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Validation of a peritoneal surface disease severity score in stage IIIC-IV ovarian cancer treated with cytoreduction and hyperthermic intraperitoneal chemotherapy

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ABSTRACT

Background: The aim of the present study is to evaluate and validate the PSDSS score as a prognostic tool in patients with stage IIIC–IV epithelial ovarian cancer (EOC) who are treated with a first cytoreduction with peritonectomy procedures and HIPEC, and to discuss the usefulness and applicability of this approach in decision making in clinical practice.

Patients and methods: We analyzed a consecutive series of patients with stage IIIC–IV epithelial ovarian cancer treated by cytoreductive surgery and HIPEC between January 2012 and December 2016.

Results: A total of 115 consecutive patients diagnosed of stage IIIC–IV EOC were included. After the multivariate analyses, the impossibility of performing a complete cytoreduction (CC-score = 1, HR: 4.56, p = 0.012), the PSDSSov (III–IV, HR: 3.59, p = 0.024), a high (> 20) PCI (HR: 3.16, p = 0.032), and the histological type of the tumor (G3, HR: 2.28, 95% CI: 1.14–8.14, p = 0.033) were factors that were independently related with lower DFS. Other variables included in PSDSSov such as pathological lymphadenopathy and the clinical symptoms were not independently related to lower DFS in our series.

Conclusions: PSDSSov is a useful tool in the prognostic stratification of patients with advanced ovarian cancer with peritoneal dissemination (IIIB/IIIC).

1. Introduction

Ovarian cancer is the leading cause of death of all gynecological cancers in developed countries. Because of scant symptoms associated with ovarian cancer and the absence of effective screening programs, more than two-thirds of patients are diagnosed in advanced stages, which means macroscopic peritoneal dissemination or distant metastasis exists (FIGO IIIB–C or IV). After diagnosis, the current management strategy continues to be surgery to completely remove the disease and the administration of platinum-based adjuvant chemotherapy [1].

Even in patients with complete cytoreduction, more than half will present with disease recurrences, frequently in the abdominal cavity, due to the persistence of active microscopic disease that is invisible to the surgeon's eye [2,3]. With the intention of treating this microscopic component, the use of intraperitoneal chemotherapy has increased significantly in recent decades.

Three large prospective and randomized clinical trials conducted by the Gynecologic Oncology Group (GOG) showed the utility of intraperitoneal chemotherapy after a first surgery of ovarian cancer [4–6]. The last one, GOG-172, was re-evaluated in 2013 by Landrum et al. [7], who reported a disease-free survival (DFS) of more than 60 months, with an overall survival (OS) of more than 120 months in stage-III patients who underwent a complete cytoreduction. However, the high rate of toxicity and problems derived from the intraperitoneal catheter meant that only 42% of patients complied with the protocol that was designed at the beginning of the study, although benefits have been described even with the administration of a single intraperitoneal treatment.

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The use of hyperthermic intraperitoneal chemotherapy (HIPEC) has also increased. During the last decade, several nonrandomized and randomized studies have established the safety of HIPEC for the treatment if epithelial ovarian cancer (EOC) and have established convincing evidence that HIPEC provides a similar benefit to intraperitoneal therapy [8–11]. Spiliotis et al. [12] published the results of a prospective randomized study of 120 patients with recurrent disease (60 patients/group). That article provides evidence for a statistically significant difference in OS in favor of patients treated with HIPEC after cytoreduction compared to those treated only with surgery (75% vs 18% at 3 years). Some papers have reported interesting results, such as the study of the National Cancer Institute of Milan in patients with primary cytoreduction and HIPEC, which showed an OS after 5 years of follow-up of 61% [13].

The recent publication by van Driel et al. [14] has shed light on the role of HIPEC treatment (Cisplatin 100 mg per square meter of body surface area) after interval debulking surgery in patients with ovarian cancer and peritoneal carcinomatosis. The paper included a series of 245 patients divided into 2 groups: interval cytoreduction with HIPEC (123 patients) and cytoreduction alone (122 patients). The survival results were higher in the group in which HIPEC was administered, with statistically significant differences in both disease-free (14.2 versus 10.7 months) and overall (45.7 versus 33.9 months) survival, without increasing postoperative morbidity and mortality rates. Similar morbidity results have been reported by Lim et al. [15] clinical trial, although no differences in the survival rates between the two groups could be established in this study.

