Gynecologic Oncology 152 (2019) 235–242

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

# Early tumor regrowth is a contributor to impaired survival in patients with completely resected advanced ovarian cancer. An exploratory analysis of the Intergroup trial AGO-OVAR 12

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## HIGHLIGHTS

- In a considerably high frequency of patients with complete resection, tumorous lesions are found in pre-chemotherapy CT scans.
- Survival is significantly impaired in patients with tumorous lesions compared to patients without tumorous lesions.
- There is evidence that tumor at pre-chemotherapy CT has predictive impact on targeted therapies

## ARTICLE INFO

*Article history:*
Received 24 September 2018
Received in revised form 30 October 2018
Accepted 6 November 2018

## ABSTRACT

*Objective.* Surgical assessment of residual tumor provides the strongest prognostic information in advanced ovarian cancer (AOC), with the best outcome observed after complete resection. Postoperative radiological assessment before initiation of chemotherapy can supplement the information obtained by surgical assessment; however, it may also reveal conflicting findings.

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[10] Both authors contributed to the same extend to the study concept, execution, analyses and manuscript writing.

https://doi.org/10.1016/j.ygyno.2018.11.008
0090-8258/

Available online 20 November 2018

*Keywords:*
Advanced ovarian cancer
Debulking surgery
Pre-chemotherapy imaging
Prognosis

*Methods.* Patients with AOC enrolled in the AGO-OVAR 12 trial underwent baseline imaging before the first chemotherapy cycle. The findings from surgical and radiologic assessment for disease extend were compared. Additionally, an integrated approach was assessed.

*Results.* Complete data from all 3 assessment methods were available for 1345 patients. Of 689 patients with complete resection, tumor was observed in 28% and 22% of patients undergoing radiologic and integrated assessment, respectively. Patients with surgical- radiological and surgical-integrated concordant findings showed a 5-year overall survival (5Y-OS) of 72% and 71%, whereas patients with surgical-radiological and surgical-integrated discordant results showed inferior 5Y-OS of 47% and 49%, respectively. Patients with surgically assessed residual disease had a 5-YOS of 37%. The interval between surgery and baseline assessment was independently associated with discordance between assessment methods, which might reflect early tumor regrowth.

*Conclusions.* Baseline tumor assessment before chemotherapy provides information that stratifies patients with complete resection into different prognostic groups. Integrating the data from different assessment methods might lead to improved definitions of prognostic groups. Further investigation to determine if earlier initiation of chemotherapy after debulking surgery could increase survival of patients with early tumor regrowth is warranted.



## 1. Introduction

The treatment of advanced epithelial ovarian cancer (AOC) consists of debulking surgery and chemotherapy. The effects of tumor debulking in patients with AOC have evolved over the decades since the 1960's [1]. Decreasing amounts of residual disease (RD) have shown increasing median survival rates [2]. "Optimal" debulking was considered for a long time to be resection of tumor to ≤1 cm of residual intra-abdominal lesions [3]. With the introduction of extensive upper abdominal surgery, the rates of optimal debulking [4,5] and complete resection [6] have increased. Complete resection is the universal goal of surgery for most patients with AOC, since it is associated with the longest survival [7,8] and the assessment of RD is performed at the end of the debulking procedure by the operating surgeon, which however might be associated with bias [9]. The standard chemotherapy regimen after surgery comprises carboplatin and paclitaxel [10], with the optional addition of bevacizumab [11]. Pre-chemotherapy imaging might improve tumor assessment by detecting surgically not registered residual tumor; however, imaging might be prone to false-positive findings related to tissue repair or scarring, or finally detect new lesions of rapid postoperative tumor regrowth [12,13]. The aim of this study was to determine the frequency and the prognostic impact of tumor lesions visualized on prechemotherapy imaging in patients who had obtained complete resection based on surgical assessment in a large phase III trial.

## 2. Patients and methods

### 2.1. Clinical trial

Patients included in the current analysis underwent treatment in the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO)-studygroup led OVAR 12 trial (NCT01015118). This was, a randomized placebo-controlled double-blind Gynecologic Cancer InterGroup (GCIG)/European Network of Gynaecological Oncological Trial Groups (ENGOT) phase III trial of standard frontline chemotherapy with carboplatin + paclitaxel ± nintedanib for AOC. Detailed trial information and results have been reported elsewhere [14]. In brief, 1366 patients with histologically proven epithelial ovarian cancer or fallopian tube or primary peritoneal cancer with advanced-stage disease (International Federation of Gynecology and Obstetrics [FIGO] stage IIB–IV) who had upfront surgery were included. Treatment consisted of 200 mg nintedanib BID or placebo (PO) combined with paclitaxel 175 mg/m$^2$ + carboplatin AUC-based dose of 5 or 6 every 21 days for 6 courses. After the completion of chemotherapy, maintenance monotherapy with nintedanib or placebo was administered for up to 120 weeks.

