGO-positive and -negative patients, respectively]. A total of 27 patients (38.6%) with negative AGO score had a poor performance status before undergoing secondary cytoreductive surgery. FIGO stage IIB-IV EOC at initial diagnosis were determined in 183 patients (87.6%), 117 patients in the AGO-positive group (84.2%) and 66 patients in the AGO-negative group (94.3%) ($p<0.001$). After first-line chemotherapy, 156 patients (74.6%) were categorized as having platinum-sensitive disease (recurrence after more than 12 months from the end of platinum-based chemotherapy).

Secondary cytoreductive surgery outcomes in both groups. Optimal surgical debulking in terms of total macroscopic tumor clearance was obtained during secondary cytoreductive surgery in 127 patients (61%), 93 (67%) in the AGO-positive group and 34 (48.5%) in the AGO-negative group (*p*-value=0.016) OR=2.141 (95% CI=1.142-4.019). Sensitivity for AGO score in predicting complete tumor resection on secondary cytoreductive surgery was 73.2% (95% CI=0.677-0.786), the specificity was only 43.9% (95% CI=0.353-0.522), the positive predictive value 66.9% (95% CI=0.618-0.718) and the negative predictive value 51.4% (95% CI=0.414-0.612).

The median overall survival in the AGO-positive group was 54 months (95% CI=39.175-68.825 months), and in the AGO-negative group 21.7 months (95% CI=1.874-41.526 months)

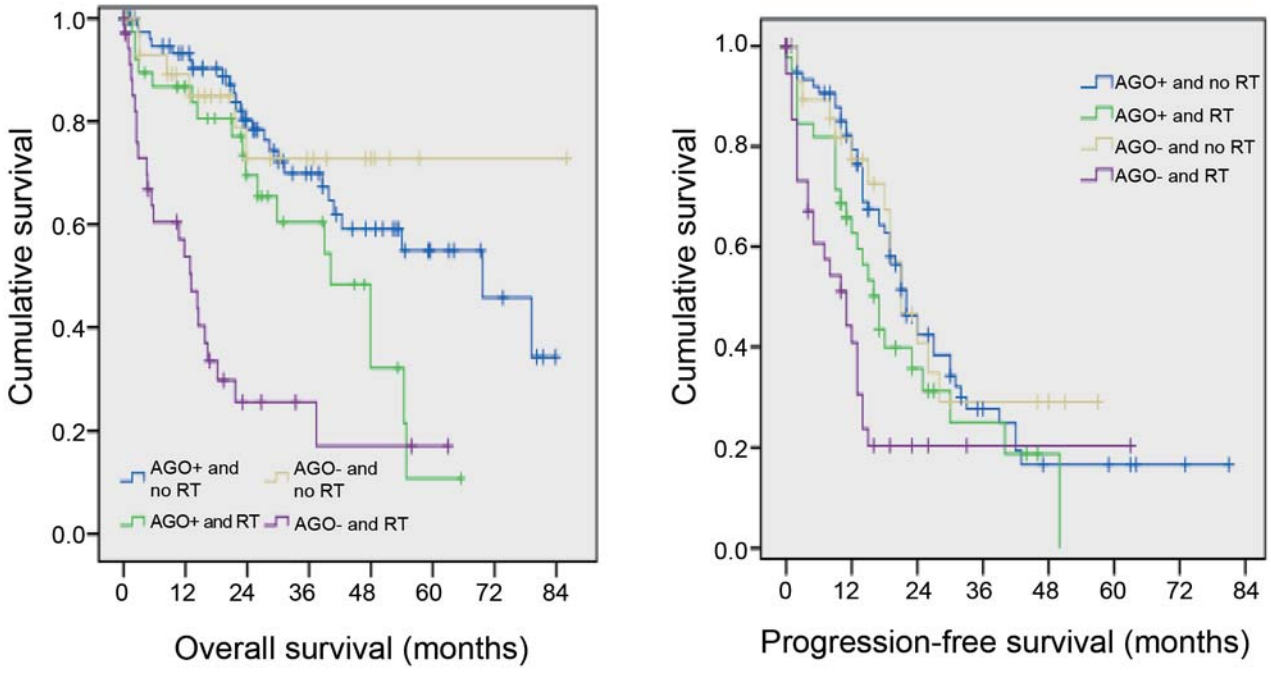

Figure 3. *The overall and progression free survival in combination with residual toumors for positive and negative AGO-score patients.*

(p=0.005). The progression-free survival from secondary cytoreductive surgery was 21 months (95% CI=17.343-24.657 months) in the AGO-positive group compared to 14 months (95% CI=11.179-16.821 months) in the AGO-negative group (p=0.143). Figure 2 shows the overall and progression-free survival according to AGO score.

