HHS Public Access

Author manuscript

Gynecol Oncol. Author manuscript; available in PMC 2021 November 01.

Published in final edited form as:

Gynecol Oncol. 2020 November ; 159(2): 434–441. doi:10.1016/j.ygyno.2020.08.028.

Role of delayed interval debulking for persistent residual disease after more than 5 cycles of chemotherapy for primary advanced ovarian cancer. An international multicenter study

Helmut Plett[1,8], **Olga T. Filippova**[2], **Annalisa Garbi**[3], **Stefan Kommoss**[4], **Mikkel Rosendahl**[5], **Carrie Langstraat**[6], **Saurabh Phadnis**[7], **Mustafa Zelal Muallem**[8], **Thaïs Baert**[1,9], **Dennis S. Chi**[2,10], **Giovanni Damiano Aletti**[3], **Florin-Andrei Taran**[4,11], **Jan Philipp Ramspott**[1], **Oliver Zivanovic**[2,10], **Andreas du Bois**[1], **Yukio Sonoda**[2,10], **Ginger Gardner**[2,10], **Alexander Traut**[1], **Kara Long Roche**[2,10], **Philipp Harter**[1]

[1]Department of Gynecology and Gynecologic Oncology, Ev. Kliniken Essen-Mitte, Essen, Germany

[2]Gynecology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA, Department of Obstetrics and Gynecology, Weill Cornell Medical College, New York, NY, USA

[3]Division of Gynecology, Department of Gynecologic Oncology, IRCCS European Institute of Oncology, Milan, Italy. Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy

[4]Department of Women's Health, Tübingen University Hospital, Tübingen, Germany

[5]Department of Gynecology, The Juliane Marie Centre, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

[6]Department of Obstetrics and Gynecology, Division of Gynecologic Surgery, Mayo Clinic, Rochester, MN, USA

[7]Department of Gynaecological Oncology, Barts Health NHS Trust, Royal London Hospital, United Kingdom

[8]Department of Gynecology with Center for Oncological Surgery, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universiät zu Berlin, Germany

[9]Department of Oncology, Laboratory of Tumor Immunology and Immunotherapy, ImmunOvar Research Group, KU Leuven, Leuven, Belgium

To whom correspondence should be addressed: Dr. med. Helmut Plett, Dept. of Gynecology & Gynecologic Oncology, Ev. Kliniken Essen-Mitte, Henricistrasse, 92, 45136 Essen, Germany, pletth@googlemail.com, Phone: +49 20117434044, Facsimile: +49 20117434540.

Authors contribution

P·H. and A. dB. and H.P. designed and directed the project. H.P., O.T.F., A.G., M.Z.M., C.L. S.P., S.K., M.R. and A.T., worked on the data and follow up. A. T. worked out almost all of the technical details, and performed the numerical calculations. H.P. wrote the manuscript with the input of all authors. P.H., A.dB., G.D.A., T.B., J.P.R., C.L., O.T.F., S.P., D.C., and M.R. revised the data and the manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript.

[10]Department of Obstetrics and Gynecology, Weill Cornell Medical College, New York, NY, USA

[11]Department of Gynecology, University Hospital Zürich, Comprehensive Cancer Center Zürich

Abstract

Background—Standard of care in patients with advanced ovarian cancer (AOC) is upfront surgery followed by chemotherapy. Neoadjuvant chemotherapy (NACT) and interval debulking surgery (IDS) is an alternative in selected patients. Most data exist with IDS following 3-4 cycles chemotherapy, however, some patients experience a delay of IDS. So far, the impact of a "delayed" interval debulking surgery (DID) is poorly defined.

Methods—We analyzed data from eight international gynecology-oncology referral centers. Patients were included if they had newly diagnosed AOC and were prone to DID (minimum 5 cycles of NACT) between 2011 and 2017.

Results—308 patients underwent DID. 89.6% had a high-grade serous ovarian cancer. The median number of pre-op NACT was 6 cycles (range 5-9) and 6.1% of patients received additionally bevacizumab. The majority of patients had stage-IV disease (51.3%). Median duration of surgery was 210 minutes (range 34-561), the median surgical complexity score was 4 (range 1-16). Complete resection was achieved in 60.1%. The median number of post-op chemotherapy cycles was 2 (range 0-5). The rate of severe complications (Clavien-Dindo£3°) was 9.7% and 30 days post-op mortality was 0.3%. The median PFS and OS in patients with complete resection was 19.5 and 49.2 months compared to 14.8 and 33.0 months in patients with incomplete resection (p=0.001), respectively. We did not observe any survival benefit for patients with cytoreduction to small residuals (1-10 mm) compared to residual disease > 1 cm.

Conclusion: Our data may suggest that offering surgery to patients with persistent disease after 5+ cycles could be associated with favourable outcome if a complete resection is achieved. Patients who had residual disease postoperatively may experience rather peri-operative treatment burden than any benefit from DID.

Keywords

Ovarian cancer; Debulking Surgery; Chemotherapy; Interval debulking; Neo-adjuvant

Introduction

Ovarian cancer is the second most common and the most lethal of gynecologic malignancies [1]. The standard of care for advanced ovarian cancer (AOC) is primary surgery with the aim of macroscopically complete resection, followed by adjuvant chemotherapy with carboplatin and paclitaxel [2]. Adjuvant chemotherapy may also include bevacizumab or a Poly (ADP-ribose) polymerase (PARP)-inhibitor [3–5]. Residual disease after surgery is the single most important prognostic factor which may be affected and therefore has been the focus of investigation with the goal to achieve higher rates of macroscopically complete resection [6]. More recently chemotherapy before and after surgery (neoadjuvant setting, NACT) became an alternative approach as randomized controlled trials demonstrated non-inferiority of this type of management over primary surgery in selected patients [7, 8]. This approach has been increasingly adopted by physicians worldwide. In the US, some centers

reported an increased use of NACT up to 62% for FIGOstage IV disease [9]. Indications for NACT could be poor performance status of the patient, contraindication to surgery (e.g. pulmonary embolism at diagnosis, etc.), or simply insufficient surgical resources, especially when high complexity surgery is needed to achieve complete cytoreduction. The ongoing TRUST trial is prospectively investigating the role of NACT in centers that fulfilled specific pre-determined criteria on surgical quality [10].