Patients who had received neoadjuvant therapy and planned interval debulking surgery were not included. All patients were required to undergo baseline imaging computer tomography (CT) or magnet resonance imaging (MRI) of the abdomen and pelvis, chest X-ray or chest CT before chemotherapy. First dose of treatment within trial had to be started ≤70 days after surgery. Baseline imaging had to be performed in all patients after surgery within 4 weeks prior to starting systemic therapy. CA125 baseline values were extracted from the database to correlate with baseline imaging. The dates between imaging and CA125 assessment should not exceed 2 weeks and CA125 should be available before starting chemotherapy.

### 2.2. Study-specific definitions

Analyses were performed according to an independent central review process. At study entry, specific surgical information for each study patient was required for entry into the database. The required data included the following: details of the surgical procedures; and the presence, localization, and size of postoperative residual tumors. In addition, data from radiological imaging at each investigator site, performed before the onset of chemotherapy with a detailed description of target and nontarget lesions, were documented, if applicable. All data were monitored.

Residual disease assessments were used in 3 consecutive levels for this study (Fig. 1): Level 1: surgical assessment performed by the local surgeon. For patients with known data in level 1 individual data of level 2 which was the central radiological assessment were allocated. Patients with complete resection as determined by surgical assessment, but with findings in level 2, were assigned to an integrated assessment in level 3. Patients were further divided into the following 3 groups for prognostic analyses: patients with surgically assessed residual postoperative tumor (regardless of radiological visualization) ("surgically macroscopic residual disease"); patients without any macroscopic tumor as declared by both surgeon and radiologists ("surgical-radiologic concordance"); and patients with complete resection as defined by the surgeon but discrepancies with respect to tumor found during baseline radiological imaging ("surgical-radiologic discordance"). Only patients with "surgical-radiologic discordance" were allocated to integrated assessment, and queries to the study center were generated in order to re-evaluate all discrepancies with respect to postoperative residual tumors and prechemotherapy tumor lesions, as assessed by imaging. The local investigator was asked to discuss discrepancies with the surgeon and local radiologist, to perform a repeat review of the CT scans, and to classify the discrepant findings as either of the following:

- No postoperative tumor and probably no prechemotherapy tumor, CT findings probably due to postoperative scarring ("concordance in integrated assessment") or
- Surgical assessment probably overlooked tumor in an area where no surgical exploration had been performed, but postoperative CT

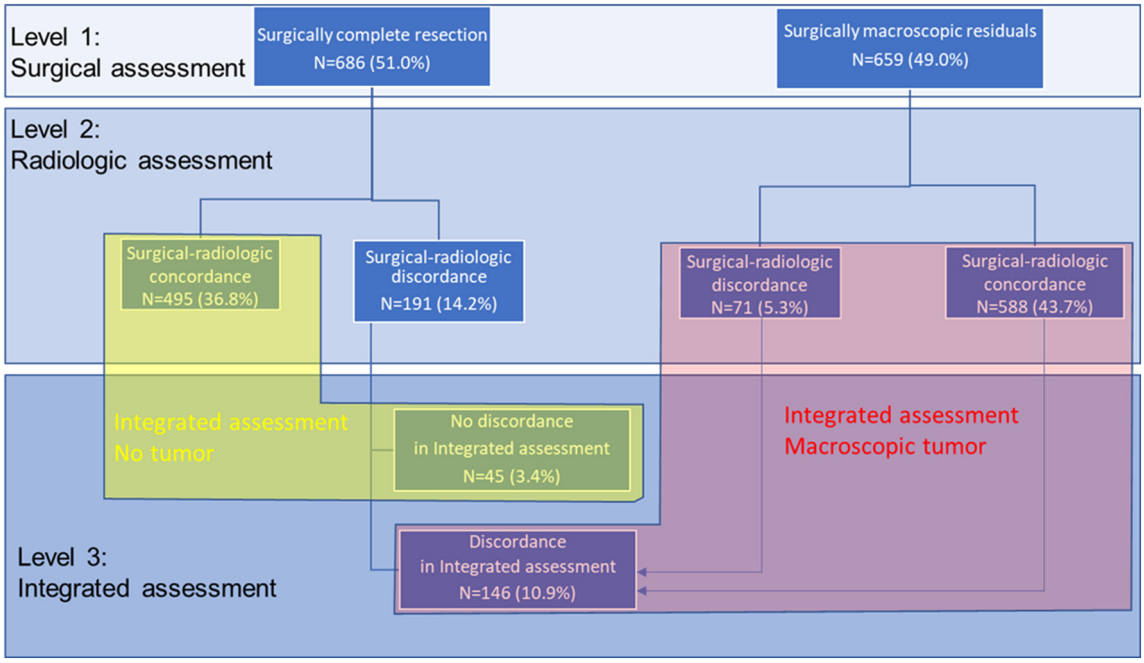


**Fig. 1.** Definition of groups based on assessment methods: Level 1: surgical assessment (SA), Level 2: radiologic assessment (RA), Level 3: integrated assessment (IA). Definitions for prognostic evaluation: Integrated assessment macroscopic tumor (red scattered); Integrated assessment no tumor (yellow scattered); all % frequencies are referred to the complete study population ($N = 1345$).

