

RESEARCH

Open Access



# A predictive score for optimal cytoreduction at interval debulking surgery in epithelial ovarian cancer: a two-centers experience

Eleonora Ghisoni<sup>1,2</sup>, Dionyssios Katsaros<sup>3</sup>, Furio Maggiorotto<sup>1</sup>, Massimo Aglietta<sup>1,2</sup>, Marco Vaira<sup>1</sup>, Michele De Simone<sup>1</sup>, Gloria Mittica<sup>1,2</sup>, Gaia Giannone<sup>1,2</sup>, Manuela Robella<sup>1</sup>, Sofia Genta<sup>1,2</sup>, Fabiola Lucchino<sup>3</sup>, Francesco Marocco<sup>1</sup>, Fulvio Borella<sup>3</sup>, Giorgio Valabrega<sup>1,2\*</sup> and Riccardo Ponzzone<sup>1</sup>

## Abstract

**Background:** Optimal cytoreduction (macroscopic Residual Tumor, RT = 0) is the best survival predictor factor in epithelial ovarian cancer (EOC). It doesn't exist a consolidated criteria to predict optimal surgical resection at interval debulking surgery (IDS). The aim of this study is to develop a predictive model of complete cytoreduction at IDS.

**Methods:** We, retrospectively, analyzed 93 out of 432 patients, with advanced EOC, underwent neoadjuvant chemotherapy (NACT) and IDS from January 2010 to December 2016 in two referral cancer centers. The correlation between clinical-pathological variables and residual disease at IDS has been investigated with univariate and multivariate analysis. A predictive score of cytoreduction (PSC) has been created by combining all significant variables. The performance of each single variable and PSC has been reported and the correlation of all significant variables with progression free survival (PFS) has been assessed.

**Results:** At IDS, 65 patients (69,8%) had complete cytoreduction with no residual disease ( $R = 0$ ). Three criteria independently predicted  $R > 0$ : age  $\geq 60$  years ( $p = 0.014$ ), CA-125 before NACT  $> 550$  UI/dl ( $p = 0.044$ ), and Peritoneal Cancer Index (PCI)  $> 16$  ( $p < 0.001$ ). A PSC  $\geq 3$  has been associated with a better accuracy (85,8%), limiting the number of incomplete surgeries to 16,5%. Moreover, a PCI  $> 16$ , a PSC  $\geq 3$  and the presence of  $R > 0$  after IDS were all significantly associated with shorter PFS ( $p < 0.001$ ,  $p < 0.001$  and  $p = 0.004$  respectively).

**Conclusions:** Our PSC predicts, in a large number of patients, complete cytoreduction at IDS, limiting the rate of futile extensive surgeries in case of presence of residual tumor ( $R > 0$ ). The PSC should be prospectively validated in a larger series of EOC patients undergoing NACT-IDS.

**Keywords:** Ovarian cancer, Interval debulking surgery, Optimal cytoreduction, Predictive score, Peritoneal cancer index

\* Correspondence: [giorgio.valabrega@ircc.it](mailto:giorgio.valabrega@ircc.it)

<sup>1</sup>Candiolo Cancer Institute FPO-IRCCS, Strada Provinciale 142 km 3.95, 10060 Candiolo, TO, Italy

<sup>2</sup>Department of Oncology, University of Torino, Turin, Italy

Full list of author information is available at the end of the article



## Background

Ovarian cancer is the leading cause of death from gynecological malignancies. In 2017, 22,400 new cases are expected in the United States. Currently, more than 75% of women with ovarian cancer have advanced disease [International Federation of Gynecology and Obstetrics (FIGO) stage IIIC or IV] at diagnosis and their 5-years survival rate is less than 30% [1].

Primary debulking surgery (PDS) followed by platinum-based chemotherapy has long been considered the only standard treatment for advanced epithelial ovarian cancer (EOC) [2]. This approach validity has been supported by several retrospective studies consistently demonstrating that upfront optimal cytoreduction (residual tumor nodules  $\leq 1$  cm or  $R \leq 1$ ) is associated with longer survival [3, 4]. Unfortunately, PDS is not always associated with optimal cytoreduction and can be complicated by severe perioperative morbidity [5, 6]. More recently, neoadjuvant chemotherapy (NACT) with delayed surgery (interval debulking surgery, IDS) is increasingly adopted in patients with advanced EOC [7]. This tendency is sustained by the results of two randomized phase III trials, showing that NACT-IDS improves optimal debulking rates and reduces surgery-related complications with no detrimental effect on survival, in comparison with PDS, at least in patients with high tumor load [8, 9]. However both trials have been criticized for the poor performances of PDS arm [10, 11].