However, some patients only attend a referral center after having received 5 or more cycles of NACT with persistent disease, or were not offered surgery before for other reasons. There is paucity of literature in the setting of extended use of NACT (more than 4 cycles). The JCOG0602 trial included 4 cycles of NACT and found IDS to be less invasive in comparison to PDS but could not confirm non-inferiority of NACT followed by IDS [11]. A study by Meyer et al. demonstrated that PDS was associated with significantly improved survival among women with stage IIIC ovarian cancer in comparison to NACT (median of 4 cycles), which was not the case for stage IV disease [9]. Furthermore, the impact of high complexity surgery in patients who received 5 or more cycles of NACT is still poorly studied.

The purpose of this study was to evaluate the impact of a high number of cycles of NACT and the role of a “delayed interval debulking” with a focus on patients who were treated for AOC at international gynecologic oncology referral centers.

Methods

We performed a retrospective review of medical charts of patients who had been consecutively diagnosed with AOC between January 1, 2011 and December 31, 2017. We selected only patients who underwent a DID after five or more cycles of chemotherapy with the goal of complete resection. Women who did not undergo any surgery or underwent only laparoscopy were excluded from the study. All patients were managed by a team of trained gynaecologic oncologists.

Data were collected prospectively in accordance to protocols approved by the local institutional review boards of all eight institutions. After signing data sharing agreements (if demanded) and receiving approval from the local Institutional Review Boards in accordance to local regulations, patient data were pooled into a common database.

Overall survival (OS) was defined from the time of first diagnosis to the date of death by any cause or loss to follow-up. Progression-free survival (PFS) was defined from the time of first diagnosis to the date of first tumor recurrence necessitating either medical or surgical intervention.

Response to NACT was evaluated by imaging (when a computed tomography (CT) scan before surgery was available for intermediate evaluation of the response to chemotherapy) and serological CA-125 values. RECIST is usually only used in prospective clinical trials and thus was not available for all patients. Definition of response for a retrospective multicenter trial is not clearly defined. Therefore, we used the term “radiological response” and classified the results into 3 categories: Response (including Complete Response (CR)/ Partial Response (PR)), stable disease (SD), and progressive disease (PD). Additionally,

we applied the chemotherapy response score (CRS-Score) in accordance to the protocol published by Böhm et al., when available[12].

We used International Federation of Gynecology and Obstetrics (FIGO) classification (according to the classification of 2014) [13] for staging. FIGO IVA and B were pooled. Postoperative complications were collected and classified according to Clavien-Dindo classification [14]. Complexity of surgery was measured by the surgical complexity score (SCS) [15] and categorized into low (0-3), intermediate (4-7) and high (8 and more).

We also divided the cohort in to two groups according to resection status: complete vs incomplete resection, and subdivided incomplete resection into 1-10mm residual and >10mm of residual disease. Patients comorbidity was measured by the Charlson Comorbidity Index (CCI) [16].

Statistical analysis

All statistical analyses were performed using SPSS version 23.0 (IBM Corporation, New York, USA).

Survival curves for univariable survival analysis were constructed using the Kaplan-Meier method, and were compared using the log-rank test.

The Cox proportional hazard model (Wald stepwise backward regression) was utilized to evaluate all parameters that were significant in univariate analyses (Histology, FIGO-stage, Result of NACT, and Residual disease). The multivariate adjusted odds ratios (ORs) and 95% confidence intervals (CIs) are expressed. All analyses were thought to be hypothesis generating and a p-value of <0.05 was interpreted as being significant.

Data and findings of the study were partially presented and discussed on the 2018 ASCO annual meeting [17].

Results

Between January 2011 and December 2017, 308 patients underwent DID and were included in this analysis. Of these patients 59 (19.2%) received five cycles of NACT, 215 (69.8%) received six cycles, 34 (11.0%) received seven to nine cycles and 30 patients (6.1%) received additionally Bevacizumab before surgery. Median time from first diagnosis to surgery was 152 days.

Patients' characteristics are shown in detail in Table 1. Eastern Cooperative Oncology Group (ECOG) performance status was 0 in 27.9% of patients, ECOG 1 in 41.6%, ECOG 2 in 7.8%, ECOG 3 in 1 patient, and 22.7% had unknown performance status. 12.3% of patients had a Charlson Comorbidity Index (CCI) of 2 or higher. 89.6% of patients had a high-grade serous carcinoma. History of a 2nd malignancy was present in 9.7% of patients, most common of which was breast cancer (52.9%).

The median duration of debulking surgery was 210 minutes (range: 34-561 minutes). High complexity surgery (SCS 8 and more) was performed in 12.3% of patients and median blood

loss was 450 ml (range 50-5000ml). Complete clinical response to NACT was observed in 9.1%, while 73.4% showed partial response. Of the 308 patients, complete resection was achieved in 185 patients (60.1%) and incomplete resection in 123 patients (39.9%). Severe postoperative complications (Clavien-Dindo grade 3-5) were noted in 9.7% of the study population. The median follow-up period was 54 months and 59.2% of patients died of disease in this period of time.

The median OS was 40.7 months (95% CI 34.9–46.5 months) and the median PFS 16.6 months (95% CI 15.3–17.9 months). After surgery a median of 2 more cycles of chemotherapy were additionally administered (range 0-6). The number of cycles after DID (<2 vs. >2; p=0.881; HR = 1.03; 95% CI = 0.70-1.51) and total number of cycles (<6 vs. >6; p=0.533; HR = 1.18; 95% CI = 0.70-2.02) were not predictive for OS. In total 259 patients (84.1%) had recurrent disease. 44 patients (17%) relapsed within 6 months after last administration of platinum-based chemotherapy, while the majority, 215 patients (83%), has a platinum-sensitive recurrence.

Cox regression analysis identified two significant variables with a positive correlation to OS: Residual disease and chemotherapy response (Response vs. SD/PD).