The increase in the number of patients included in the malignant peritoneal disease treatment programs, including patients with ovarian cancer, has aroused the interest of researchers studying prognostic profiles that would justify the risks and benefits of combination treatments with cytoreduction and HIPEC. Scores such as the Peritoneal Carcinomatosis Index (PCI), Completeness Cytoreductive Score (CCS), and the R score require a surgical procedure to be able to calculate the scores [16–18]. The Peritoneal Surface Disease Severity Score (PSDSS) [19], initially described in patients with peritoneal carcinomatosis from colorectal cancer, has proven to be an independent predictive tool and a good way to find a grading before a surgery in patients with colorectal carcinomatosis. The calculation of that type of score has guided the therapeutic approach. The score, which is calculated using preoperative data, allows for the identification of four prognostic categories that are based on the scores obtained from the following: the evaluation of the symptoms derived from the disease, the radiologic peritoneal carcinomatosis index calculated by computerized tomography (PCI-CT), the histological grade, and the lymph node status of the original tumor. Recently, Foster et al. [20] have reported the results of a retrospective multicenter study of the American Society of Peritoneal Surface Malignancies (ASPSM). The study adapted the application of the PSDSS score in patients with ovarian cancer who were treated by cytoreduction and HIPEC (PSDSSov), with a good prognostic correlation depending on the different categories used.

The aim of the present study is to validate the PSDSSov score as a prognostic tool to predict disease-free survival in patients with stage IIIC–IV epithelial ovarian cancer who are first treated with cytoreduction with peritonectomy and HIPEC procedures, and to discuss the usefulness and applicability of this approach in decision making in clinical practice.

2. Patients and methods

We analyzed a consecutive series of patients treated by cytoreductive surgery with peritonectomy and HIPEC procedures after being diagnosed with stage IIIC–IV serous epithelial ovarian carcinoma. Patients included in the study were treated between January 2012 and December 2016 in a level-three university hospital with experience in complex oncological diseases. All patients were treated with the same systemic chemotherapy regimen, which consisted of a total of six to eight cycles of a combination of platinum and taxane schemes. Patients in whom a neoadjuvant approach was decided (that is, patients with unresectable disease at diagnosis), were treated with three to four cycles of systemic chemotherapy before surgery. In these patients, adjuvant chemotherapy was completed to reach a total of six to eight cycles. All of the patients were evaluated and treated by the same surgical team.

Our operative protocol and the administered HIPEC scheme have been previously described [21]. Briefly, the staging of the degree of tumor extension was performed with the peritoneal cancer index (PCI), as described by Sugarbaker [16]. A value between 1 and 39 was established, and the result of the cytoreduction was classified according to a completeness of cytoreduction score (CC-score) [22]. Paclitaxel was used at doses of 60 mg/m^2 of body surface area. Cisplatin, at doses of 75 mg/m^2 body surface area, was reserved at the beginning of the series for patients with allergies to taxanes, which has been the drug of choice for our group since January 2012. The cytostatic agent was diluted in 3 l of 1.5% dextrose solution for peritoneal dialysis, and it the infusion was maintained at a constant flow of 0.5–0.7 l/min for 60 min. Two intra-abdominal thermometers (positioned in the pelvis and in the diaphragm area) were used to monitor the temperature inside of the peritoneal cavity during the infusion; the temperature remained constant, between 42 °C and 43 °C, for 60 min.

2.1. Peritoneal surface disease severity score for ovarian cancer

The variables that were necessary to calculate the Peritoneal Surface Disease Severity Score for ovarian cancer (PSDSSov) were included prospectively from January 2012, with the objective of validating the score. The PSDSSov calculation was performed in the patients included in the present study, which was analogous to the original calculation for patients with peritoneal carcinomatosis due to colorectal carcinoma [19] that was recently published in patients with EOC [20]. To this effect, three main variables were considered for the calculation: the presence of preoperative symptoms; the extension of peritoneal carcinomatosis, according to the calculation of the PCI; and the tumor histology. Preoperative PCI was calculated using a CT scan with contrast images. The data referring to histology were obtained from biopsies performed before cytoreduction and HIPEC. The sum of the scores assigned to each of the three clinical–pathological categories was used for the PSDSSov calculation (PSDSS I: < 4 points; PSDSS II: 4–7 points; PSDSS III: 8–10 points; PSDSS IV: > 10 points), resulting in the establishment of four stages (I–IV). After the PSDSSov calculation, a new analysis was completed that took into account each stage separately and the groupings of stages I–II and III-–IV.