However, a significant proportion of patients cannot be optimally cytoreduced even after NACT-IDS and this leads to the morbidity of surgery with no expected survival benefit [12–14]. Although it is common practice to attempt IDS only in patients responding to NACT, this approach causes several unnecessary laparotomies, if optimal cytoreduction cannot be achieved, and in other cases they are not applied also if the conditions are appropriate. Single variables have been combined into predictive cytoreduction models to improve accuracy in the settings of PDS [15] and recurrent disease [16, 17]. Unfortunately, predictive models have not been developed for patients undergoing IDS.

Therefore, the aim of this study is to develop a predictive model of surgical outcome at IDS, to improve the selection of patients that can benefit of a maximal surgical effort.

## Methods

### Study population

A total of 432 patients with histologically confirmed diagnosis EOC have been operated between January 1st, 2010, and December 31st, 2016 at Candiolo Cancer Institute-IRCCS and Sant'Anna Hospital, two high-volume gynecological cancer centers in the North-West of Italy. All patients had preoperative computed tomography (CT)

of the chest, abdomen and pelvis with intravenous contrast and serum Ca-125 assessment. In all cases, a multidisciplinary board, including a gynecologist and/or a surgeon, a medical oncologist and a radiologist with specific training and expertise in ovarian cancer evaluated the feasibility of surgical resection. The patients underwent PDS when optimal cytoreduction has been deemed achievable, while NACT - IDS was the preferred option when the extent/localization of the disease would likely preclude optimal cytoreduction and/or the patient would not tolerate extensive surgery due to age or co-morbidities. All 93 patients who underwent both NACT and IDS were included in the present study. The following variables has been prospectively entered into a database and retrospectively analyzed: age, performance status (PS) according to Eastern Cooperative Oncology Group (ECOG), comorbidities according to the Chronic Disease Score (CDS) [18], FIGO stage, grade and histology, serum CA-125 at diagnosis before surgery and after IDS [19], type of chemotherapy, peritoneal cancer index (PCI) according to Sugarbaker [20] at IDS assessed during laparoscopy, residual disease (R) after IDS, date of radiological progression (PD) after chemotherapy or last follow-up.

All patients signed a written informed consent and the institutional review board of our Institutions provided their approval.

### Statistical analysis

We performed univariate and multivariate logistic regression analysis, Fisher exact test and chi-square test to search patients' and tumors' characteristics that were predictive of complete cytoreduction. Receiver Operating Curve (ROC) analysis has been also adopted to assess the best cut-off values to predict the likelihood of incomplete cytoreduction at IDS of continuous variables. We used all significant variables at multivariate analysis to create a predictive score of cytoreduction (PSC). We assigned one or two points to each criterion, according to accuracy (1 point if  $< 75\%$ , 2 points if  $\geq 75\%$ ). We estimated progression-free survival (PFS) with the Kaplan-Meier method and we compared it using the log-rank test. We considered  $p < 0.05$  statistically significant. We performed all analyses using the SPSS statistical software program, version 22.0 (IBM SPSS Inc., Chicago, IL, United States of America).

## Results

Ninety-three patients with predominantly advanced stage (FIGO IIIC-IV: 75,3%), serous high grade (87%) EOC undergoing NACT and IDS were enrolled. At the time of diagnosis, median CA-125 was 2121 UI/dL (range 28–10,454 UI/dL) and Chronic Disease Score (CDS) was  $\geq 2$  in 34,4% of the patients. Carboplatin plus

paclitaxel was the most utilized chemotherapeutic regimen (87,3%), with only three patients receiving carboplatin single-agent and two patients receiving carboplatin plus pegylated liposomal doxorubicin, due to hypersensitivity to paclitaxel. Sixty-five patients (69,8%) had complete cytoreduction at IDS. For continuous variables, ROC analysis identified age  $\geq 60$  years, CA-125

levels before NACT  $> 550$  UI/dL, CA-125 levels after NACT  $> 33$  UI/dL, CA-125 reduction after NACT  $< 96\%$  and PCI  $> 16$  as optimal cut-offs to predict the surgical outcome. All the above mentioned variables were significantly correlated with incomplete cytoreduction at univariate analysis. However, at multivariate analysis, only age ( $p = 0.007$ ), CA-125 before NACT ( $p = 0.014$ )