Patients with complete resection demonstrated a significantly longer median OS of 16.6 months compared to patients who had residual disease (p<0.001; HR 1.82; 95% CI 1.34-2.48; 49.2 vs. 33.6 months) and median PFS of 8.1 months (p<0.001; HR 1.76; 95% CI 1.36-2.28; 19.5 vs. 11.4 months). This was statistically significant independent to response to NACT, histology and FIGO-stage (OS: p<0.001; HR=1.76; 95% CI 1.29-2.41, and PFS: p<0.001; HR=1.73; 95% CI 1.33-2.24).

Age, CCI score, 2nd malignoma, histology, FIGO stage, number of NACT cycles, administration of bevacizumab, time from diagnosis to first NACT cycle, time from 1st diagnosis to DID, number of postoperative cycles, and total number of chemotherapeutic drug cycles did not show any statistically significant influence on OS or PFS (see supp. material). There was no statistically significant differences in size of residual disease, comparing 1-10mm with >10mm (p=0.313 for OS) (Table 2; supplementary material with table 1 and 2) (Fig. 1 and 2).

We did further subgroup analysis regarding stage: median OS in stage IIIC disease was 43 months. It was 56 months in case of complete resection compared to 33 months (p<0.001) with residual disease. In patients with stage IV disease was median OS 40 months and the breakdown by complete resection was 44 versus 35 months which was not statistically significant (p=0.151).

Response to NACT by Chemotherapy Response Score (CRS)

A univariable analysis confirms significant correlation between chemotherapy response and overall survival (p=0.03; HR 1.69; 95% CI 1.05-2.71). This correlation was not statistically significant on multivariable analysis when adjusted for residual disease (p=0.093; HR 1.5; 95% CI 0.93-2.42). The correlation between chemotherapy response and PFS was not statistically significant in both univariable (p=0.183; HR 1.31; 95% CI 0.89-1.96) and

multivariable analysis (p=0.279; HR 1.25; 95% CI 0.83-1.27) when adjusted for histology, FIGO stage and residual disease. Therefore, Residual disease is the single most important prognostic factor for OS and PFS.

Evaluating Chemotherapy Response Score (CRS) 1-3 we identified that the CRS3 group was associated with a lower CCI (p=0.044), with favorable surgical features as less blood loss (p=0.080), shorter time of surgery (p=0.036), and a higher rate of complete resection (p=0.001). CRS 3 was also associated with improved PFS and OS (PFS p=0.006 and OS p=0.090) (Table 3).

Surgical Complexity Score (SCS) outcomes

Subgroup analysis demonstrated that patients receiving a high complexity surgery (n=38) had in comparison to patients who received low or intermediate complexity surgery (n=252) similar survival patterns (p=0.543; HR=1.15; 95%CI 0.73-1.83). The OS in the group of SCS-high was 40 months.

All SCS-groups were equally distributed by numbers of cycles of NACT. Patients from the SCS-high group were more frequently treated with bevacizumab (34%) in the neoadjuvant setting (p<0.001).

Severe Complications

26 patients (9.7%) had severe complications following DID. One patient died due to severe complications within 30 days after surgery. High surgical complexity score (p <0.001), time of surgery (p=0.013), blood loss (p=0.009), and a response to NACT (p=0.032) were statistically significant in relation to severe complication rate. Complete cytoreduction was not associated with a higher Clavien-Dindo score (p=0.905).

Discussion

Our study focuses on a selected group of patients with AOC that were not suitable for PDS or IDS and underwent instead a “delayed” interval debulking surgery after 5 or more cycles of NACT. Our large series highlights the importance of complete cytoreduction as it remains a significant independent marker of survival and should be the goal of each cytoreductive surgery in ovarian cancer, including DID. Patients with 1-10 mm had a similar survival to those with RD >10 mm suggesting that DID is mainly beneficial to patients if complete cytoreduction is achieved (Fig. 1 and 2). Thus, if complete cytoreduction is not possible, surgery should be discontinued in favor of subsequent chemotherapy and targeted therapy. These findings are consistent with other data published recently, which similarly demonstrate that adopting the philosophy of increased surgical effort leads to improved survival [18].

Although our study suffers from the usual limitations of a retrospective review, we have attempted to identify factors that may lead to bias in this population. BRCA-status was not available in most cases. Unfortunately, we cannot provide any details on the use of PARPi (poly ADP ribose polymerase inhibitors) as we did not collect specific data regarding treatment of relapsed disease, however our study period was before approval of PARPi in

the first line setting and thus only patients on trial could have received such therapy. Finally, patients were of course not routinely planned for a DID as this is not the standard of care for AOC, and possible reasons as to why patients were managed by a prolonged course of NACT were not available for our database. It could be helpful to understand centers' strategies and physicians' choices that lead to DID. Other limitations are discussed later point by point.

Complete cytoreduction in primary AOC is the single most important prognostic factor for overall survival [19–22]. Randomised controlled Trials such as CHORUS [7] or EORTC [8] reported the importance of complete cytoreduction for interval debulking surgery after 3 cycles of NACT. Data on DID after 5 and more cycles of NACT was recently investigated by Phillips at al. [23] and other authors [24–27] who confirmed the importance of complete cytoreduction, but data remains scarce. So far the standard of management of AOC remains primary debulking surgery, 3 or 4 cycles of NACT might be an alternative suggested by "The Joint Society of Gynecologic Oncology" [28] and by the ESMO-ESGO consensus paper [29].

The rate of complete cytoreduction in our analysis was 60.1% and is comparable to studies recently published. Phillips et al. reported a rate of 53.9% (OS of 36.5 months) [23], Akladios et al. reported 60.5% (OS of 33.1 months, calculated from the date of DID) [24], and Stoeckle et al. 83% (OS 37 months) [25]. Further studies as the one by de Frémville et al. (who included 43 patients, all with stage III disease) reported a complete resection rate of 86% (OS of 34 months) [26] and Xu et al. reported 25.8 months of OS in their cohort of 42 patients without specifying any detailed resection-rate [27]. Recently also Delga et al. reported a complete resection rate of 78.1% with an OS of 48.6 months [30]. All authors underline the importance of complete cytoreduction. Interestingly, in subgroup analysis (stage IIIC vs. IV) the benefit of complete resection was very strong in stage IIIC ($p<0.001$) while in stage IV disease it was not significant ($p=0.151$).

