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A score system for complete cytoreduction in selected recurrent ovarian cancer patients undergoing secondary cytoreductive surgery: predictors- and nomogram-based analyses

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ABSTRACT

Objective: To test the applicability of the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) and Memorial Sloan Kettering (MSK) criteria in predicting complete cytoreduction (CC) in patients undergoing secondary cytoreductive surgery (SCS) for recurrent ovarian cancer (ROC).

Methods: Data of consecutive patients undergoing SCS were reviewed. The Arbeitsgemeinschaft Gynäkologische Onkologie OVARian cancer study group (AGO-OVAR) and MSK criteria were retrospectively applied. Nomograms, based on AGO criteria, MSK criteria and both AGO and MSK criteria were built in order to assess the probability to achieve CC at SCS.

Results: Overall, 194 patients met the inclusion criteria. CC was achieved in 161 (82.9%) patients. According to the AGO-OVAR criteria, we observed that CC was achieved in 87.0% of patients with positive AGO score. However, 45 out of 71 (63.4%) patients who did not fulfilled the AGO score had CC. Similarly, CC was achieved in 87.1%, 61.9% and 66.7% of patients for whom SCS was recommended, had to be considered and was not recommended, respectively. In order to evaluate the predictive value of the AGO-OVAR and MSK criteria we built 2 separate nomograms (c-index: 0.5900 and 0.5989, respectively) to test the probability to achieve CC at SCS. Additionally, we built a nomogram using both the aforementioned criteria (c-index: 0.5857).


Conclusion: The AGO and MSK criteria help identifying patients deserving SCS. However, these criteria might be strict, thus prohibiting a beneficial treatment in patients who do not met these criteria. Further studies are needed to clarify factors predicting CC at SCS.

Keywords: Ovarian Neoplasms; Recurrence; Cytoreduction Surgical Procedures

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Conceptualization: B.G., T.E., S.M., D.A., M.F., L.D., R.F.; Data curation: M.L., S.I., L.R.M.U.; Formal analysis: B.G., T.E., C.V.; Investigation: S.M., D.A., M.F.; Writing - original draft: B.G., T.E., S.M., D.A., M.F., C.V., M.L., S.I., L.R.M.U., L.D., R.F.

INTRODUCTION

Ovarian cancer is considered one of the most lethal malignancies in developed countries, due to its high death to incidence ratio [1]. In the United States, more than 22,400 newly diagnosed cases and 14,000 cancer-related deaths are estimated, every year [1].

Recurrence rate after primary treatment is high, reaching 75%–80% across different series despite recent improvements in primary treatments [2-4]. The mainstay of treatment for patients with recurrent ovarian cancer (ROC) is chemotherapy [2-4]. However, accumulating data support that secondary cytoreductive surgery (SCS) might have a role in a selected population of ROC [5-7]. Since the pioneeristic report from Berek et al. [8], reporting outcomes of 32 patients having SCS for ROC, several studies investigated the role of SCS in this cluster of patients, highlighting the importance of complete cytoreduction (CC) at SCS [8]. However, CC is not achievable in all cases, thus making SCS deleterious and delay chemotherapeutic treatments. Therefore, a correct patient selection is paramount to identify patients at high probability of having CC, thus reducing a number of ineffective surgeries for patients who are likely to have residual disease (RD).

Various models have been built [9-14]. The Arbeitsgemeinschaft Gynäkologische Onkologie Descriptive Evaluation of preoperative Selection KriTeria for OPERability in recurrent OVARian cancer (AGO DESKTOP OVAR) I trial showed that patients having CC for ROC had median overall survival (OS) of 45 months compared with 19 months in patients with incomplete cytoreduction [9]. This study suggested that CC was assumed if 3 factors were present: 1) no RD at first surgery; 2) good performance status; and 3) absence of ascites. The AGO DESKTOP OVAR II prospectively validated this score [12]. The “Memorial Sloan Kettering (MSK) criteria” are useful as well in predicting CC [13]. These criteria are based on the site of recurrence (i.e., single, multiple, and carcinomatosis) and disease-free interval (DFI) [2,13]. However, as suggested by Cowan et al. [2], some criteria might be strict, thus excluding patients from the opportunity of having successful surgical procedures for ROC.