**Table 1** Univariate and multivariate analysis of variables associated with incomplete cytoreduction at interval debulking surgery

	Total (93Pts.)	R0 (65Pts.)	Non-R0 (28 Pts.)	Uni-variate <i>p</i> value	Multi-variate <i>p</i> value
Age, years					
Median (range)	60 (36–82)	59,5 (36–82)	65,7 (47–82)	NS	
Age $\geq 60$	54 (58%)	32 (49,2%)	22 (78,6%)	0.011	0.007
FIGO stage					
IIIA	9 (9,7%)	6 (9,2%)	3 (10,7%)		
IIIB	14 (15%)	9 (13,8%)	5 (17,9%)	NS	
IIIC	58 (62,4%)	43 (66,2%)	15 (53,5%)		
IV	12 (12,9%)	7 (10,8%)	5 (17,9%)		
Histology					
High-grade serous	81(87%)	57 (87,6%)	24 (85,7%)		
Endometrioid	4 (4,3%)	2 (3,1%)	2(7,1%)	NS	
Mucinous	2 (2,2%)	1 (1,5%)	1 (3,6%)		
Clear cell	2 (2,2%)	2 (3,1%)	0		
Other/non specified	4 (4,3%)	3 (4,6%)	1 (3,6%)		
ECOG Performance Status					
0	34 (37%)	26 (40%)	8 (29,6%)	NS	
1	44 (47,8%)	30 (46,2%)	14 (51,9%)		
2	15 (15,2%)	9 (13,8%)	6 (21,4%)		
Ca 125 values, UI/dl					
Median CA-125 at diagnosis (range)	2121 (10454–28)	1964	2793	NS	NS
CA-125 at diagnosis $> 550$	71 (76,3%)	46 (70,8%)	25 (89,3%)	0.044	0.014
Median CA-125 post NACT (range)	342 (2620–7)	163	598	0.055	NS
Ca 125 post NACT $> 33$	60 (65,9%)	35 (55,6%)	25 (89,3%)	0.002	NS
CA 125 reduction post NACT $< 96\%$	34 (38,2%)	26 (41,9%)	8 (29,6%)	0.034	NS
Chronic Disease Score (CDS)					
1	61 (65,6%)	44 (67,7%)	17 (60,7%)		
2	24 (25,8%)	17 (26,2%)	7 (25%)	NS	
3	8 (8,6%)	4 (6,2%)	4 (14,3%)		
Peritoneal Cancer Index					
0–16	68 (73,1%)	58 (85,3%)	10 (35,8%)	$< 0.001$	$< 0.001$
$> 16$	25 (26,9%)	7 (10,7%)	18 (64,2%)		
Chemotherapy regimen					
- Carboplatin plus paclitaxel	81 (87,3%)	57 (87,6%)	24 (85,7%)	NS	
- Single agent carboplatin	3 (3,2%)	2 (3,1%)	1 (3,6%)		
- Carboplatin plus PLD	2(2,2%)	2 (3,1%)	0		
- Carboplatin plus paclitaxel plus bevacizumab	7 (7,6%)	4 (6,2%)	3 (10,7%)		

*Pts* patients, *R0* complete cytoreduction, *FIGO* International Federation of Gynaecology and Obstetrics, *ECOG* Eastern Cooperative Oncology Group, *NACT* neoadjuvant chemotherapy, *PLD* pegylated liposomal doxorubicin, *NS* not significant

**Table 2** Diagnostic performance and assigned score of significant variables of incomplete cytoreduction at interval debulking surgery

Variable	Sens (%)	Spec (%)	NPV (%)	PPV (%)	Acc (%)	Assigned score <sup>a</sup>
Age > 60 years	78,6	50,7	84,6	40,7	59,1	1
CA-125 at diagnosis $\geq 550$ UI/dl	89,2	29,2	86,3	35,2	47,3	1
PCI > 16	62,5	90,1	85,9	71,4	82,3	2

<sup>a</sup>To develop a predictive score of cytoreduction (PSC) for each criterion 1 point was assigned if accuracy is < 75% and 2 points if > 75%. SE sensitivity, SP specificity, NPV negative predictive value, PPV positive predictive value, Acc accuracy

and PCI ( $p < 0.001$ ) maintained the statistical significance. For complete baseline patients' characteristics and statistical correlations see Table 1.