revealed highly suspicious lesions ("discordance in integrated assessment"). For cases in which the discrepancies could not be resolved, the study chair and his deputy (AdB and PH) each performed an integrated baseline assessment that used all available data including surgical reports and images, imaging including further imaging beyond the basic CT, serologic markers, and pathology results to classify each case into one of the respective categories. The "surgical-radiologic concordance" and "surgical-radiologic discordance" groups were compared to determine the prognostic impact of radiologic assessment. The "surgical-radiologic concordance" and "concordance in integrated assessment" groups were compared to the "surgically macroscopic residual disease" and "discordance in integrated assessment" to determine the prognostic impact of integrated assessment.

### 2.3. Statistical analysis

The Kaplan-Meier method and Cox proportional hazard regression models were used for estimating and analyzing progression-free survival (PFS) and overall survival (OS), which were assessed from the date of randomization. Median OS was not reached in most of the reported analyses, thus, we report 5-year OS instead. We used Akaike and Schwartz Bayesian information criteria (AIC and SBIC) to compare the effect of each of the 3 assessment methods (surgical assessment, radiologic assessment, integrated assessment) on model fit when regressing PFS and OS on residual tumor. Logistic regression models were used to explore the association of patient characteristics with discordance between the results from the different assessment methods. Stepwise selection of covariates was used to identify variables to enter into the final multivariate regression model, with the following thresholds: p-entry = 0.2; *P*-stay = 0.15). The following parameters were used: Age (<50, 50–70, >70 years), FIGO stage (II, III, IV), Eastern Cooperative of Oncology Group (ECOG) (0, >0), histopathology (high-grade serous, low-grade serous, others), ethnic origin (white, African or African-American, Asian, missing), surgical access (vertical incision, Pfannenstiel, laparoscopy, missing), treatment arm (placebo, nintedanib), and time between surgery and imaging (weeks).

## 3. Results

Data on surgical, radiologic, and integrated assessment were available for 1345 patients (98.5% of 1366 included patients). The median age of patients was 58 years, and most patients (85.7%) had FIGO stage III or IV disease, were of Caucasian ethnicity (90.9%), and had high-grade serous tumors (63.0%). Table 1 summarizes the baseline characteristics of the study patients. Time between surgery and baseline imaging was not different between patients with different FIGO stages ($P = 0.76$).

**Table 1**
Patients' characteristics; ECOG: Eastern Cooperative Oncology Group; FIGO: Federation of Gynecologists and Obstetricians.

| Parameter | All ($N = 1345$) *N* (%) |
|---|---|
| Age (years); median (range) | 58 (21–84) |
| ECOG performance status | |
| 0 | 888 (66.0) |
| >0 | 457 (34.0) |
| FIGO stage | |
| II | 137 (10.2) |
| III | 884 (65.7) |
| IV | 323 (24.0) |
| Time to imaging (days), median (IQR) | 28 (21–36) |
| Tumor histology | |
| High-grade serous | 848 (63.0) |
| Low-grad eserous | 71 (5.3) |
| Serous, grade unknown | 116 (8.6) |
| High-grade endometrioid | 102 (7.6) |
| Low-grade endometrioid | 19 (1.4) |
| Clear cell | 33 (2.5) |
| Mucinous | 37 (2.8) |
| Mixed/others/unspec. | 119 (8.8) |
| Surgical evaluation | |
| Vertical incision | 1192 (88.6) |
| Pfannenstiel | 51 (3.8) |
| Laparoscopy | 58 (4.3) |
| Missing | 44 (3.3) |
| Treatment arm | |
| Nintendanib | 898 (66.8) |
| Placebo | 447 (33.2) |

With the different methods used to assess pre-chemotherapy tumor burden frequencies of patients with perceivable tumor lesions were different: 49.0% ($N = 659$) by surgical assessment, 57.9% ($N = 779$) by radiologic assessment, and 59.9% ($N = 805$) by integrated assessment (definition of levels in Fig. 1). In 495 patients (72.2% of patients with "surgically complete resection") no discordance was found by radiologic assessment; and in 191 patients (27.8% of patients with "surgically complete resection") radiologic assessment determined discordant findings (Fig. 1). Integrated assessment led to a division of the "surgical-radiologic discordance" group into: "concordance in integrated assessment", (6.7% of patients with "surgically complete resection", and 23.6% of the "surgical-radiologic discordance" group), and into the "discordance in integrated assessment" group (21.3% of patients with "surgically complete resection", and 76.4% of "surgical-radiologic discordance" group). Supplement Table 1 displays the location with tumor lesions in radiologic assessment causing surgical-radiologic discordance.