In the present paper we sought to evaluate predictors of CC at SCS, building a reliable model to allow the selection of patients for SCS. As secondary endpoint we aimed to externally validate the Arbeitsgemeinschaft Gynäkologische Onkologie OVARian cancer study group (AGO-OVAR) and MSK criteria for surgical resectability.

MATERIALS AND METHODS

1. Patients

We conducted a single institution cohort study that was approved by the National Cancer Institute Institutional Review Board (approval number: INT/6812). This is a retrospective evaluation examining the role of SCS in a series of consecutive patients with ROC undergoing surgery. From January 1, 2001 through December 31, 2015, 199 patients presenting with ROC were surgically managed at National Cancer Institute of Milan (Italy). We excluded 5 women (2.5%) who did not provide consent to use their medical information for research purposes. All the included patients signed written consent for research purpose.

Since the endpoint of this study was to evaluate predictors of CC at SCS and validate AGO-OVAR and MSK criteria, we searched medical records of patients undergoing SCS in order

to analyze outcomes. The computerized surgical database, containing data on every surgical procedure performed for patients enrolled into the study was of research quality and had been updated by trained residents and nurses. Individual records were screened in order to identify baseline patients' and diseases' characteristics. Inclusion criteria were: 1) age ≥ 18 years; 2) histologically-proven recurrence of invasive epithelial ovarian, primary peritoneal and fallopian tube cancer (i.e., ROC); and 3) execution of SCS. Exclusion criteria were: 1) consent withdrawn; 2) absence of gross disease at the time of SCS; and 3) performance status not allowing surgical treatment. Central pathology review was performed in all cases, before having SCS.

The primary goal of SCS was to achieve CC of the ROC. Over the study period the majority of patients had open abdominal procedures; while laparoscopic approach was reserved in selected cases and just for patients with single retroperitoneal ROC. Details of our surgical protocol are reported elsewhere [15]. Generally, SCS was offered to patients with recurrent disease with a DFI longer than 6 months. DFI was the time between the end of platinum-based adjuvant chemotherapy and the diagnosis of recurrence. Although no specific guidelines are available for the section to SCS, a surgical attempt was offered after the evaluation of the parameters included in both the AGO-OVAR and MSK criteria: 1) no RD at first surgery; 2) good performance status; 3) absence of ascites; 4) site of recurrence; and 5) DFI. According to the AGO-OVAR criteria, ascites was recorded when free fluid was 500 mL or more. The diagnosis of carcinomatosis included the presence of diffuse peritoneal spread of the disease, into multiple anatomical sites.

Generally, preoperative workup included physical examination, dosage of serum markers and the execution of evaluation of the diffusion of the recurrent disease via computed tomography (CT) scan or positron emission tomography (PET). Magnetic resonance imaging (MRI) was executed only in cases of suspicious invasion of the structures surrounding the tumor.

2. Statistical methods

Data were summarized using standard descriptive statistics. Univariate logistic regressions were performed to evaluate the association between predicting variables and CC. All variables with a p-value ≤ 0.10 were included in a multivariate unconditional logistic regression model. Correspondent odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Nomograms were created to improve the clinical interpretation of predicted probability of CC at SCS due to different parameters based on AGO-OVAR criteria, MSK criteria and both. Particularly, multivariate logistic regression was used to build the nomograms considering the variables: Eastern Cooperative Oncology Group (ECOG) performance status, RD at primary surgery and ascites (first nomogram), site of recurrence and DFI (second nomogram), and all variables together (third nomogram). Performance testing of the nomograms developed here was assessed in terms of discrimination (Harrell's c-index). C-index provides an estimate of the probability that the model will correctly identify patients with ROC who had CC at SCS.