PCI was the best predictor of surgical outcome, with accuracy more than 80% (Table 2). Therefore, we modeled a predictive score of incomplete cytoreduction (PSC) by assigning a value of 1 point to age and CA-125 at diagnosis and 2 points to PCI according to accuracy.

If applied, a PSC  $\geq 3$  could have selected all patients for whom complete cytoreduction was not achievable (100%) by limiting at 16,5% the rate of surgical attempts leading to a  $R > 1$  cm (Table 3).

After a mean follow up of 27 months (range 19.6–34.6 months), 39 patients showed disease progression. Among the variables considered, a PCI > 16 at IDS ( $p < 0.001$ ), a PSC  $\geq 3$  ( $p < 0.001$ ) and the presence of residual disease after IDS ( $p = 0.004$ ) were all significantly associated with shorter PFS (Fig. 1).

## Discussion

A key issue in patients with advanced EOC is the selection of patients suitable for complete surgical cytoreduction. Predictive models of surgical outcome based on computed tomography alone [15], or integrated by serum CA-125 levels [21, 22], patient age and performance status [23] have been developed to assist physicians in the decision between PDS or NACT – IDS. Laparoscopic scores have also been proposed [24], with a recent randomized study demonstrating that triage laparoscopy could limit the rate of laparotomies leading to incomplete cytoreduction (“futile laparotomies”) at 10% [25].

If the choice between PDS and NACT-IDS is complex [7], even more controversial is the optimal clinical management of women who undergo NACT according to the indication, timing and extent of IDS based on their stage, comorbidities and, most of all, clinical

response [26]. As recently reported, there is still an absence of selecting criteria for patients suitable for NACT/IDS underlining that this approach is still object of debate [27].

Resection of all visible disease should always be the goal in advanced EOC, but it may be particularly important after NACT when patients face their last best chance to receive an effective surgery. Furthermore, selection is crucial, since patients who can be cytoreduced to no macroscopic residual disease may be the only once gaining a survival benefit from surgery at IDS. This opinion is sustained by the randomized study of Vergote et al. where the hazard ratio (HR) of overall survival was not significantly different for  $R = 0$  at IDS (HR 1.11;  $p = 0.561$ ) or  $R \leq 1$  cm at PDS (HR 1.37;  $p = 0.130$ ) as compared to  $R = 0$  at PDS (reference), but was significantly worse for  $R \leq 1$  cm at IDS (HR 1.73;  $p = .0054$ ) [8]. The randomized phase III trial TRUST (NCT02828618) is investigating the role of PDS versus NACT+IDS in large volume comprehensive cancer centers and has already enrolled one third of 686 estimated patients; final results are expected for 2019.

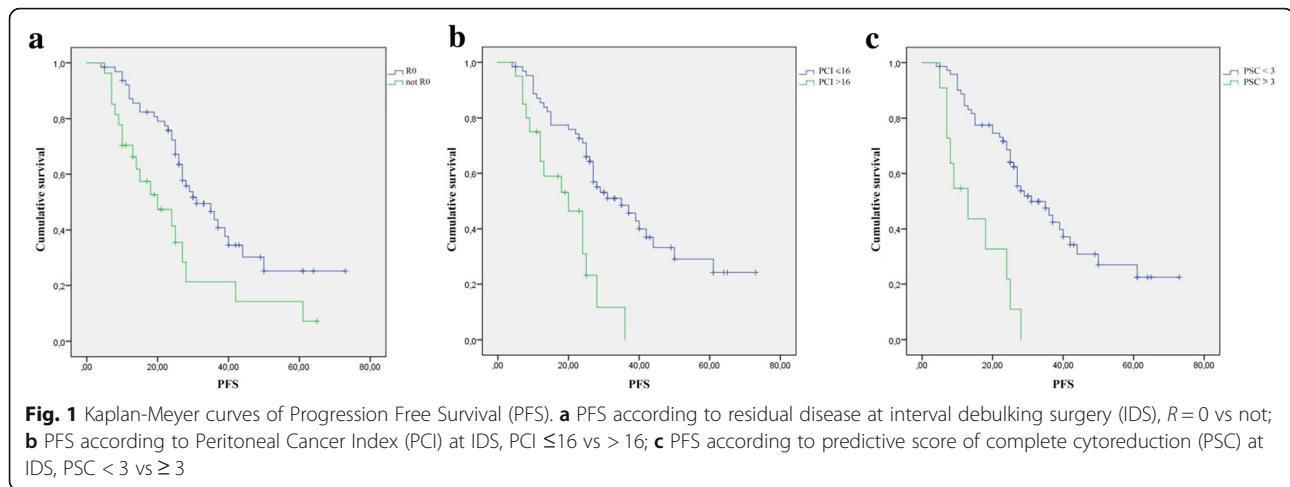
Computed tomography, serum markers and staging laparoscopy have all been investigated for the prediction of complete resection at IDS with variable results. Evaluation of response to NACT by computed tomography is challenging [28] and serum CA-125 variations [29–31] or thresholds [32, 33] have limited accuracy. It has been reported that a laparoscopic score could identify all patients likely to be optimally debulked at IDS, but with the drawback of 32.6% futile laparotomies [34].