Literature, so far, including the above, suggests there is no correlation between high rate of complete resection and overall survival within surgical centers. Overall survival is of course multi-factorial and patients receiving 5 or more cycles of NACT are a heterogenous cohort. Decision to offer patients debulking surgery after 5 or more cycles of NACT is multi-disciplinary and depends on a multitude of factors such as chemotherapy response, fitness for a high complexity surgery and national recommendations. There is room for subjective assessment leaving room to create bias. Therefore, we decided to pool a cohort by conducting an international study including a significant number of patients that were treated in cancer centers with surgical expertise and a like-minded surgical philosophy to try and reduce this bias.

Chemotherapy response is an important factor in deciding the timing of surgery. 85.6% of our patients showed a response which is slightly higher than the one reported by Akladios et al. (67.3% after 3 cycles of chemotherapy) [24] and Stoeckle et al. (81%) at time of "late IDS" [23]. Colombo et al. demonstrated, that in case of complete resection, the prognostic effect of a good response to chemotherapy is lost ($p=0.124$) as well as on relapse free survival ($p=0.242$) [31]. We can confirm this finding underlining the importance of complete

resection, especially in case of persistent disease after NACT. In histological subtypes of ovarian cancer which are poor responders to chemotherapy, complete cytoreduction is key. [32]. Adopting the Goldie-Coldman hypothesis of the pathogenesis of ovarian cancer, residual disease after DID will probably also have a higher proportion of resistant clones [33].

Chemotherapy response score (CRS) on histology has been validated after 3 cycles of chemotherapy by Böhm et al. [12]. Applying a similar principle we have observed CRS 2 in 44.7% and CRS 3 in 30.6% of our patients. We also observe that patients with a CRS 3 had less extensive surgery with short duration, less blood loss and lower complexity score as compared to patients with a CRS 2. There is a positive correlation between response to NACT (CRS 3) and PFS (p=0.006), however the association of CRS and OS was not significant (p=0.09).

Interestingly the CCI of 0 or 1 was in favor for a higher CRS implying that healthier patients had a better response on NACT. This point merits further investigation. We do not have detailed information on chemotherapy regimens and associated complications for these patients. Further studies should investigate the effect of chemotherapy alone and chemotherapy alone vs. DID, particularly in the cohort of patients with a higher Charlson Comorbidity Index who are not fit for surgery.

The proportion of patients with FIGO stage IV disease was 51.3% in our analysis and thus much higher in comparison to other authors who reported rates between 0 and around 30% [23–27]. We could probably expected an impact on survival, though in uni- and multivariate analysis FIGO stage did not influence survival (p=0.519). But the higher number of stage IV patients could explain the higher percentage of high-complexity surgery in our cohort of patients (12.3%). Analogous to Philipps et al. who reported a SCS-high-rate of 5.4% [23] we could not identify significant differences between SCS-groups in terms of OS and complete cytoreduction rates.

The question whether patients should or could have been operated at diagnosis or after less than 5 cycles of NACT was not a focus of our investigation. Nonetheless, we could demonstrate that comparing the period of time from 1st diagnosis to delayed interval debulking surgery (<150d vs. >150d) within our cohort of patients did not influence survival (p=0.361). Similarly, we observed no significant difference on survival in patients who received 5 vs. more than 5 cycles of NACT (p=0.386). Various authors found that patients undergoing a delayed interval debulking surgery seem to show a poorer prognosis than patients operated earlier. Bogani et al. observed that the administration of more than 3 cycles worsens survival outcomes [34], Philipps et al. and Akladios et al. demonstrated instead no significant difference in OS between an interval debulking surgery and delayed interval debulking surgery in patients who underwent complete resection [23, 24]. The median OS in our cohort of patients who had a complete resection was 49.2 months.

The challenge in the management of patients who underwent 5 and more cycles of NACT is the evaluation whether the patients are eligible for surgery or not. Surgery with residual disease will more likely harm patients than resulting in any kind of benefit.

Conclusion:

The survival in patients undergoing DID appears to be mainly determined by complete resection. Complete cytoreduction should be the goal when DID is performed. When complete resection is not feasible, surgery should be discontinued.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Declarations of interest

H. Plett, O.T. Filippova, J.P. Ramspott, A. Garbi, G.D. Aletti, MZ Muallem, C. Langstraat, S. Phadnis, O. Zivanovic, Y. Sonoda, G. Gardner, A. Traut, F.A. Taran, S. Kommoss, M. Rosendahl, and K. Long Roche have nothing to disclose;

P. Harter: Honoraria: Astra Zeneca, Roche, Sotio, Tesaro, Stryker, ASCO, Zai Lab,MSD; Advisory Board: Astra Zeneca, Roche, Tesaro, Lilly, Clovis, Immunogen, MSD/Merck; Research funding (Inst): Astra Zeneca, Roche, GSK, Boehringer Ingelheim,Medac, DFG, European Union, DKH, Tesaro, Genmab;

A. du Bois: personal fees fromRoche, personal fees fromAstra Zeneca, personal fees fromTesaro, personal fees from Clovis, personal fees from Pfizer, personal fees from Genmab, personal fees from Pharmar, personal fees from Biocad, outside the submitted work;

Dr. Chi reports personal fees from Bovie Medical Co., Verthermia Inc. (now Apyx Medical Corp.), and C Surgeries; is a former stock owner of Intuitive Surgical, Inc. (sold 12/18) and TransEnterix, Inc. (sold 12/18); and served on the Medical Advisory Board of Biom ‘Up (4/19/19). Dr. Chi is funded in part through the NIH/NCI Cancer Center Support Grant P30 CA008748. T. Baert has been an advisor for Tesaro and received research grant from Amgen, non-financial support from Amgen, MSD, Roche and Tesaro, outside the submitted work.