Factors associated with discordant results in 191 patients ("surgical-radiologic discordance") were assessed by a multivariate logistic regression model that included 686 patients with "surgically complete resection". Factors significantly associated with discordant results were as follows: FIGO III vs II (Odds ratio (OR) 1.839, 95% Confidence Interval (CI) 1.097–3.083; $P = 0.0331$), FIGO IV vs II (OR 7.954, 95% CI 4.048–15.629; $P < 0.001$), and time between surgery and imaging (OR per week 1.232, 95% CI: 1.113–1.364; $P < 0.001$). Factors associated with discordant results in 146 patients ("discordance in integrated assessment") were assessed by a multivariate logistic regression model that included 686 patients with "surgically complete resection". FIGO IV vs II (OR 17.958, 95% CI 7.777–41.467; $P < 0.001$) and time between surgery and imaging (OR per week 1.272, 95% CI: 1.139–1.420; $P < 0.001$) were significantly associated with discordance.

Fig. 2 displays the frequency of discordant results between assessment methods for 4 distinct time intervals between the date of definitive surgery for ovarian cancer and the prechemotherapy assessment. The frequency of discordance was lowest for the shortest interval (time to imaging <21 days; 3.26% surgical assessment/integrated assessment, 13.36% surgical assessment/radiologic assessment). The frequency of discordance for the 31–40–day interval increased (15.22% surgical assessment/integrated assessment, 24.53% surgical assessment/radiologic assessment), suggesting that tumor regrowth might be the most important factor accounting for discordance. In an analysis combining FIGO stages with time to imaging it was shown, that the rates of discordance increased significantly by each FIGO stage (II > III > IV); $P < 0.0001$. Supplement Fig. 1 shows the proportion of discordances over the period of baseline imaging based on FIGO stages. The time between surgery and imaging was 28 days in median and not different between FIGO stages, $P = 0.76$.

To validate imaging results, CA125 correlation was conducted in a subset of 1.225 patients with available data. In 495 patients with surgical-radiologic concordance, median CA125 was 56.4 U/ml (lower quartile: 24.6; upper quantile: 133,7) and therewith significantly lower, compared to 191 patients with surgical-radiologic discordance, in whom median CA125 was 77.0 U/ml (lower quartile: 31.8; upper quantile: 170.4); Wilcoxon-Mann-Whitney-Test; $P = 0.004$. Patients with "surgically macroscopic residuals" had a median CA125 of 226.5 U/ml (lower quartile: 79.5; upper quantile: 577.6).

### 3.1. Prognostic impact of different assessment methods

Survival analyses with respect to residual tumor as defined by the 3 different assessment methods showed that the PFS estimates for the subgroup with assumed complete resection increased based on assessment method from 27.6 months (surgical assessment RT0, $N = 686$), to 27.8 months (radiologic assessment RT0, n = 566), and finally to 28.9 months (integrated assessment RT0, $N = 540$), in line with the hypothesis that the decreasing proportion of patients with perceivable tumor lesions in according to the respective assessment methods lead to an increasing survival. If radiologic assessment was taken into account for prognostic analyses, the outcomes of patients with "surgically complete resection" led to 2 distinct prognostic groups. Patients with "surgical-radiologic concordance" obtained longer PFS (median 28.9 months) and a 5-year OS rate of 72% compared with the entire group of patients with "surgically complete resection" (PFS: median 27.6 months; 5-year OS: 67%). Patients with "surgical-radiologic discordance" obtained shorter PFS (median 19.0 months) and a 5-year OS rate of 47% (Supplement Fig. 2 and Fig. 3). Patients with "surgically macroscopic residuals" had a median PFS of 13.5 months and a 5-year OS