At our Institutions, patients with clinical/radiological progressive disease during the first 3–4 courses of NACT, either underwent diagnostic laparoscopy or withdrew chemotherapy, were excluded from the current study. In patients with radiological response/stable disease to

**Table 3** Diagnostic performance of significant variables of incomplete cytoreduction at interval debulking surgery

Variable	NPV (%)	Unnecessarily explored (1-NPV) (%)	PPV (%)	Inappropriately unexplored (1-PPV) (%)
Age > 60 years	84,6	15,4	40,7	59,1
CA-125 at diagnosis > 550 UI/dl	86,3	13,7	35,2	64,6
PCI > 16	85,9	14,1	71,4	28,6
PSC > 3	83,5	16,5	100	0

CA-125 Cancer Antigen 125, PCI Peritoneal Cancer Index, PSC Predictive score of cytoreduction, NPV negative predictive value, PPV positive predictive value, Acc accuracy, Unnecessarily explored (1-NPV): number of cases that would be considered as resectable disease but non-optimally cytoreduced at laparotomy; Inappropriately unexplored (1-PPV): number of cases that would be considered as unresectable but optimally cytoreduced after laparotomy



NACT we rely on laparotomy to define if radical surgery is appropriate or not. In fact, direct visualization and palpation of the whole abdominal cavity is essential for accurate PCI estimation, which is in turn correlated with tumor resectability and prognosis [20, 35]. Although we acknowledge that the role of PCI in ovarian cancer is under discussion [36, 37] due to its assessment, its low reproducibility and limited utilization, in our series PCI outperformed all other significant predictors and a cut-off  $< 16$  was able to identify almost 90% of patients who could be completely debulked. Nevertheless, this high PPV was obtained with the drawback of 28,6% of unexplored laparotomies. Therefore, we assessed whether other information could add predictive value to PCI by modeling a PSC. Four significant variables reflecting patient (age) and tumor characteristics (PCI and preoperative CA 125), as well as response to NACT (CA 125 decrease) has been used. Our results indicate that, with a cut a cut-off set at  $> 4$ , our PSC may allow to identify all patients who cannot be completely cytoreduced at the price of 15% of futile laparotomies.

In our series,  $R = 0$  after IDS was the only parameter significantly associated with PFS. Conversely, in a recent retrospective series from the Mayo Clinic, older age (HR 1.60 per 10-years increase in age) and elevated CA-125 before IDS (HR 2.30 for CA-125  $> 35$  U/mL) were negatively correlated with OS, while residual disease after IDS did not reach statistical significance (median OS 1.9 vs. 2.6 years;  $P = 0.08$ ) [38]. Indeed, some studies suggest that the degree of pathological response to chemotherapy could be more closely correlated to OS than the absence of residual tumor at IDS [39–42]. Although only  $R = 0$  reached statistical significance, the limited number of events of our study may have hindered associations between PFS and other variables, such as age and CA 125 decrease after NACT.