The duration of secondary cytoreductive surgery was slightly different between the two patients groups [207 minutes (16-631) *versus* 185 minutes (20-490) for AGO-positive and -negative groups, respectively, p=0.715]. No deaths in the first 30 postoperative days in this study collective were reported.

Overall and progression-free survival were identical in both groups of patients when secondary cytoreductive surgery succeeding in achieving complete tumor resection. progression-free survival was 22 months (95% CI=18.514-25.486) in AGO-positive patients who were tumor-free after secondary cytoreductive surgery and 21 months (95% CI=14.379-27.621) in AGO-negative patients with a complete resection after a secondary cytoreductive surgery. Figure 3 illustrates the overall and progression-free survival in combination with residual toumors for patients with positive and negative AGO scores.

Discussion

Even though primary cytoreduction surgery is internationally accepted as standard therapy for patients with ovarian cancer, for relapse there is no clear evidence of the benefit of secondary cytoreduction. In a retrospective study, Harter *et al*. demonstrated that only patients experiencing complete resection might benefit from surgery (5). Median survival was 45.2 and 19.7 months in patients without and with macroscopic residual tumor, respectively (hazard ratio (HR)=3.71; 95% CI=2.27-6.05 months; p<0.0001). The size of residual tumor did not impact on survival of patients not completely debulked. The median survival of patients with a residual tumor and largest diameter of 1-10 mm and >10 mm was 19.6 months and 19.7 months, respectively (HR=0.84; 95% CI=51-1.40; p=0.502). Nevertheless, there are no predictive clinical parameters, biomarkers or signatures to predict optimal surgical outcome in patients with a first platinum-sensitive relapse of ovarian cancer. Therefore identifying clinical or pre-clinical parameters is mandatory.

The AGO score, developed within a retrospective analysis and validated in a prospective independent cohort, has gained more attention in treatment of patients with recurrent ovarian cancer. Harter *et al*. concluded that the positive predictive value of the AGO score in patients with first relapse was 76% (7); the negative predictive value was only 38% and specificity was low at 53%.

In the current study, we aimed to validate the AGO score in an independent, retrospective cohort of patients obtained from the Ovarian Cancer Tumor Bank database. Our results are similar to those published by Harter *et al*.

The rate of complete tumor resection was in this study higher than that registered by Harter *et al*. (5) (61.4% *vs*. 49.8%). This rate ranged in other studies between 9% and 82% (2, 10-27). This difference could be due to the procedures having been performed in a tertiary center by highly experienced surgeons.

Harter *et al*. reported about 62% total tumor resection rate in the primary cytoreduction surgery in their institute between 2004 and 2008 (28). This rate does not diver from the rate of complete resection in our study for the secondary cytoreduction surgery. Subsequently, it seems illogical to recognize this good optimal debulking rate for primary ovarian cancer surgery and not for secondary surgery, especially as it does not associate with higher rates of morbidity or mortality, as shown by our study.

In another publication 2011 from our center, Braicu *et al*. (29) concluded that a complete macroscopic tumor resection could be achieved significantly more often during primary *versus* secondary surgery (77% *vs*. 50%; $p<0.001$) in comparable operative times (242 min *vs*. 199 min; $p=0.15$) and by equivalent operative morbidity (25% *vs*. 29%; $p=0.424$).

A limitation of our study is the retrospective character of the analysis and the inherent bias of a single center.

Conclusion

The present study achieved complete resection in AGO-negative patients in 48.6% of cases. This almost reaches the rate of complete resection for all secondary cytoreductive surgery in 2011. By optimizing surgical skills, and infrastructure we can expect to achieve complete tumor resection for the first recurrence of ovarian cancer in more than 60% of cases. This rate does not divert from the rate of complete resection in primary advanced ovarian cancer and does not increase morbidity and mortality. The AGO score is a useful predictor for operability in patients with ovarian cancer with a first recurrence. But patients with negative AGO scores may still have a 50% chance of achieving optimal tumor resection after secondary cytoreductive surgery. This will be a pivotal factor when counseling patients with recurrent disease on further management options.

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