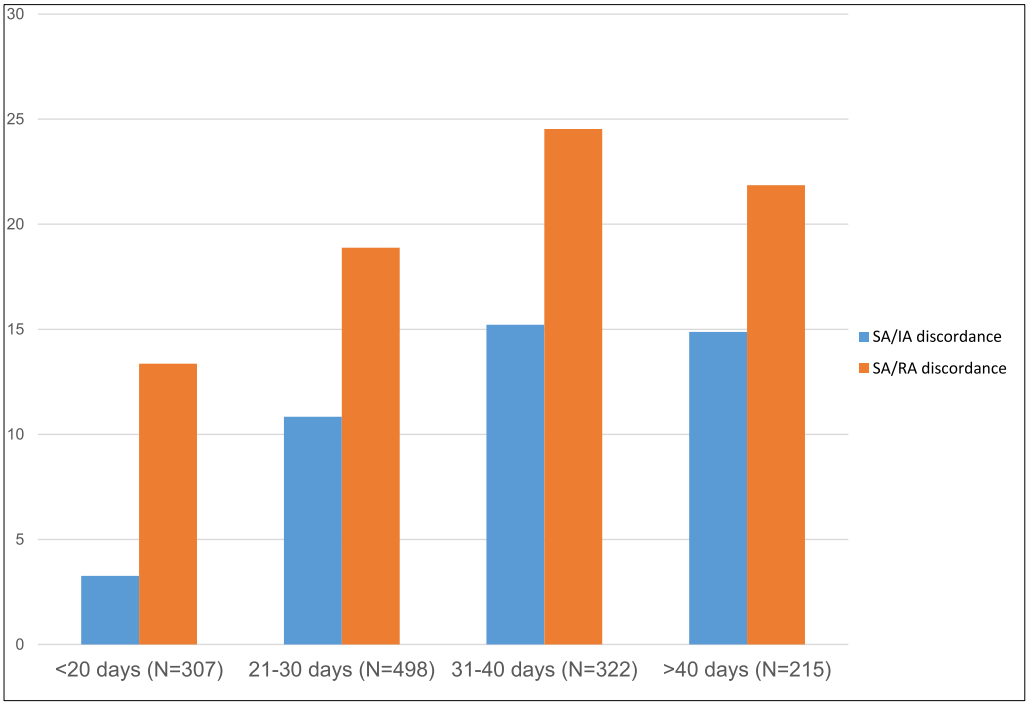


**Fig. 2.** Frequency of discordance depending on time between surgery and pre-chemotherapy imaging; SA: surgical assessment; IA: integrated assessment; RA: radiologic assessment.

rate of 37%. The survival of patients with "surgically complete resection" (PFS and 5-year OS for the entire group of patients with surgical assessment RD0 again were 27.6 months and 67%) was compared, with the survival of the patients undergoing integrated assessment. Again, 2 distinct prognostic groups resulted. Patients with "concordance in integrated assessment" (yellow overlay in Fig. 1) obtained a PFS of 28.9 months and a 5-year OS rate of 71%. Patients with "discordance in integrated assessment" obtained a PFS of 16.9 months and a 5-year OS rate of 49% (Supplemental Fig. 3 and Fig. 4).

To examine which of the assessment methods led to the best prognostic model, we compared Akaike (AIC) and Schwartz Bayesian information criteria (SBIC) for Cox regression models of PFS on residual tumors and residual tumors plus treatment. For both models and based on both information criteria, integrated assessment provided the best prognostic accuracy (lowest values for AIC and SBIC), followed by surgical assessment and radiologic assessment (data not shown). The same held true for the corresponding OS models.

The primary publication of the AGO-OVAR 12 trial reported a trend towards an improved effect of nintedanib in patients with complete resection compared with patients with macroscopic residual disease. In our study, it was evaluated, if the different results in terms of residual disease as determined by the different assessment methods could further elucidate the treatment effect of nintedanib. Supplemental Figs. 4–6 show that nintedanib did not benefit patients with RD > 0. The differences in the PFS estimates of the patients with RD0 based on surgical assessment, radiologic assessment, or integrated assessment who were treated by nintedanib or placebo were 3.9 months (HR 0.831, 95% CI 0.652–1.057; $P = 0.13$), 4.9 months (HR 0.753, 95% CI 0.574–0.986; $P = 0.0392$), and 5.8 months (HR 0.769, 95% CI 0.577–1.025; $P = 0.073$), respectively.

## 4. Discussion

The evolution of the goal of surgical debulking to complete resection in patients with AOC took place over 4 decades. We now face a new era, where patients who undergo complete resection will be further categorized into patients with and without any visible tumor burden at the onset of chemotherapy. The radiologic assessment of tumor burden before the onset of chemotherapy identified >25% of patients with complete resection after surgical assessment- with suspect tumor lesions. Integrated assessment, which combines the information from radiologic assessment with the data from surgical and histopathology reports, reduced the proportion to 20% of patients in whom discordances remained. In total, only 80% of the patients with a complete resection determined by the surgeon are tumor-free at the baseline imaging. What are the possible reasons for discordant findings? Has discordance any clinical impact? Patients with discordant findings showed worse survival than patients with concordant findings between surgical and pre-chemotherapy assessment. Two explanations are possible for these controversial findings. Either the postoperative residual lesions were overlooked by the surgeon and the surgical assessment was false-negative, or the patients with discordant results were those with early postoperative tumor regrowth. The latter explanation is supported by the finding that the length of the interval between surgery and imaging was an independent factor associated with discordant assessments and not the surgical approach used. Furthermore, the observation that the survival of this subgroup of patients was not as poor as the survival of patients with residual disease at the end of surgery supports the tumor regrowth hypothesis. In this model, early tumor regrowth has resulted in a tumor burden that is smaller than the tumor burden for patients with surgically assessed macroscopic residual tumor. On the other