In all presented analyses, the MSK criteria were modified subdividing sites of recurrence in 4 categories. In addition to the 3 standard categories of single site, multiple sites, and carcinomatosis, we added the variable "retroperitoneal" that is generally associated with better prognosis than the others. Furthermore, for analysis purpose, we categorized DFI in 2 intervals: < 12 and ≥ 12 months.

OS in patients with and without CC was represented using Kaplan-Meier curves and the log-rank test was used to compare the risk of death over the time between the 2 groups of patients. Cox univariate and multivariate regression models were performed to evaluate OS in study population accordingly to predict variables based on AGO-OVAR criteria, MSK modified criteria, and CC. Statistical significance was set to the conventional p-value ≤ 0.05 , with the exception of the univariate analyses (significant $p \leq 0.10$). Statistical analyses were performed using GraphPad Prism version 6.0 (GraphPad Software, San Diego, CA, USA), IBM-Microsoft SPSS (SPSS Statistics version 20.0; International Business Machines Corporation [IBM], Armonk, NY, USA), R software (version 3.2.3; R Foundation for Statistical Computing, Vienna, Austria), and SAS software (version 9.4; SAS Institute, Cary, NC, USA).

RESULTS

Overall 194 patients met the inclusion criteria and were evaluated in order to identify predictors of CC. **Table 1** reports baseline patients' characteristics. Mean (\pm standard deviation [SD]) patients' age was 61.7 (± 12.6) years. Mean (\pm SD) DFI was 43.9 (± 38.5) months. International Federation of Gynecology and Obstetrics (FIGO) stage at primary diagnosis was stage I, II, III, and IV in 5 (2.6%), 9 (4.6%), 139 (71.6%), and 21 (10.8%) patients, respectively. No clear information about stage of disease at presentation were available for 20 (10.2%) patients. Primary diagnosis was high-grade serous, low-grade serous, mucinous, endometrioid, clear cells, and undifferentiated histology in 140 (72.2%), 4 (2.0%), 2 (1%), 19 (9.8%), 9 (4.6%), and 20 (10.4%), respectively.

Forty-two (21.6%) patients had RD at primary surgery. At the time of SCS 39 (20.1%), 62 (31.9%), 77 (39.7%), and 16 (8.3%) were diagnosed with retroperitoneal, single peritoneal, multiple peritoneal, and carcinomatosis, respectively. Twenty-three (11.8%) patients had ascites at the time of SCS. Among those, 7 (3.6%), 9 (5.6%), and 7 (3.6%) patients were classified with single peritoneal disease, multiple peritoneal disease and carcinomatosis.

Open surgery was the primary approach in 172 (88.7%) patients, while 22 (11.3%) patients had laparoscopic exploration. Conversion to open surgery occurred in 9 (4.6%) cases, while laparoscopic cytoreduction was performed in 13 (6.7%) patients. CC was achieved in 161 (82.9%) out of 194 patients having SCS. According to the AGO-OVAR criteria, we observed that CC was achieved in 87.0% of patients who met the 3 criteria. However, 45 out 66 patients who did not fulfill the AGO criteria had CC. Of note, 3 out of 4 (75%) women who did not meet any criteria (no complete resection, ECOG > 0 and ascites) had complete resection (**Supplementary Table 1**).

Supplementary Table 2 reports data about modified MSK criteria in our population. We observed that 87.1% ($n=142/163$) of women for whom SCS was recommended had CC at SCS and 61.1% ($n=11/18$) of patients for whom SCS was considered had CC. Furthermore, 2 out of 3 (66.7%) patients for whom SCS was not recommended had CC.

Table 2 reports uni- and multivariate analyses evaluating factors predicting CC at SCS. At univariate analyses, histotype, RD at primary cytoreductive surgery, presence of ascites and DFI were associated with the probability to have CC at SCS ($p=0.019$, 0.037, 0.086, and 0.019, respectively). At multivariate analysis, no factors were associated with CC even if undifferentiated histotype seemed to have a borderline trend towards lower CC probability.