## Conclusions

In conclusion, we showed that our PSC might help surgeons to give a surgical chance to all patients that could be completely debulked, therefore limiting the number of suboptimal surgeries at 16.5%. Both patient's and tumor's characteristics likely concur to determine the chance of complete debulking at IDS. Although the influence of tumor chemosensitivity on survival may supersede the once of surgery, the selection of those patients who can be cytoreduced to  $R = 0$  after NACT is crucial to derive the best trade-off from the benefits and the risks of an extensive surgical effort. Our preliminary results suggest that IDS after NACT should be performed in patients with a PSC up to 2, while the value of surgery in patients scoring 4 is likely minimal. In our analysis, we provide a two high-volume-centers experience with standardized multidisciplinary care of EOC. The extrapolation equivalence of PDS and NACT-IDS from the results of randomized studies [8, 9], has been questioned due to patients selection and their poor surgical quality, which led to low both cytoreduction and survival rates [43]. At IDS we obtained a 69% complete cytoreduction rate by performing operations characterized by high surgical complexity, that were guided by the same objective and performed with the same effort as PDS. A prospective validation of the PSC has been already planned at our Institutions.

## Abbreviations

CA-125: cancer antigen-125; CDS: Chronic Disease Score; CT: Computed tomography; ECOG: Eastern Cooperative Oncology Group (ECOG); EOC: epithelial ovarian cancer; FIGO: International Federation of Gynecology and Obstetric; HR: Hazard ratio; IDS: interval debulking surgery; NACT: neoadjuvant chemotherapy; PCI: peritoneal cancer index; PDS: Primary debulking surgery; PFS: progression free survival; PS: performance status; PSC: predictive score of cytoreduction; R: Residual tumor; ROC: Receiver Operating Curve analysis

## Acknowledgements

We are grateful to Prof. Di Renzo for insightful discussion and to Ms. Ann Wright for careful proof reading of the manuscript.



**Funding**

This work was supported by grant VALG\_RIC\_LOC\_14\_01 (G Valabrega); Fondazione del Piemonte per l'Oncologia (FPRC Onlus) 5 X 1000 fondi Ministero della Salute 2012 (R. Ponzone and M. De Simone).

**Availability of data and materials**

All data are available in the manuscript.

**Authors' contributions**

GV and RP conceived of the concept. EG, MDS, GM, FM and MV participated in data collection and interpretation of results. GV, RP, CS and EG analyzed data and wrote the manuscript. All authors read and approved the final manuscript.

**Ethics approval and consent to participate**

Due to the retrospective nature of the study, informed consent was waived by the Medical Ethics Committee of Candiolo Cancer Institute, FPO/IRCCS Candiolo.

**Consent for publication**

Written informed consents for the publication of related Tables and figures had been obtained from the individuals.

**Competing interests**

The authors declare that they have no competing interests.

**Publisher's Note**

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

**Author details**

<sup>1</sup>Candiolo Cancer Institute FPO-IRCCS, Strada Provinciale 142 km 3.95, 10060 Candiolo, TO, Italy. <sup>2</sup>Department of Oncology, University of Torino, Turin, Italy. <sup>3</sup>Department of Surgical Sciences, Gynecology, AOU, Città della Salute e della Scienza, Turin, Italy.