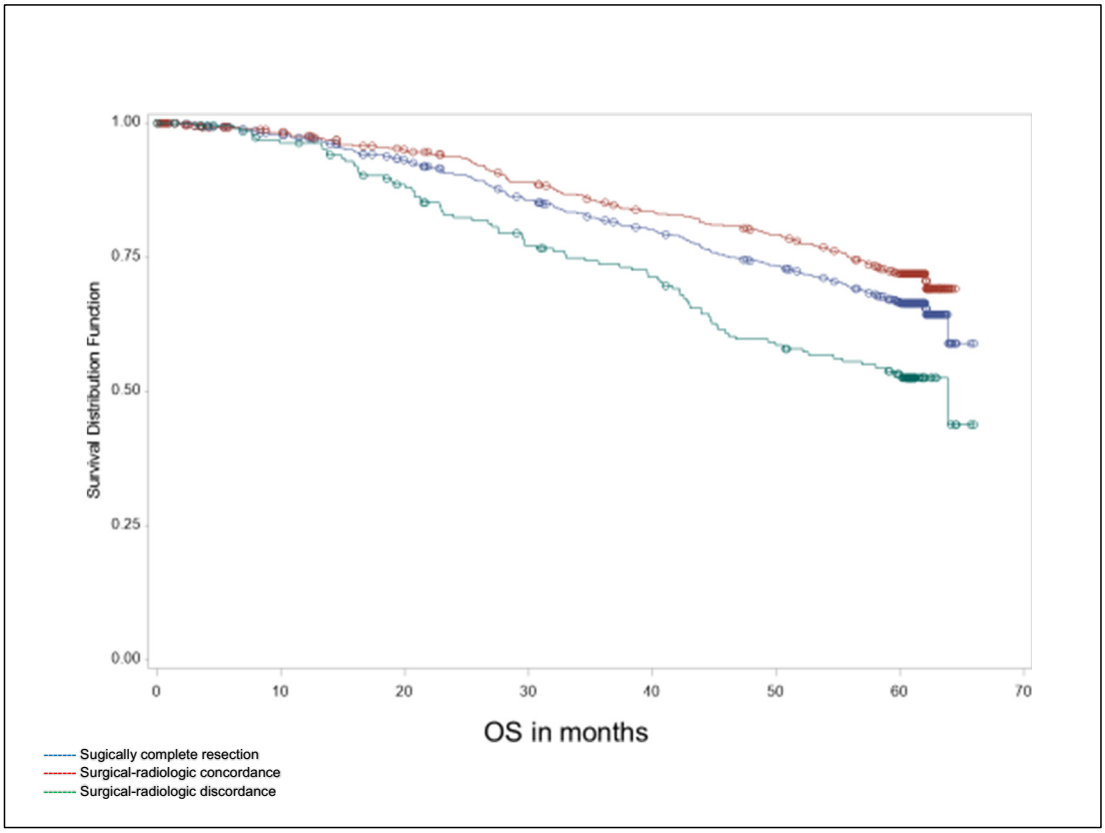


**Fig. 3.** Kaplan-Meier plots of OS of patients with "surgically complete resection" (blue); and additional information of radiologic assessment; 5-year OS of "surgically complete resection" ($N = 689$): 67%; "surgical-radiologic concordance" (red) ($N = 495$): 72%; "surgical-radiologic discordance" (green) ($N = 192$): 47%; patients with "surgically macroscopic disease" had a 5-year OS rate of 37% (data not shown); circles: censored.