References

1. Siegel RL, Miller KD, and Jemal A, Cancer statistics, 2020. CA Cancer J Clin, 2020. 70(1): p. 7–30. DOI: 10.3322/caac.21590. [PubMed: 31912902]
2. du Bois A, Lück HJ, Meier W, et al., A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. J Natl Cancer Inst, 2003. 95(17): p. 1320–1329. DOI: 10.1093/jnci/djg036. [PubMed: 12953086]
3. Ray-Coquard I, Pautier P, Pignata S, et al., Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. N Engl J Med, 2019. 381(25): p. 2416–2428. DOI: 10.1056/NEJMoa1911361. [PubMed: 31851799]
4. González-Martín A, Pothuri B, Vergote I, et al., Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med, 2019. 381(25): p. 2391–2402. DOI: 10.1056/NEJMoa1910962. [PubMed: 31562799]
5. Moore K, Colombo N, Scambia G, et al., Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med, 2018. 379(26): p. 2495–2505. DOI: 10.1056/NEJMoa1810858. [PubMed: 30345884]
6. Griffiths CT, Surgical resection of tumor bulk in the primary treatment of ovarian carcinoma. Natl Cancer Inst Monogr, 1975. 42: p. 101–104. [PubMed: 1234624]
7. Kehoe S, Hook J, Nankivell M, 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): p. 249–257. DOI: 10.1016/s0140-6736(14)62223-6. [PubMed: 26002111]
8. Vergote I, Tropé CG, Amant F, et al., Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med, 2010. 363(10): p. 943–953. DOI: 10.1056/NEJMoa0908806. [PubMed: 20818904]

9. Meyer LA, Cronin AM, Sun CC, et al., Use and Effectiveness of Neoadjuvant Chemotherapy for Treatment of Ovarian Cancer. J Clin Oncol, 2016. 34(32): p. 3854–3863. DOI: 10.1200/jco.2016.68.1239. [PubMed: 27601552]
10. Reuss A, du Bois A, Harter P, et al., TRUST: Trial of Radical Upfront Surgical Therapy in advanced ovarian cancer (ENGOT ov33/AGO-OVAR OP7). Int J Gynecol Cancer, 2019. 29(8): p. 1327–1331. DOI: 10.1136/ijgc-2019-000682. [PubMed: 31420412]
11. Onda T, Satoh T, Saito T, et al., Comparison of treatment invasiveness between upfront debulking surgery versus interval debulking surgery following neoadjuvant chemotherapy for stage III/IV ovarian, tubal, and peritoneal cancers in a phase III randomised trial: Japan Clinical Oncology Group Study JCOG0602. Eur J Cancer, 2016. 64: p. 22–31. DOI: 10.1016/j.ejca.2016.05.017. [PubMed: 27323348]
12. Bohm S, Faruqi A, Said I, 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): p. 2457–2463. DOI: 10.1200/jco.2014.60.5212. [PubMed: 26124480]
13. Prat J, Staging classification for cancer of the ovary, fallopian tube, and peritoneum. Int J Gynaecol Obstet, 2014. 124(1): p. 1–5. DOI: 10.1016/j.ijgo.2013.10.001. [PubMed: 24219974]
14. Dindo D, Demartines N, and Clavien PA, Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg, 2004. 240(2): p. 205–213. DOI: 10.1097/01.sla.0000133083.54934.ae. [PubMed: 15273542]
15. Aletti GD, Podratz KC, Moriarty JP, Cliby WA, and Long KH, Aggressive and complex surgery for advanced ovarian cancer: an economic analysis. Gynecol Oncol, 2009. 112(1): p. 16–21. DOI: 10.1016/j.ygyno.2008.10.008. [PubMed: 19027146]
16. Charlson ME, Pompei P, Ales KL, and MacKenzie CR, A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis, 1987. 40(5): p. 373–383. DOI: 10.1016/0021-9681(87)90171-8. [PubMed: 3558716]
17. Harter P, Plett H, Prader S, et al., Role of primary surgery for persistent residual disease after more than 5 cycles of chemotherapy for primary advanced ovarian cancer. Journal of Clinical Oncology, 2018. 36(15_suppl): p. 5543–5543. DOI: 10.1200/JCO.2018.36.15_suppl.5543.
18. Hall M, Savvatis K, Nixon K, et al., Maximal-Effort Cytoreductive Surgery for Ovarian Cancer Patients with a High Tumor Burden: Variations in Practice and Impact on Outcome. Ann Surg Oncol, 2019. 26(9): p. 2943–2951. DOI: 10.1245/s10434-019-07516-3. [PubMed: 31243666]
19. Wimberger P, Lehmann N, Kimmig R, Burges A, Meier W, and Du Bois A, Prognostic factors for complete debulking in advanced ovarian cancer and its impact on survival. An exploratory analysis of a prospectively randomized phase III study of the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group (AGO-OVAR). Gynecol Oncol, 2007. 106(1): p. 69–74. DOI: 10.1016/j.ygyno.2007.02.026. [PubMed: 17397910]
20. Eisenhauer EL, Abu-Rustum NR, Sonoda Y, Aghajanian C, Barakat RR, and Chi DS, The effect of maximal surgical cytoreduction on sensitivity to platinum-taxane chemotherapy and subsequent survival in patients with advanced ovarian cancer. Gynecol Oncol, 2008. 108(2): p. 276–281. DOI: 10.1016/j.ygyno.2007.10.022. [PubMed: 18063020]
21. du Bois A, Reuss A, Pujade-Lauraine E, Harter P, Ray-Coquard I, and 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 Etudes des Cancers de l'Ovaire (GINECO). Cancer, 2009. 115(6): p. 1234–1244. DOI: 10.1002/cncr.24149. [PubMed: 19189349]
22. Peiretti M, Zanagnolo V, Aletti GD, et al., Role of maximal primary cytoreductive surgery in patients with advanced epithelial ovarian and tubal cancer: Surgical and oncological outcomes. Single institution experience. Gynecol Oncol, 2010. 119(2): p. 259–264. DOI: 10.1016/j.ygyno.2010.07.032. [PubMed: 20800269]
23. Phillips A, Sundar S, Singh K, et al., Complete cytoreduction after five or more cycles of neo-adjuvant chemotherapy confers a survival benefit in advanced ovarian cancer. Eur J Surg Oncol, 2018. 44(6): p. 760–765. DOI: 10.1016/j.ejso.2018.01.097. [PubMed: 29426779]