2.2. Follow-up

All patients were evaluated after hospital discharge every 3 months during the first 2 years with complete analysis and CT scans, and then every 6 months. The disease-free survival was calculated taking into account the period between the date on which the surgical procedure and the date set for the diagnosis of recurrent disease was performed. The criteria used to establish the final diagnosis of recurrence was based on the finding of lesions suggestive of recurrence on CT scan and/or histologic confirmation of the same.

2.3. Statistical analysis

All of the data collected during the present study were included in a prospective database that was initiated at the same time as the Peritoneal Carcinomatosis Surgery Program at our center. The aim of the database was to validate the PSDSSov in this series of patients. In a first phase, a descriptive analysis of each variable was performed using the median and the mean with the standard deviation for the

continuous variables. For the qualitative variables, the absolute frequencies of the variables and their percentages were used. For the univariate analysis, the Student's t-test and the $\chi 2$ (chi-squared) test were applied; Fisher's test was also applied when necessary. In all situations, the statistical association was considered when the value of p was less than 0.05. The magnitude of association between the qualitative variables was determined by calculating the relative risk, and between the quantitative variables by means of the Pearson correlation coefficient. Survival analysis was performed using the Kaplan–Meier estimation method, with an analysis of the survival curves by means of the Log–Rank test or the Breslow test if the studied factor accumulated cases with little survival time censored in the different groups defined. In order to investigate the association between the variables studied and disease-free survival, a multivariate logistic regression analysis was undertaken with the factors that were statistically significant in the univariate analysis; the output from that analysis was a hazard ratio (HR) with an associated 95% confidence interval (CI). The main end point in this study was disease-free survival (DFS), a parameter that we consider to be the most appropriate based on the main objective of HIPEC treatment (that is, treatment of the microscopic disease that is responsible for recurrences).

3. Results

A total of 115 consecutive patients with a recent diagnosis of stage IIIC–IV epithelial ovarian cancer were included in the present study. Median age of the patients was 59 years (28–79 years). Primary cytoreduction and HIPEC were performed in 24 patients (upfront), with the remaining 91 patients undergoing surgery with neoadjuvant systemic chemotherapy (interval cytoreduction surgery). Of the latter, neoadjuvant chemotherapy was indicated in 14 patients who were categorized as stage IV at diagnosis according to the International Federation of Gynecology and Obstetrics (FIGO) guidelines (that is, malignant pleural effusion confirmed after thoracocentesis). A summary of the main clinical variables are presented in Table 1.

Median PCI of patients in the series was 10 (range: 4–32). In 96 patients, a complete cytoreduction of the disease was achieved (83%); in the remaining 19 patients (17%), the surgery was considered to be optimal (CC-1, with a tumor residual less than 0.25 cm). The surgical procedures performed are presented in Table 2. The HIPEC treatment scheme included 61 patients treated with paclitaxel and 54 patients with cisplatin. After calculating the scores obtained in each variable as part of the PSDSSov calculation, a total of 24 patients were labeled as PSDSSov-I, 20 patients as PSDSSov-II, 38 patients as PSDSSov-III, and 33 patients as PSDSSov-IV. A brief summary of postoperative outcomes is shown in Table 3.

Median follow-up was 35 months (12–60 months). At the point that the databased was closed for analysis, the median DFS of the patients in the series was 26 months, with a DFS rate of 74%, 43%, and 31% at 1, 3, and 5 years, respectively. In patients with PSDSSov I–II, the median DFS was not reached, being 16 months for patients classified as PSDSSov III–IV. Rates of DFS at 1, 3, and 5 years in patients with PSDSSov I–II were 88%, 76% and 61% and in patients with PSDSSov III–IV were 63%, 22% and 11%, respectively ($p < 0.001$) (Fig. 1).

After the multivariate analyses, the impossibility to achieve a complete cytoreduction (CC-score = 1, HR: 4.56, 95% CI: 1.95–11.23, p = 0.012), the PSDSSov (III–IV, HR: 3.59, 95% CI: 1.89–9.57, p = 0.024), a high PCI (> 20) (HR: 3.16, 95% CI: 1.13–4.56, p = 0.032), and the histological type of the tumor (G3, HR: 2.28, 95% CI: 1.14–8.14, p = 0.033) were factors that were independently related with lower DFS. Other variables included in the PSDSSov calculation such as lymph node status and the clinical symptoms, were not independently related to lower DFS in our series (Figs. 2 and 3).