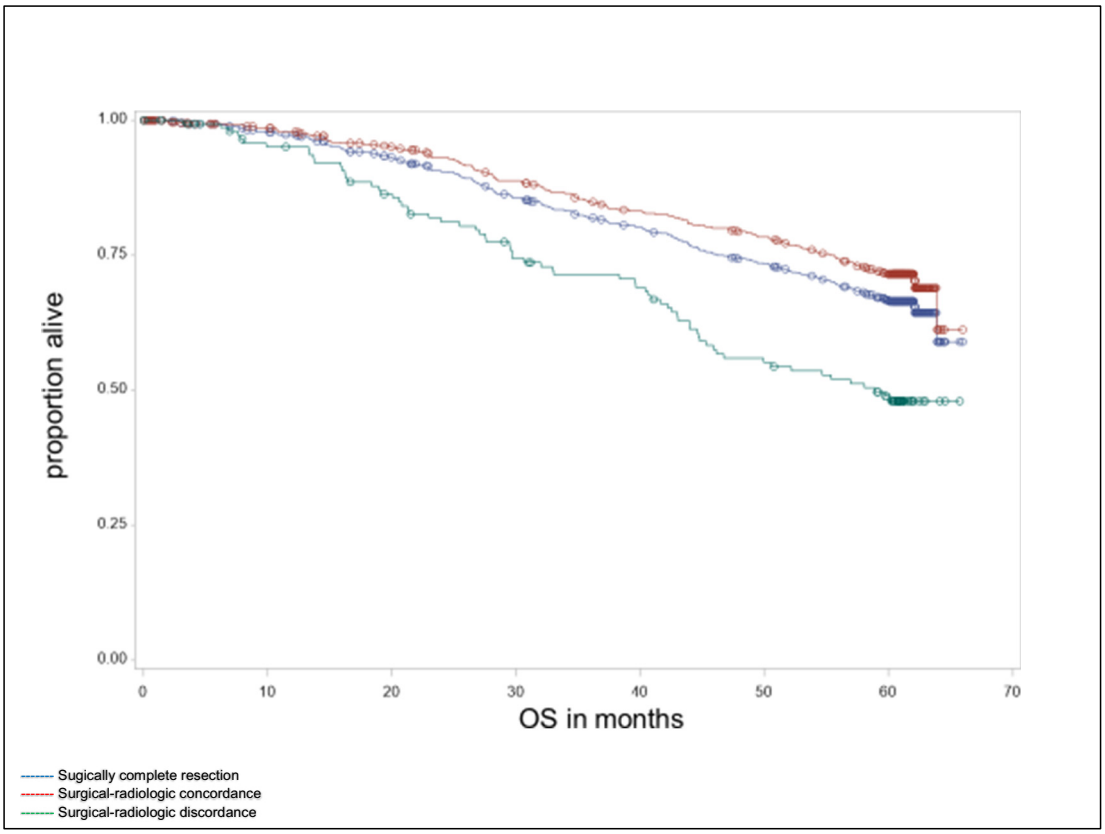


**Fig. 4.** Kaplan-Meier plots of OS of patients with "surgically complete resection" (blue); and additional information of integrated assessment (IA); 5-year OS of "surgically complete resection" ($N = 686$): 67%; "surgical-radiologic concordance" (red) ($N = 540$): 71%; "surgical-radiologic discordance" (green) ($N = 146$): 49%; patients with "surgically macroscopic disease" had a 5-year OS rate of 37% (data not shown); circles: censored.

hand, early tumor regrowth distinguishes this patient subgroup from those patients who also obtained complete resection but did not develop early tumor regrowth. Patients obtaining complete resection and early tumor regrowth might constitute a third prognostic group, splitting patients who obtained complete resection into patients with and without disease at the onset of chemotherapy. This latter assumption might challenge the definition of residual disease in patients with AOC as disease seen by the intraoperative visual and manual assessment by the surgeon only, an assessment method that might be prone to bias [9]. Retrospective series of radiological assessment of tumor disease status prior to chemotherapy in patients with AOC have reported discrepancy rates between surgical determined residual disease and radiologic findings pre-chemotherapy ranging between 20.3% and 41.0% [15–18], and 48.0% in the setting of a prospective study [12]. However, the latter study had reclassified optimal debulking as small residual tumor up to 1 cm. The risk to find a discordance between a surgical classification of, e.g. 1 cm, in contrast to a radiological finding of, e.g. a 1.3-cm lesion, is higher than the risk to find a discordance between no tumor on surgical assessment and radiologically visible tumor. Therefore, our discordance rates not only confirm the sparse available data but suggest even higher discrepancy rates between surgical assessment and radiologic assessment. Our analyses did not reveal any association between histopathological subtypes and discordance rates. This result might be accounted for by the low frequency of non- high grade serous ovarian cancers. A biological component that accounts for our finding on lack of association should, however, not be ruled out. In this study, the feasibility and performance of a new method for tumor burden assessment, namely integrated assessment, was evaluated in patients with surgical-radiologic discordance. In 25% of these cases, a false-positive radiological finding was present. Among the 3 different assessment methods, the most accurate prognostic method for outcome was integrated assessment. Hence, we propose that integrated assessment provides the highest diagnostic accuracy, and that further research to validate this assessment method is warranted. The drawback of radiologic assessment methods is the subjective interpretation by the individual radiologist and the general limitation of CT scans with a detection threshold of ~5 mm [17]. Other radiologic methods like PET-CT or diffusion-weighted MRI might increase sensitivity, but not to an acceptable high threshold [19]. Thus, reliable independent methods such as analysis of cell-free DNA might increase the diagnostic accuracy of assessments for residual tumor. In a proof-of-principle study that included patients with high-grade serous ovarian cancer, the allelic frequency of *TP53* mutations in cell-free DNA was used to distinguish between patients with and without complete resection. The allelic frequency of *TP53* mutations was significantly reduced at postoperative day 10 in all patients obtaining complete resection compared to patients with residual disease, in whom the increasing frequency of *TP53* allelic mutations was also observed [20].