24. Akladios C, Baldauf JJ, Marchal F, et al., Does the Number of Neoadjuvant Chemotherapy Cycles before Interval Debulking Surgery Influence Survival in Advanced Ovarian Cancer?Oncology, 2016. 91(6): p. 331–340. DOI: 10.1159/000449203. [PubMed: 27784027]

25. Stoeckle E, Boubli B, Floquet A, et al., Optimal timing of interval debulking surgery in advanced ovarian cancer: yet to be defined?Eur J Obstet Gynecol Reprod Biol, 2011. 159(2): p. 407–412. DOI: 10.1016/j.ejogrb.2011.07.014. [PubMed: 21835539]

26. de Fréminville Q, Licaj I, Frenel JS, et al., [Retrospective study: Late surgery post chemotherapy versus after 3-4 cures in treatment of advanced ovarian cancer]. Bull Cancer, 2020. 107(2): p. 157–170. DOI: 10.1016/j.bulcan.2019.10.004. [PubMed: 31858981]

27. Xu X, Deng F, Lv M, and Chen X, The number of cycles of neoadjuvant chemotherapy is associated with prognosis of stage IIIc-IV high-grade serous ovarian cancer. Arch Gynecol Obstet, 2017. 295(2): p. 451–458. DOI: 10.1007/s00404-016-4256-x. [PubMed: 27913927]

28. Wright AA, Bohlke K, Armstrong DK, et al., Neoadjuvant Chemotherapy for Newly Diagnosed, Advanced Ovarian Cancer: Society of Gynecologic Oncology and American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol, 2016. 34(28): p. 3460–3473. DOI: 10.1200/jco.2016.68.6907. [PubMed: 27502591]

29. Colombo N, Sessa C, du Bois A, et al., ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease. Ann Oncol, 2019. 30(5): p. 672–705. DOI: 10.1093/annonc/mdz062. [PubMed: 31046081]

30. Delga B, Classe JM, Houvenaeghel G, et al., 30 Years of Experience in the Management of Stage III and IV Epithelial Ovarian Cancer: Impact of Surgical Strategies on Survival. Cancers (Basel), 2020. 12(3). DOI: 10.3390/cancers12030768.

31. Colombo PE, Labaki M, Fabbro M, et al., Impact of neoadjuvant chemotherapy cycles prior to interval surgery in patients with advanced epithelial ovarian cancer. Gynecol Oncol, 2014. 135(2): p. 223–230. DOI: 10.1016/j.ygyno.2014.09.002. [PubMed: 25220627]

32. Grabowski JP, Martinez Vila C, Richter R, et al., Ki67 expression as a predictor of chemotherapy outcome in low-grade serous ovarian cancer. Int J Gynecol Cancer, 2020. 30(4): p. 498–503. DOI: 10.1136/ijgc-2019-000976. [PubMed: 31996397]

33. Goldie JH and Coldman AJ, A model for tumor response to chemotherapy: an integration of the stem cell and somatic mutation hypotheses. Cancer Invest, 1985. 3(6): p. 553–564. DOI: 10.3109/07357908509039817. [PubMed: 3910195]

34. Bogani G, Matteucci L, Tamberi S, et al., The Impact of Number of Cycles of Neoadjuvant Chemotherapy on Survival of Patients Undergoing Interval Debulking Surgery for Stage IIIC-IV Unresectable Ovarian Cancer: Results From a Multi-Institutional Study. Int J Gynecol Cancer, 2017. 27(9): p. 1856–1862. DOI: 10.1097/igc.0000000000001108. [PubMed: 29064913]

Highlights

The impact of a Delayed Interval Debulking surgery is poorly defined.

Option for Delayed Interval Debulking in patients with ovarian cancer after neoadjuvant chemotherapy should be discussed.

Delayed Interval Debulking resulting in residual disease may cause rather peri-operative treatment burden than any benefit.

The survival in patients undergoing Delayed Interval Debulking appears to be mainly determined by complete resection.

When complete resection is not feasible, surgery should be discontinued.