Table 1
Main clinicopathological characteristics of the patients included in this paper (n = 115).

Clinical characteristics	n = 115
Age (median and range)	59 (28–79) years
Tumor (number of patients and %)	
Ovarian cancer	96 (83.5%)
Primary peritoneal carcinoma	15 (13%)
Tubarian cancer	4 (3.5%)
Comorbidity	
No	53 (46.1%)
Yes	62 (53.9%)
Previous chemotherapy	
No	91 (79.1%)
Yes	24 (20.9%)
Toxicity to sistemic chemotherapy	
No	73 (80.2%)
Yes	18 (19.8%)
Hematological	17 (18.7%)
Alergy to Platinum	1 (1.1%)
Cytoreduccion	
CC-0	96 (83.5%)
CC-1	19 (16.5%)
ASA	
I-II	81 (70.4%)
III	34 (29.6%)
PSDSS	
I	24 (20.9%)
II	20 (17.4%)
III	38 (33.0%)
IV	33 (28.7%)
PSDSS	
I-II	44 (38.3%)
III-IV	71 (61.7%)
Tumor differentiation grade	
Low grade	43 (37.3%)
High grade	72 (62.6%)

Table 2
PCI and surgical procedures performed in the patients described in the present series.

Variable	n (% of total)
PCI (median and range)	10 (4–32)
< 10	54 (46.9%)
10–20	47 (40.9%)
> 20	14 (12,2%)
Lymphadenectomy	30 (38.3%)
Pelvic lymph node disection	23 (20.0%)
Paraotic lymph node dissection	1 (0.9%)
Pelvic and paraaortic lymph node disection	6 (5.1%)
Large intestine resection	36 (31.3%)
Extensive upper abdominal	54 (46.9%)
Diaphragm peritonectomy/resection	42 (36.5%)
Glisson's Capsule Resection	12 (10.4%)
Splenectomy	16 (13.9%)
Cholecystectomy	6 (5.2%)
Liver resection	3 (2.6%)
Pancreatectomy	1 (0.1%)
Abdominal wall resection	4 (3.5%)
Blood transfusion (Yes)	54 (47.0%)
Operative time (min)*	300 (0–630) min

*Including HIPEC.

4. Discussion

The initial surgical approach in advanced ovarian cancer remains a challenge because of the complexity needed to achieve complete cytoreduction and to offer the best prognostic results [23]. In patients for whom it is impossible to achieve this initial complete cytoreduction, the use of neoadjuvant chemotherapy (NACT) prior to surgery it is a generally accepted alternative [24]. Several studies show that the best

Table 3
Adverse postoperative events after cytoreductive and HIPEC in the present series.

complications	NCI-CTCAE 3.0			
	I-II	III	IV	Total
Gastrointestinals				
Paralitic ileus	1 (0.9%)	1 (0.9%)	4 (3.5%)	6 (5.2%)
Rectovaginal fistula	0	1 (0.9%)	0	1 (0.9%)
Hemorraghe				
Self-limited bleeding	1 (0.9%)	0	1 (0.9%)	2 (1.7%)
Abdominal wall hematoma	0	2 (1.7%)	0	2 (1.7%)
Hemoperitoneum	0	1 (0.9%)	1 (0.9%)	2 (1.7%)
Infectious				
Wound infection	0	0	2 (1.7%)	2 (1.7%)
Respiratory				
Pleural effusion	1 (0.9%)	0	2 (1.7%)	3 (2.6%)
Others				
Urinary tract infection	0	0	1 (0.9%)	1 (0.9%)
Disorientation in ICU	1 (0.9%)	0	0	1 (0.9%)
Total	4 (3.5%)	5 (4.3%)	11 (9.6%)	20 (17.4%)

*Percentages refer to the total number of patients (n = 115).