Table 1. Main characteristics of the study population

Characteristics	Value
Age (yr)	
Mean (SD)	61.6 (±12.5)
Median (quartiles*)	63.0 (53, 71)
BMI (kg/m ²)	
Mean (SD)	24.7 (±4.2)
Median (quartiles*)	25.4 (20, 36)
ECOG performance status	
0	151 (77.8)
1	43 (22.2)
CA125 at first diagnosis (U/L)	
Mean (SD)	328.5 (±682.2)
Median (quartiles*)	103 (42, 234.3)
Type of ovarian cancer	
High-grade serous	140 (72.5)
Low-grade serous	4 (2.0)
Endometrioid	19 (9.8)
Clear cells	9 (4.6)
Undifferentiated	20 (10.3)
Mucinous	2 (1.0)
FIGO stage	
I	5 (2.6)
II	9 (4.6)
III	139 (72.7)
IV	21 (10.8)
Unknown	20 (10.3)
RD	
No macroscopic tumor at the end of surgery (RD=0)	146 (75.2)
Macroscopic tumor at the end of surgery (RD>0)	42 (21.6)
Unknown	6 (3.1)
Site of recurrent disease	
Retroperitoneal	39 (20.1)
Single peritoneal	62 (31.9)
Multiple peritoneal	77 (39.7)
Carcinomatosis	16 (8.3)
Ascites	
Yes	23 (11.9)
No	124 (63.9)
Unknown	47 (24.2)
DFI, (mo)	
Mean (SD)	43.9 (±38.5)
Median (quartiles*)	32.5 (18, 59.5)
Follow-up (mo)	
Mean (SD)	32.2 (±20.9)
Median (quartiles*)	26 (17, 43.7)

Values are presented as number (%).

BMI, body mass index; CA125, cancer antigen 125; DFI, disease-free interval; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; RD, residual disease; SD, standard deviation.

*Quartiles indicates the 25 and 75 percentiles.

Fig. 1 shows survival curves for patients with and without CC. Patients with CC had OS significantly higher than patients without CC ($p < 0.001$), with median survival time of 40.5 and 23 months, respectively.

Looking at OS in **Supplementary Table 3**, we observed that patients with CC at SCS had lower probability to die than patients without CC at SCS (hazard ratio [HR]=0.25; 95% CI=0.16–0.40; $p < 0.001$). RD and site of recurrence were significantly associated with an increase

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Table 2. Factors predicting complete cytoreduction at the time of secondary cytoreductive surgery

Characteristic	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age (years)*	1.01 (0.80–1.46)	0.616	-	-
BMI (kg/m ²)*	0.93 (0.84–1.17)	0.544	-	-
ECOG		0.22		-
ECOG 0	Reference		-	
ECOG 1	0.59 (0.25–1.36)		-	
Histotype		0.019		0.14
High-grade serous	Reference	-	Reference	-
Low grade serous & mucinous	0.31 (0.05–1.83)	0.198	0.45 (0.04–4.85)	0.508
Endometrioid	2.83 (0.36–22.42)	0.325	2.02 (0.23–17.77)	0.525
Clear cells	0.31 (0.07–1.36)	0.122	0.20 (0.03–1.23)	0.083
Undifferentiated	0.24 (0.09–0.65)	0.005	0.29 (0.09–1.00)	0.05
CA125 levels	0.99 (0.99–1.001)	0.266	-	-
Stage at presentation		N.E.		-
I–II	Reference		-	
III–IV	N.E.		-	
RD at primary cytoreductive surgery		0.037		0.239
RDO	Reference		Reference	
RD>0	0.42 (0.19–0.95)		0.55 (0.20–1.49)	
Site of recurrent disease		0.137		
Peritoneal multiple site	Reference		-	-
Retroperitoneal	1.78 (0.54–5.87)	0.345	-	-
Peritoneal single site	1.06 (0.43–2.60)	0.905	-	-
Carcinomatosis	0.34 (0.11–1.10)	0.071		
Ascites		0.086		0.138
No	Reference		Reference	
Yes	0.43 (0.16–1.13)		0.44 (0.15–1.31)	
Disease-free interval		0.019		0.43
<12 months	Reference		Reference	
≥12 months	3.16 (1.21–8.26)		1.62 (0.49–5.36)	

BMI, body mass index; CA125, cancer antigen 125; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; N.E., no estimate; OR, odds ratio; RD, residual disease.