Received: 21 February 2018 Accepted: 16 May 2018

Published online: 30 May 2018

**References**

- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin*. 2017; 67(1):7–30.
- Ledermann JA, et al. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2013;24(Suppl 6):vi24–32.
- Chi DS, et al. Improved progression-free and overall survival in advanced ovarian cancer as a result of a change in surgical paradigm. *Gynecol Oncol*. 2009;114(1):26–31.
- du Bois A, Reuss A, Pujade-Lauraine E, Harter P, Ray-Coquard I, Pfisterer J. Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux pour les études des cancers de l'Ovaire (GINECO). *Cancer*. 2009;115(6):1234–44.
- Chi DS, et al. The incidence of major complications after the performance of extensive upper abdominal surgical procedures during primary cytoreduction of advanced ovarian, tubal, and peritoneal carcinomas. *Gynecol Oncol*. 2010;119(1):38–42.
- Fagotti A, et al. phase III randomised clinical trial comparing primary surgery versus neoadjuvant chemotherapy in advanced epithelial ovarian cancer with high tumour load (SCORPION trial): final analysis of peri-operative outcome. *Eur J Cancer*. 2016;59:22–33.
- Wright AA, et al. Neoadjuvant chemotherapy for newly diagnosed, advanced ovarian cancer: Society of Gynecologic Oncology and American Society of clinical oncology clinical practice guideline. *Gynecol Oncol*. 2016; 143(1):3–15.
- Vergote I, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIc or IV ovarian cancer. *N Engl J Med*. 2010;363(10):943–53.
- Kehoe S, et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. *Lancet*. 2015;386(9990):249–57.
- Gasparri ML, Panici PB, Papadia A. Primary chemotherapy versus primary surgery for ovarian cancer. *Lancet*. 2015;386(10009):2142–3.
- Meyer LA, et al. Use and effectiveness of neoadjuvant chemotherapy for treatment of ovarian Cancer. *J Clin Oncol*. 2016;34(32):3854–63.
- Tangjitgamol S, Manusirivithaya S, Laopaiboon M, Lumbiganon P, Bryant A. Interval debulking surgery for advanced epithelial ovarian cancer. *Cochrane Database Syst Rev*. 2016; no. 1, p. CD006014
- Pepin K, et al. Intensive care admissions among ovarian cancer patients treated with primary debulking surgery and neoadjuvant chemotherapy-interval debulking surgery. *Gynecol Oncol*. 2017;147(3):612–16
- Aletti GD, Dowdy SC, Podratz KC, Cliby WA. Relationship among surgical complexity, short-term morbidity, and overall survival in primary surgery for advanced ovarian cancer. *Am J Obstet Gynecol*. 2007;197(6):676.e1–7.
- Rutten MJ, et al. Predicting surgical outcome in patients with International Federation of Gynecology and Obstetrics stage III or IV ovarian cancer using computed tomography: a systematic review of prediction models. *Int J Gynecol Cancer*. 2015;25(3):407–15.
- Harter P, et al. Prospective validation study of a predictive score for operability of recurrent ovarian cancer: the multicenter intergroup study DESKTOP II. A project of the AGO Kommission OVAR, AGO study group, NOGGO, AGO-Austria, and MITO. *Int J Gynecol Cancer*. 2011;21(2):289–95.
- van de Laar R, et al. Cytoreductive surgery followed by chemotherapy versus chemotherapy alone for recurrent platinum-sensitive epithelial ovarian cancer (SOCceR trial): a multicenter randomised controlled study. *BMC Cancer*. 2014;14:22.
- Putnam KG, et al. Chronic disease score as a predictor of hospitalization. *Epidemiology*. 2002;13(3):340–6.
- Suidan RS, et al. A multicenter prospective trial evaluating the ability of preoperative computed tomography scan and serum CA-125 to predict suboptimal cytoreduction at primary debulking surgery for advanced ovarian, fallopian tube, and peritoneal cancer. (in eng), *Gynecol Oncol*. 2014; 134(3):455–61.
- Lampe B, Kroll N, Piso P, Forner DM, Mallmann P. Prognostic significance of Sugarbaker's peritoneal cancer index for the operability of ovarian carcinoma. *Int J Gynecol Cancer*. 2015;25(1):135–44.
- Shen Y, Li L. Serum HE4 superior to CA125 in predicting poorer surgical outcome of epithelial ovarian cancer. *Tumour Biol*. 2016;37(11):14765–72.
- May T, et al. A comparison of survival outcomes in advanced serous ovarian Cancer patients treated with primary Debulking surgery versus neoadjuvant chemotherapy. *Int J Gynecol Cancer*. 2017;27(4):668–74.
- Suidan RS, et al. Predictive value of the age-adjusted Charlson comorbidity index on perioperative complications and survival in patients undergoing primary debulking surgery for advanced epithelial ovarian cancer. *Gynecol Oncol*. 2015;138(2):246–51.
- Petrillo M, et al. Definition of a dynamic laparoscopic model for the prediction of incomplete cytoreduction in advanced epithelial ovarian cancer: proof of a concept. *Gynecol Oncol*. 2015;139(1):5–9.
- Rutten MJ, et al. Laparoscopy to predict the result of primary Cytoreductive surgery in patients with advanced ovarian Cancer: a randomized controlled trial. *J Clin Oncol*. 2017;35(6):613–21.
- Milani A, et al. Switching from standard to dose-dense chemotherapy in front-line treatment of advanced ovarian cancer: a retrospective study of feasibility and efficacy. *ESMO Open*. 2017;1(6):e000117.
- Vitale SG, Marilli I, Lodato M, Tropea A, Cianci A. The role of cytoreductive surgery in advanced-stage ovarian cancer: a systematic review. *Updates Surg*. 2013;65(4):265–70.
- Baek MH, et al. Preoperative predictive factors for complete Cytoreduction and survival outcome in epithelial ovarian, tubal, and peritoneal Cancer after neoadjuvant chemotherapy. *Int J Gynecol Cancer*. 2017;27(3):420–9.
- Markman M, Federico M, Liu PY, Hannigan E, Alberts D. Significance of early changes in the serum CA-125 antigen level on overall survival in advanced ovarian cancer. *Gynecol Oncol*. 2006;103(1):195–8.
- Mahdi H, Maurer KA, Nutter B, Rose PG. The impact of percent reduction in CA-125 levels on prediction of the extent of interval Cytoreduction and outcome in patients with advanced-stage Cancer of Müllerian origin treated with neoadjuvant chemotherapy. *Int J Gynecol Cancer*. 2015;25(5):823–9.