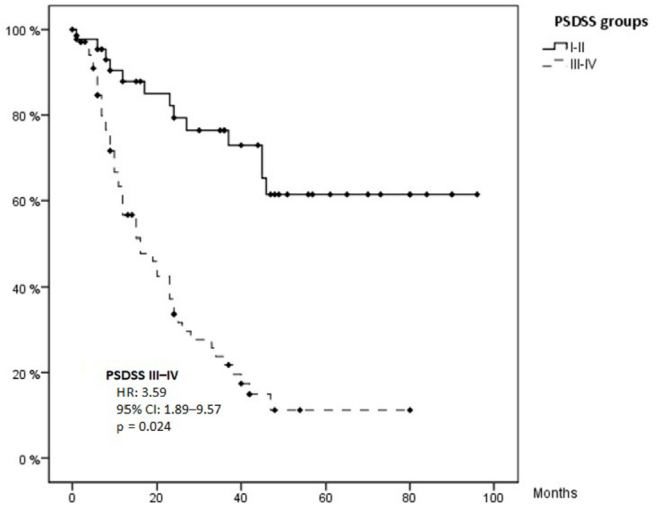

Fig. 1. Kaplan-Meier curves comparing DFS in patients according to their PSDSSov group (PSDSSov I–II vs PSDSSov III–IV, p < 0.05).

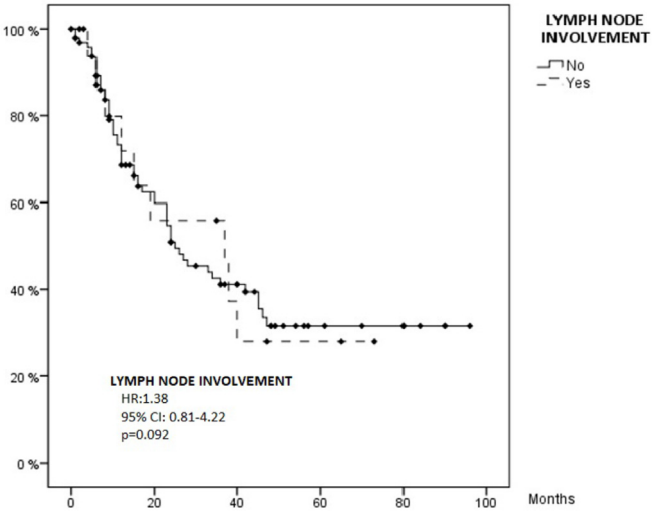

Fig. 2. Kaplan-Meier curves comparing DFS in patients according to the presence of lymph node involvement (p = n. s.).

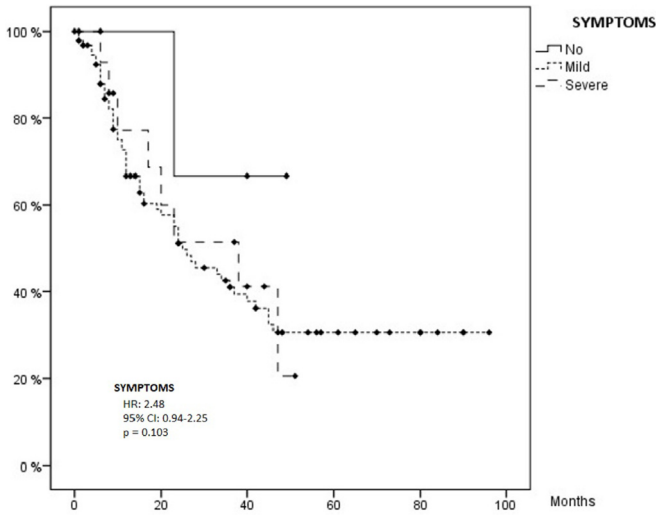

Fig. 3. Kaplan-Meier curves comparing DFS in patients according to their clinical symptomatology (absence vs mild vs severe simptoms, p = n. s.).

results are achieved in patients with complete cytoreduction during an initial surgical approach (upfront), although a dispute remains between the timing of the primary surgery and the neoadjuvant therapy [25].

Scores (with reproducible results) that are able to discriminate between different prognostic categories and that are easy to use have the capacity to guide a decision toward the best therapeutic option. The use of those scores is gaining importance within the concept of "personalized medicine". One of the most commonly used scores in patients with peritoneal surface malignancies is the PSDSS; it was initially designed in patients with colorectal peritoneal carcinomatosis [19], but a recent publication has described its adaptation for ovarian cancer (PSDSSov) [20]. In our work, PSDSSov also proven to be a useful prognostic tool for the stratification of patients with advanced ovarian cancer who were first treated with cytoreduction. Patients with PSDSSov I–II showed significantly higher DFS rates at 5 years compared to patients with PSDSS III–IV (61% and 11%, respectively).