*OR per 10-year increase in age and one-unit increase in BMI.

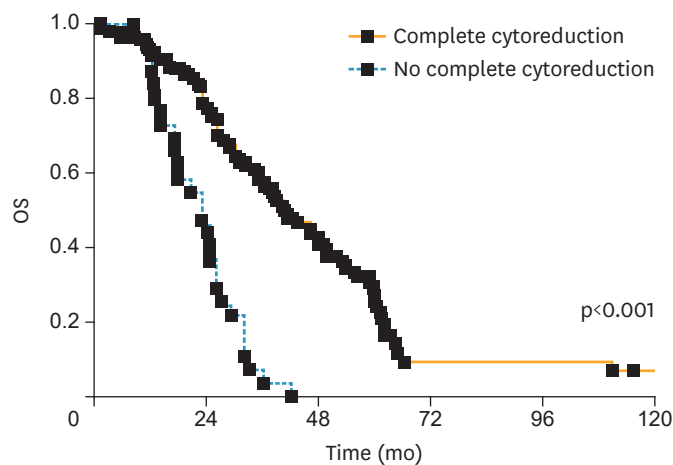


Fig. 1. OS according to CC at SCS. CC, complete cytoreduction; OS, overall survival; SCS, secondary cytoreductive surgery.

in mortality with p-values ≤ 0.10 even if the only significant site at the univariate analysis was carcinomatosis if compared with multiple peritoneal (HR=5.45; 95% CI=2.92–10.18; $p < 0.001$). Moreover, although histotype was globally not significant, low-grade serous and mucinous types showed a significant association with mortality if compared with high-

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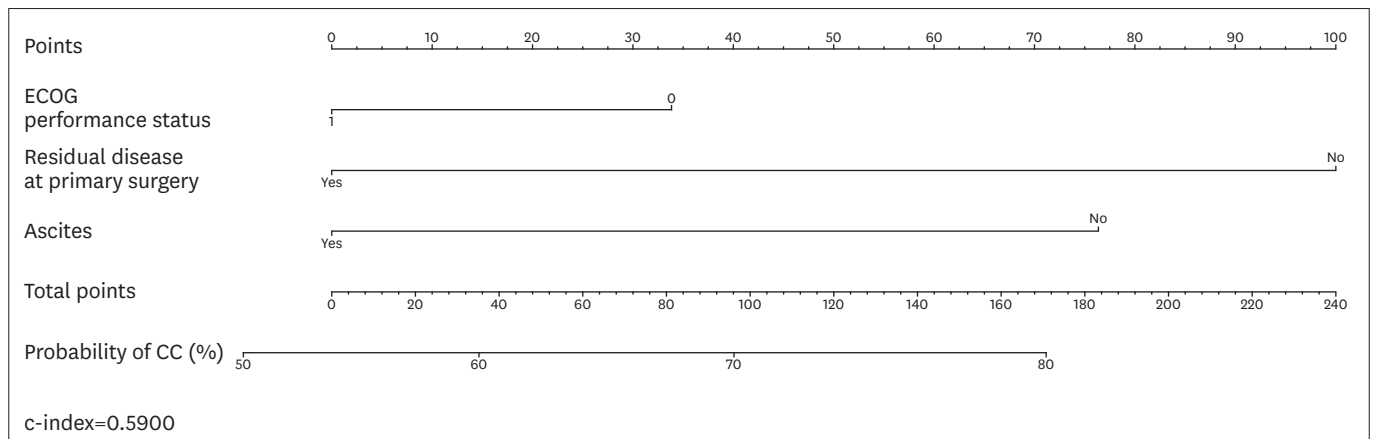


Fig. 2. Nomogram displaying the probability of CC according to the variables included in the AGO-OVAR score. AGO-OVAR, Arbeitsgemeinschaft Gynäkologische Onkologie OVARIan cancer study group; CC, complete cytoreduction; ECOG, Eastern Cooperative Oncology Group; RD, residual disease.