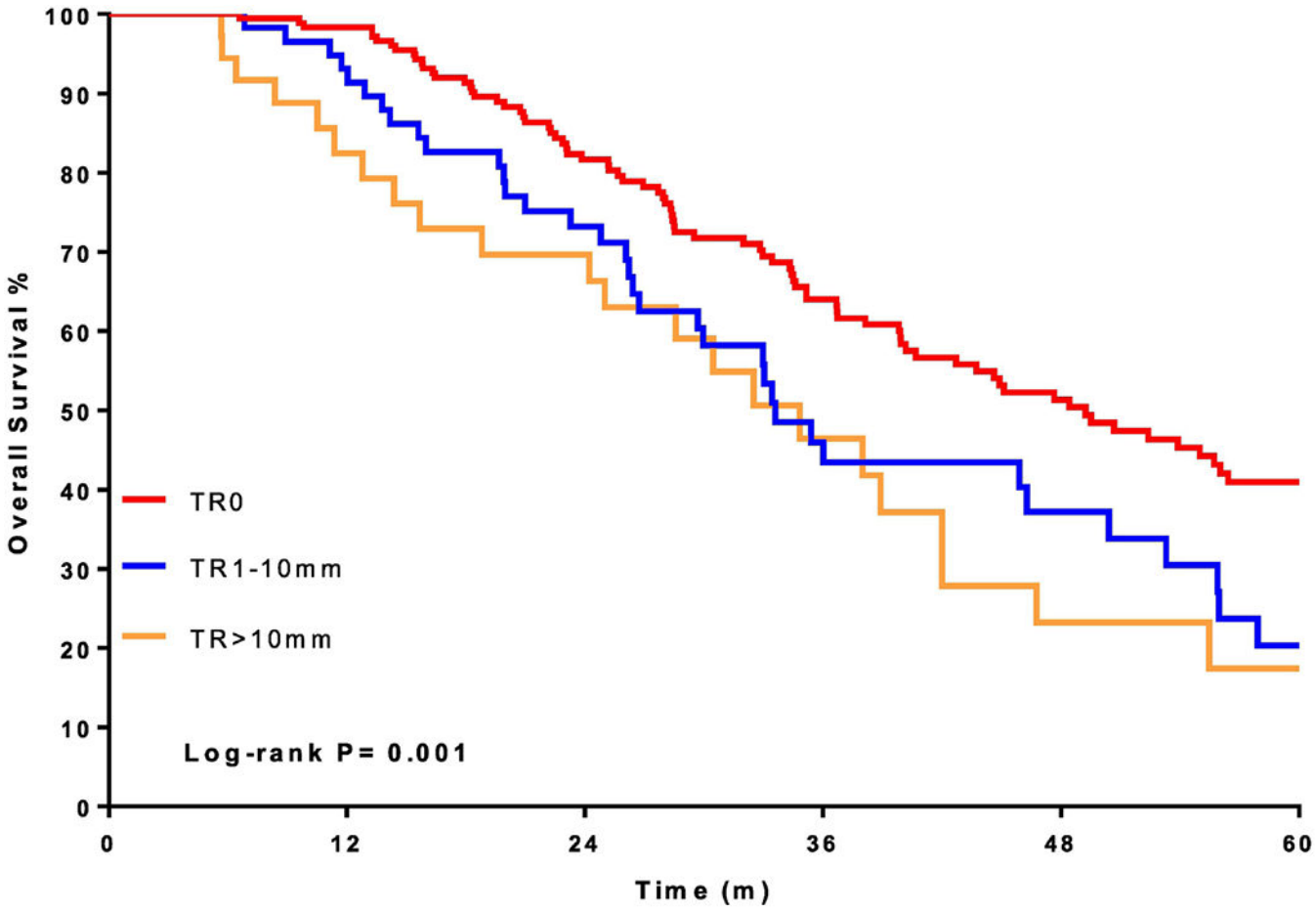

Fig. 1:
Kaplan-Meier curve comparing OS by residual disease

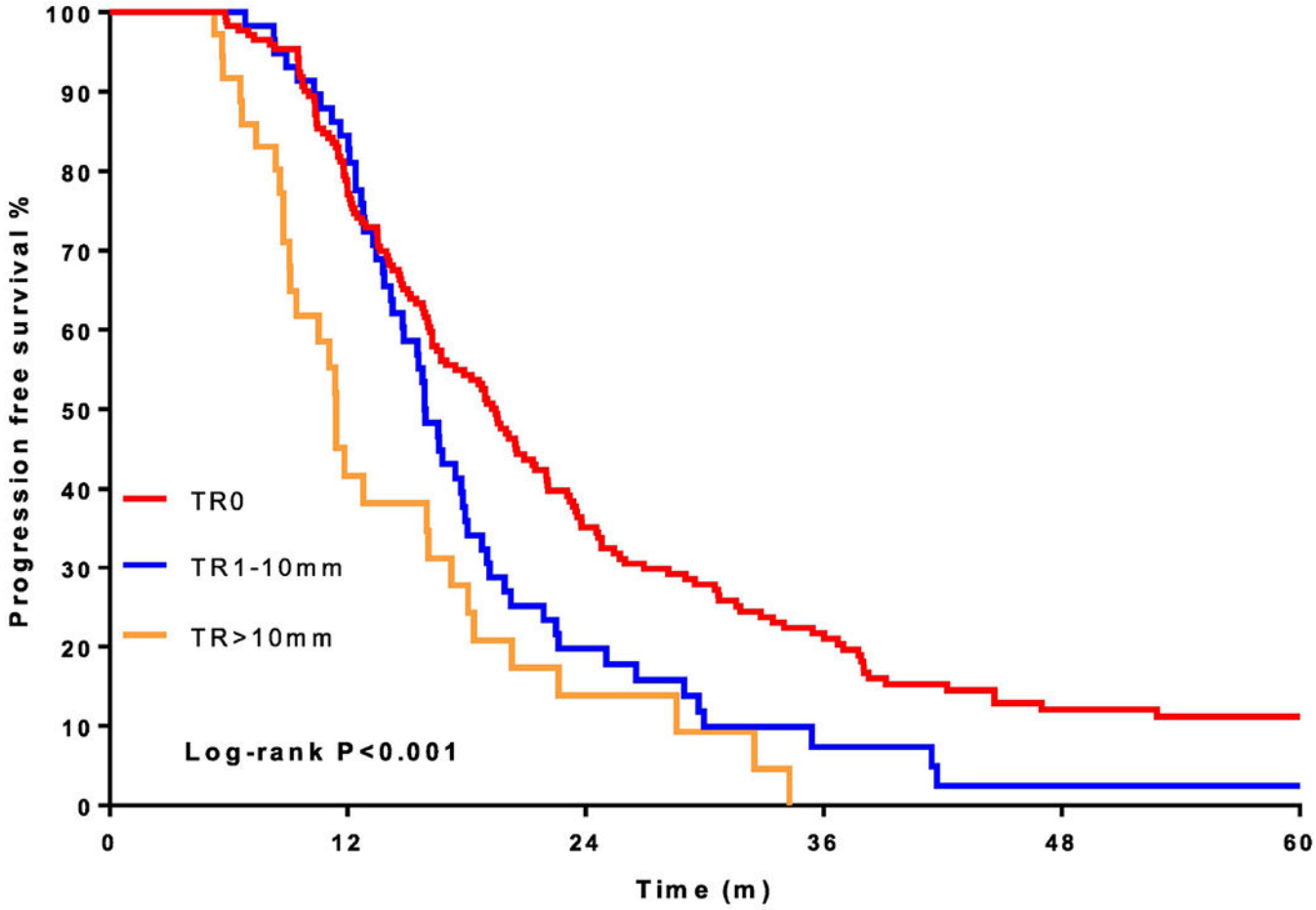

Fig. 2:
Kaplan-Meier curve comparing PFS by residual disease

Table 1.