In the original score, which was designed for patients with peritoneal carcinomatosis by colorectal cancer, the points that were assigned to each category were established arbitrarily, as recognized by the authors who developed the PSDSS [19]. Some of the prognostic variables assessed in the score—such as the extent of the disease, the histological grade of the tumor, and the lymph node status—have been described in many previous studies as prognostic variables in patients with advanced ovarian cancer. In our series, with the exception of preoperative symptoms and lymph node status, both the PCI and the histological grade were found to be independent factors in the multivariate analysis related to worse DFS rates. PCI has also been proposed as an independent prognostic tool for ovarian cancer [26]. Its calculation, especially during surgery, has been strongly correlated with the prognosis of the disease after cytoreduction in multiple published articles. In fact, its use in ovarian cancer allows clinicians, in a more specific way, to know the extent of the peritoneal disease with greater precision compared to the simple definitions of stages IIIB and IIIC in the FIGO classification. As a result, this score allows for patients to be stratified into different groups with the same FIGO stage, but with different degrees of peritoneal dissemination.

Based on the present article, we ask the following question: what is the true clinical utility of the PSDSSov in terms of the decision-making process when patients are being considered for cytoreductive surgery for ovarian cancer? The answer to this question allowed us to identify some weaknesses of using the score. In the study published by the ASPSM [20], the authors highlighted the importance of identifying different subgroups with better prognosis that could benefit from

different therapeutic options. In this sense, the score could improve the selection of patients in the preoperative period and could guide a therapeutic decision in terms of first cytoreduction, which would allow for unnecessary surgery to be avoided. This scenario is precisely why original PSDSS was designed [19]; patients with colorectal cancer were given specific action pathways depending on the PSDSS result (such as direct cytoreduction or cytoreduction after preoperative chemotherapy, and inclusion in clinical trials or palliative therapies). However, in our study, patients with stages III—IV presented OS and DFS rates that were consistent with accepted results in the literature, with a median DFS rate in the subgroup of unfavorable patients (PSDSSov III–IV) of 16 months, which is higher than the 12-month DFS reported in the study by Vergote et al. [27]. These data, which are similar to those reported in the article of the ASPSM, would not allow us, based on PSDSSov, to stop selecting patients for surgery. There is utility in using the PSDSSov as a tool to decide if patients with worse scores are treated with neoadjuvant chemotherapy. But there are also limitations too; for example, we would probably not change our treatment scheme in a patient with a recent diagnosis of epithelial ovarian cancer with a biopsy of a high grade tumor with a PCI-CT of 12 (PSDSS-IV), but with great possibilities of achieving a complete cytoreduction in experienced groups.

Probably, the question of whether or not PSDSSov is a good tool to decide if a patient with stage IIIC-IV ovarian cancer should be treated with primary surgery or NACT is secondary in this clinical scenario. There is a growing current trend to use NACT in patients with advanced stages. Some clinical trials support this attitude. The European Organization for the Research and Treatment of Cancer (EORTC) 55971 trial enrolled 670 patients with ovarian cancer in stage IIIC-IV [27]. The results in patients treated with neoadjuvant systemic chemotherapy were similar to those communicated for the control group with primary surgery (median PFS was 12 months in both groups, and median OS of 29 and 30 months, respectively), which led these researchers to conclude that neoadjuvant therapy was not an inferior treatment option. In addition to the EORTC study, the CHemotherapy OR Upfront Surgery (CHORUS) trial was a non-inferiority trial that included 550 women with stage III to IV EOC randomly assigned to primary surgery or NACT. Compared with primary surgery, NACT resulted in similar OS outcomes compared to primary surgery, including three-year OS rate (34 versus 32%, respectively), median OS (24 versus 22.6 months) and median DFS (12 versus 10 months, respectively) [28]. Results of SCORPION trial, recently presented in ASCO 2018, that investigated whether NACT was superior to primary surgery in terms of DFS, showed no differences between NACT and primary surgery in patients with advanced (IIIC-IV) epitelian ovarian cáncer [29].

In conclusion, PSDSSov has proven to be a useful tool in the prognostic stratification of patients with advanced ovarian cancer with peritoneal dissemination (IIIB/IIIC). The PSDSSov could probably have a relevant role too in recurrent ovarian cancer. Is in these cases where there are still major controversies regarding the role of surgery.

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