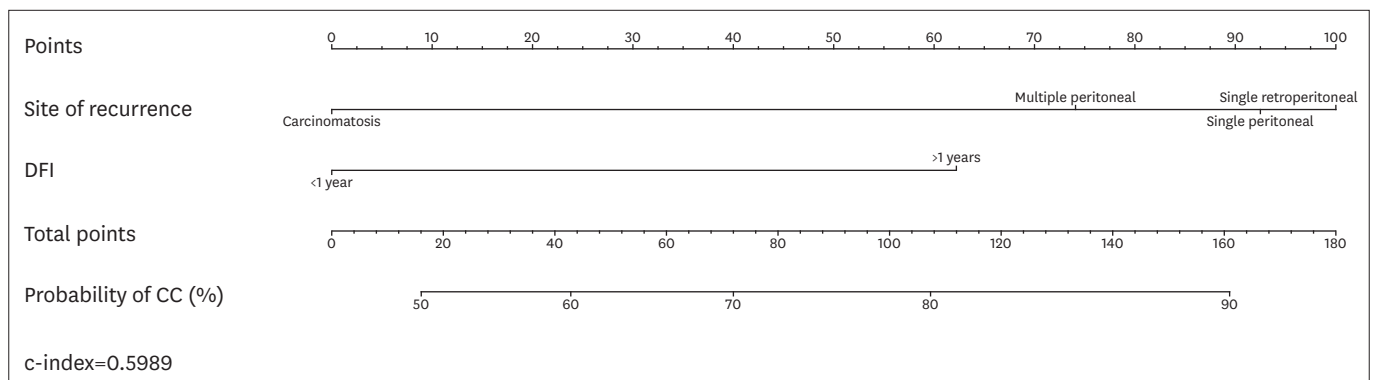


Fig. 3. Nomogram displaying the probability of CC according to the variables included in the modified MSK criteria. CC, complete cytoreduction; DFI, disease-free interval; MSK, Memorial Sloan Kettering.

grade serous (HR=3.52; 95% CI=1.27–9.73; p=0.015) and due to this, histotype was added to the multivariate model. Multivariate analysis confirmed the significance of CC in reducing mortality and the positive association of carcinomatosis (HR=3.09; 95% CI=1.53–6.23; p=0.002). Low-grade serous and mucinous histology were no longer significant associated with OS (p=0.095).

Fig. 2 shows nomogram with ECOG performance status, RD at primary surgery and ascites (according to the AGO-OVAR criteria) predicting the probability to have CC; c-index was 0.5900. **Fig. 3** shows nomogram predicting the probability to have CC based on site of recurrence and DFI (according to the modified MSK criteria); c-index was 0.5989. Additionally, we built a nomogram using both the aforementioned criteria (**Fig. 4**). C-index for this latter nomogram was 0.5857.

DISCUSSION

The present paper investigated factors predicting CC in a selected population of patients with ROC undergoing SCS, thus observing a number of noteworthy findings. First, we