31. Pelissier A, et al. CA125 kinetic parameters predict optimal cytoreduction in patients with advanced epithelial ovarian cancer treated with neoadjuvant chemotherapy. *Gynecol Oncol.* 2014;135(3):542–6.
32. Rodriguez N, et al. Changes in serum CA-125 can predict optimal cytoreduction to no gross residual disease in patients with advanced stage ovarian cancer treated with neoadjuvant chemotherapy. *Gynecol Oncol.* 2012;125(2):362–6.
33. Morimoto A, et al. A preoperative low cancer antigen 125 level ( $\leq 25.8$  mg/dl) is a useful criterion to determine the optimal timing of interval debulking surgery following neoadjuvant chemotherapy in epithelial ovarian cancer. *Jpn J Clin Oncol.* 2016;46(6):517–21.
34. Fagotti A, et al. Should laparoscopy be included in the work-up of advanced ovarian cancer patients attempting interval debulking surgery? *Gynecol Oncol.* 2010;116(1):72–7.
35. Chéreau E, Ballester M, Selle F, Cortez A, Darai E, Rouzier R. Comparison of peritoneal carcinomatosis scoring methods in predicting resectability and prognosis in advanced ovarian cancer. *Am J Obstet Gynecol.* 2010;202(2):178.e1–178.e10.
36. Heitz F, et al. Pattern of and reason for postoperative residual disease in patients with advanced ovarian cancer following upfront radical debulking surgery. *Gynecol Oncol.* 2016;141(2):264–70.
37. Heitz F, Harter P, Ataseven B, du Bois A. Response to the letter of Fagotti et al. regarding the manuscript: "pattern of and reason for postoperative residual disease in patients with advanced ovarian cancer following upfront radical debulking surgery". *Gynecol Oncol Rep.* 2016;18:55–6.
38. Gill SE, McGree ME, Weaver AL, Cliby WA, Langstraat CL. Optimizing the treatment of ovarian cancer: neoadjuvant chemotherapy and interval debulking versus primary debulking surgery for epithelial ovarian cancers likely to have suboptimal resection. *Gynecol Oncol.* 2017;144(2):266–73.
39. Le T, Williams K, Senterman M, Hopkins L, Faught W, Fung-Kee-Fung M. Histopathologic assessment of chemotherapy effects in epithelial ovarian cancer patients treated with neoadjuvant chemotherapy and delayed primary surgical debulking. (in eng), *Gynecol Oncol.* 2007;106(1):160–3.
40. Muraji M, et al. Histopathology predicts clinical outcome in advanced epithelial ovarian cancer patients treated with neoadjuvant chemotherapy and debulking surgery. *Gynecol Oncol.* 2013;131(3):531–4.
41. Böhm S, et al. Chemotherapy response score: development and validation of a system to quantify histopathologic response to neoadjuvant chemotherapy in Tubo-ovarian high-grade serous carcinoma. *J Clin Oncol.* 2015;33(22):2457–63.
42. Petrillo M, et al. Prognostic role and predictors of complete pathologic response to neoadjuvant chemotherapy in primary unresectable ovarian cancer. *Am J Obstet Gynecol.* 2014;211(6):632.e1–8.
43. Fotopoulou C, et al. Value of neoadjuvant chemotherapy for newly diagnosed advanced ovarian Cancer: a European perspective. *J Clin Oncol.* 2017;35(6):587–90.

**Ready to submit your research? Choose BMC and benefit from:**

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more [biomedcentral.com/submissions](https://biomedcentral.com/submissions)