Patients' and surgical characteristics

	N(%)
n	308
Age (median, range)	60(23-78)
CCI 0-1	238 (77.3)
CCI 2 - 7	38 (12.3)
CCI x	32 (10.4)
ECOG 0	86 (27.9)
ECOG 1	128 (41.6)
ECOG 2	24 (7.8)
Histology	
High-grade serous	276(89.6)
Low-grade serous/endometrioid	5 (1.6)
other	27 (8.7)
NACT cycles	
5	59(19.2)
6	215(69.8)
7-9	34(11)
median (range)	6(5-9)
Time from 1st NACT to DID (d)	152(75-348)
Additional Bevacizumab	30 (9.7)
FIGO-Stage (clinical)	
II	2(1)
III	140(45.5)
IV	158(51.3)
NK	7(2.3)
Response to NACT	
Response (CR/PR)	254 (82.5)
SD	29(9.4)
PD	5(1.6)
NK	20(6.5)
Surgical characteristics	
Bowel resection	37(12)
Splenectomy	33(10.7)
Liver resection	17(5.5)
Abdominal wall resection	20(6.5)
Surgical Complexity Score (SCS) (median, range)	4(1-16)
Low (0-3)	138(44.8)
Intermediate (4-7)	114(37)

	N(%)
High (8+)	38(12.3)
Residual disease (cm)	
0	185(60.1)
>0	123(39.9)
Postoperative complications (Clavien-Dindo)	
0-2	242(90.3)
3-4	26(9.7)
NK	40
Postop. CTX cycles	
cycles (median, range)	2(0-4)
0 cycles	65
1 cycle	9
2 cycles	50
≤3 cycles	82
NK	102
Follow-up (months)	54
OS months (median)	40.7
PFS months (median)	16.6

Table 2.

Statistically significant prognostic factors for OS and PFS.

OS	**N(%)**	**Ev(%↔)**	**uHR(CI95%)**	**uP**	**mHR(Ci95%)**	**mP**
Result of NACT						
Response (CR/PR)	254(82.5)	133(52.2)	1		1	
PD/SD	34(11	20(58.8)	1.69(1.05-2.71)	0.030	1.50(0.93-2.42)	0.093
NK	20(6.5)	10(50)				
Residual disease						
0	185(60.1)	87(47)	1		1	
>0	123(39.9)	76(61.8)	1.82(1.34-2.48)	<0.001	1.76(1.29-2.41)	<0.001
1-10mm	60(19.5)	36(60)	1.60(1.08-2.36)	0.018	1.56(1.05-2.31)	0.026
>10mm	36(11.7)	23(63.9)	2.10(1.32-3.33)	0.002	2.03(1.27-3.23)	0.003
PFS (without Copenhagen)						
Histology						
HGS	265(89.5)	228(86)	1		1	
other	31(10.5)	19(61.3)	0.62(0.42-1.08)	0.097	0.70(0.42-1.17)	0.172
FIGO-Stage						
II-III	138(46.6)	110(79.7)	1		1	
IV	152(51.4)	133(87.5)	1.28(0.99-1.65)	0.054	1.22(0.94-1.57)	0.134
NK	6(2)	4(66.7)				
Result of NACT						
Response (CR/PR)	254(85.6)	216(85)	1		1	
SD/PD	34(11.5)	27(79.4)	1.31(0.89-1.96)	0.183	1.25(0.83-1.27)	0.279
NK	8(2.7)	4(50)				
Residual disease						
0	177(59.8)	142(80.2)	1		1	
>0	119(40.2)	105(88.2)	1.76(1.36-2.28)	<0.001	1.73(1.33-2.24)	<0.001
1-10mm	60(20.3)	54(90)	1.51(1.10-2.08)	0.011	1.48(1.08-2.03)	0.016
>10mm	36(12.2)	30(83.3)	2.47(1.65-3.68)	<0.001	2.34(1.55-3.53)	<0.001

Table 3;

Subgroup analysis according to Chemotherapy Response Score (CRS)

	N (total)	CRS 1	CRS 2	CSR3	p
n	**N= 85**	**18 (21.2%)**	**38 (44.7%)**	**26 (30.6%)**	
CCI					0.044
CCI 0-1	66(77.6)	13(61.9)	20(76.3)	24(92.3)	
CCI =>2	19(22.4)	8(38.1)	9(23.7)	2(7.7)	
HGSOC					0.423
yes	77(90.6)	20(95.2)	35(92.1)	22(84.6)	
no	8(9.4)				
Response to NACT					0.154
Response (CR/PR)	75(88.2)	18(85.7)	33(86.8)	24(92.3)	
Progressive Disease	3(3.5)	0	3(7.9)	0	
Stable Disease	7(8.2)	3(14.3)	2(5.3)	2(7.7)	
Bevacizumab with NACT					0.440
No Bevacizumab	33(38.3)	7(33.3)	17(44.7)	9(34.6)	
Bevacizumab	25(29.4)	5(23.8)	13(34.2)	7(26.9)	
NK	27(31.8)	9(42.9)	8(21.1)	10(38.5)	
FIGO					0.104
III	52(61.2)	9(42.9)	27(71.1)	16(61.5)	
IV	33(38.8)	12(57.1)	11(28.9)	10(38.5)	
Time of surgery (median, range)					0.036
<210 min	42(49.4)	12(57.1)	13(34.2)	17(65.4)	
>210 min	43(50.6)	9(42.9)	25(65.8)	9(34.6)	
Blood loss (median, range)					0.080
<450	44(51.8)	8(31.8)	18(47.4)	18(62.9)	
>450	41(48.2)	13(61.9)	20(52.6)	8(30.8)	
Residual disease					0.001
0	54(63.5)	9(42.9)	21(55.3)	24(92.3)	
>0	31(36.5)	12(57.1)	17(44.7)	2(7.7)	
Clavien-Dindo (°)					0.766
0-2	76(89.4)	18(85.7)	34(89.5)	24(92.3)	
3-5	9(10.6)	3(14.3)	4(10.5)	2(7.7)	
OS (median)					0.090
OS (median) months	36.7	32.5	35.2	49.5	
PFS					0.006
PFS (median) months	21.5	23.8	16.9	35.4	

CCI Charlson Comorbidity Index
ECOG Eastern Cooperative Oncology Group Perfomance Status
NACT Neoadjuvant Chemotherapy
DID Delayed Interval Debulking

FIGO The International Federation of Gynecology and Obstetrics
CR/PR Complete / Partial Remission
SD Stable Disease
PD Progressive Disease
SCS Surgical Complexity Score
CTX Chemotherapy
PFS Progression Free Survival
OS Overall Survival
HGSOC High Grade Serous Ovarian Cancer
NK Not Known