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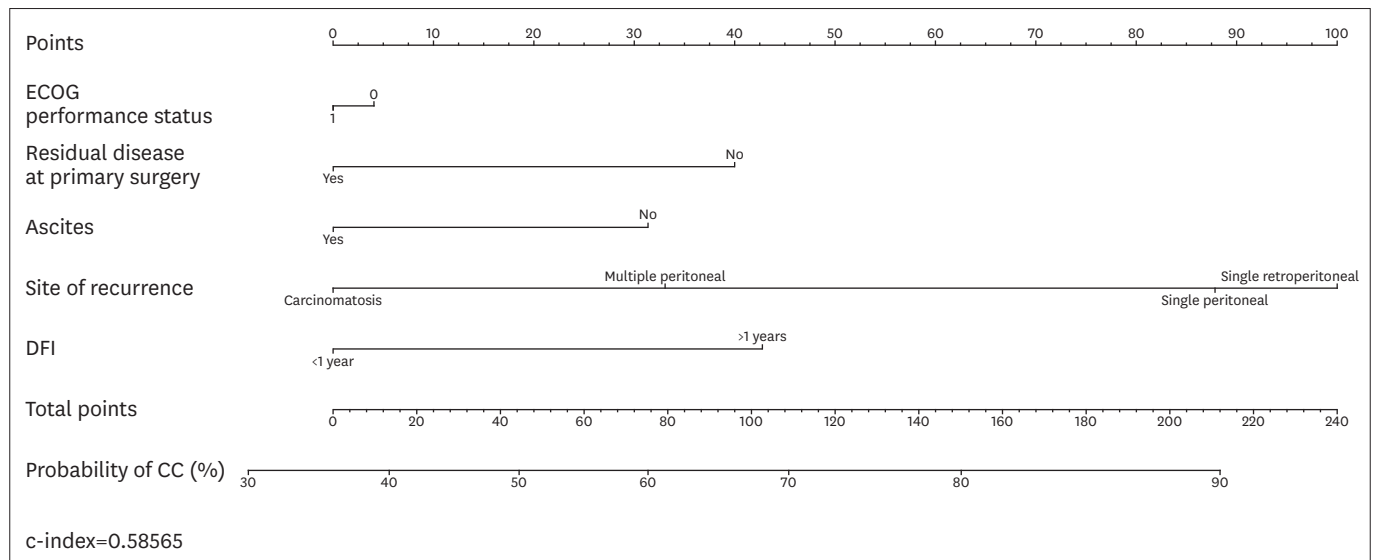


Fig. 4. Nomogram displaying the probability of CC according to the variables included in the AGO-OVAR score and MSK modified criteria. AGO-OVAR, Arbeitsgemeinschaft Gynäkologische Onkologie OVARIan cancer study group; CC, complete cytoreduction; DFI, disease-free interval; ECOG, Eastern Cooperative Oncology Group; MSK, Memorial Sloan Kettering; RD, residual disease.

retrospectively applied the AGO-OVAR and MSK criteria to our population, observing that about 87% who met these criteria had CC. However, CC was also obtained in patients who did not meet these criteria thus suggesting that SCS should not be denied just on the basis of these criteria. Second, CC strongly correlated with OS. Third, our data validated the predictive value of AGO-OVAR and MSK criteria. Moreover, we built the first available nomograms on these criteria. Fourth, for the first time we built a nomogram that considers both the AGO-OVAR and MSK criteria.

Although no mature data supporting SCS in ROC are still available, SCS becomes popular due to the growing evidence supporting the beneficial effect of cytoreduction in platinum-sensitive ROC. The preliminary data of the AGO-OVAR DESKTOP III/ENGOTov20 study (presented at ASCO 2017), comparing SCS vs. second line chemotherapy, suggested that in selected patients (DFI >6 months and with a positive AGO score) SCS resulted in a clinically meaningful increase of progression-free survival and platinum-free interval in comparison with chemotherapy alone [16]. However, data on OS are not mature, and the estimated primary completion date is December 2019. The ongoing Gynecologic Oncology Group (GOG) #213 trial and the Dutch SOCceR trial have similar objectives [17,18].

In agreement with other retrospective experiences [2-7], our investigation supported that CC at SCS improves survival. In fact, the complete removal of the tumor is associated with improved OS and reduced chemo-resistance [19-21]. A meta-analysis of 40 investigations including more than 2,000 women with ROC, suggested that each 10% increase in the proportion of patients with CC at SCS was associated with 3 months increase in OS [22].

Once again, our study validated the AGO-OVAR criteria [9,19]. Moreover, we externally validated the MSK criteria [2,13]. Other models for patient's selection have been proposed (including Tian model, SeC-Score and the Minaguchi criteria) [4,11,14]. Among those, the Tian model is the only one that received external validation [14]. However, this latter model is characterized by a high-false negative rate [2]. Tian model and SeC-Score include

the evaluation of blood markers (i.e., cancer antigen 125 [CA125] and human epididymis protein 4 [HE4]) that are not always available (CA125 levels help in identify ROC in less than 50% of cases [11,14]), depend on position of the recurrent lesions (i.e., peritoneal vs. retroperitoneal) and to histological features of the relapse (high-grade serous recurrent diseases are more likely to be associated with high CA125 and HE4 levels than ROC with clear cell histology).

Interestingly, van de Laar et al. [19], tested the performance of 2 prediction models, the AGO-OVAR criteria and the Tian model, in order to validate them. The authors observed that the AGO score and Tian model showed a positive predictive value for complete SCS of 82.0% and 80.3%, respectively, and a false negative rate of 68.5% and 55.6%, respectively [19]. The MSK criteria had similar ability in identify patients who had CC at SCS. However, even these criteria are too strict, thus prohibiting patients from beneficial SCS. In fact, albeit these models can identify patients with a high likelihood of CC at SCS, most patients with negative scores might have CC at SCS.

In our paper, we did not propose another inclusion/exclusion criteria model for SCS, but we tried to estimate the probability to achieve CC based on the 2 most reliable pre-existing criteria models (i.e., AGO-OVAR and MSK criteria). In fact, our nomograms showed that a patient with poor performance status (ECOG 1), ascites and who had RD at primary surgery has an about 50%–55% of probability to have CC at SCS. Similarly, a patient with carcinomatosis and DFI <12 months had about 40%–45% to have CC. Putting together all these variables we were able to provide a probability of the beneficial effect of SCS.

The inherent selection biases related to the retrospective study design represent the main weakness of the present paper. In fact, our population is a selected population of patients selected to undergo SCS. However, the endpoint of the study was not to test the role of SCS in ROC and the effectiveness of CC. In fact, we aimed to score the probability to have CC at SCS according to both AGO-OVAR and MSK modified criteria, thus helping physicians in identify patients who deserve SCS.

Additionally, 2 other points of the present investigation have to be addressed. First, we modified the MSK criteria subdividing site of recurrence in 4 categories. In addition to the 3 categories of single site, multiple sites, and carcinomatosis, we added the variable “retroperitoneal.” In fact, this latter variable is generally associated with better prognosis than the others. Moreover, we observed that in our series DFI had a relevant prognostic role especially if we compared patients having DFI <12 months with patients having DFI longer than 12 months. Second, although ours is a selected population, an expert team of surgeons treated all the patients thus making our results not projectable in a setting lacking a high-volume surgical experience.

In conclusion, our investigation evaluated the role of SCS in ROC. In agreement with the background, our study confirmed that CC at SCS improves OS. The accuracy of 2 predictive models estimating the probability to have CC at SCS was tested. The AGO-OVAR and MSK modified criteria were evaluated, thus suggesting that applying these criteria allows identification of patients who deserve surgical attempts. However, these criteria alone might be strict, thus prohibiting a beneficial treatment in patients who do not meet these criteria. Our nomograms might be helpful in estimating the probability of patients to have CC based on existing criteria (i.e., AGO-OVAR and MSK). External validations of our nomograms are warranted.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

The AGO-OVAR criteria applied to our population

[Click here to view](#)

Supplementary Table 2

Patients with complete cytoreduction over patients having SCS, basing on recommendations from MSK criteria

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Supplementary Table 3

Factors predicting OS in patients undergoing SCS in recurrent ovarian cancer

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