What consequences might arise from our results? Imaging before onset of chemotherapy might display postsurgical scaring or fibrosis, and correlation with imaging at the end of chemotherapy might help to avoid false positive findings. Moreover, early tumor regrowth was the main contributor of worse survival in the subset of patients with surgically complete resection. Analyses of the AGO study group have shown that delaying the onset of chemotherapy by a week was associated with an 8.7% increased risk of death in patients undergoing complete resection [21]. A NRG study showed that chemotherapy initiated >25 days after surgery had a significant impact on overall survival [22]. However, there were also other reports that did not show an effect of a delayed start of chemotherapy [23,24]. Therefore, the balance between surgical aggressiveness and anticipated postsurgical recovery and the optimal start of chemotherapy merits further investigation.

Moreover, our study revealed that the baseline assessment of tumor burden might provide a predictive measure for experimental therapy with nintedanib. Earlier data from studies of ovarian cancer and breast cancer have suggested that bevacizumab has a pronounced effect in patients with macroscopic tumor [11,25] compared to patients without macroscopic tumor [26,27]. Therefore, a baseline assessment of tumor burden in patients by CT and/or cell-free DNA might be important prior to enrollment in upfront trials for advanced ovarian cancer that evaluate the treatment effects of new drugs on varying tumor burden.

To our knowledge, this is one of the largest study to determine the frequency *and* the prognostic impact of disease burden at the onset of chemotherapy after primary debulking surgery. Moreover, data quality was ensured by quality controls required of pivotal trials and that was monitored externally.

In conclusion, this study demonstrated that radiologic assessment and integrated assessment at baseline imaging before chemotherapy identified a substantial number of patients in whom the information on tumor burden was discordant between the information derived from surgical assessment. Early tumor regrowth seemed to be a contributor to the discordance between surgical assessment and radiologic assessment/integrated assessment. The risk of losing the prognostic factor of complete resection, if chemotherapy is started >31 days after primary surgery is >15%. Thus, chemotherapy should be started as soon as feasible.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2018.11.008.

#### Conflict of interest statement

Florian Heitz: Travel grants: AstraZeneca, Tesaro, Roche; Honoraria: Roche, AstraZeneca; Advisory: Roche; Philipp Harter: Honoraria: Roche, AstraZeneca, Tesaro; Advisory: Roche, AstraZeneca, Tesaro, PharmaMar, Lilly; Alexander Reinthaller: Honoraria: Roche, PharmaMar, Amgen, Novartis, AstraZeneca, Tesaro; Travel: Roche, PharmaMar, AstraZeneca, Tesaro; Andres Poveda: Advisory: ROCHE, ASTRA ZENECA, CLOVIS, TESARO, PHARMAMAR; Lars C. Hanker: Advisory: Roche, Tesaro, AstraZeneca; Travel: Roche, Tesaro, AstraZeneca; Jérome Alexandre: Honoraria: Roche, AstraZeneca, Novartis, Ipsen; Advisory: Roche, AstraZeneca, Novartis, Ipsen; Research grant: Janssen; Travel: Janssen, Novartis; Ulrich Canzler: Honoraria: Roche, AstraZeneca; Advisory: Roche, AstraZeneca; Michael Merger: Is employed by Boehringer Ingelheim International GmbH; Andreas du Bois: Advisory boards and lectures: Roche, AstraZeneca, PharmaMar, MSD; Advisory boards: Mundipharm, Pfizer. All other coauthored declared not to have any conflicts of interest.

## Disclosure

The statement that all authors have approved the final article should be true and included in the disclosure.

## Funding

The resource trial of the present study was Boehringer Ingelheim Pharma.

## CRediT authorship contribution statement

**F. Heitz:** Resources, Conceptualization, Formal analyses, Writing - original draft, Writing - review & editing, Data curation. **P. Harter:** Resources, Conceptualization, Formal analyses, Writing - original draft, Writing - review & editing, Data curation. **E. Åvall-Lundqvist:** Resources, Writing - original draft, Writing - review & editing. **A. Reuss:** Resources, Conceptualization, Formal analyses, Writing - original draft, Writing - review & editing, Data curation. **P. Pautier:** Resources, Writing - original draft, Writing - review & editing. **G. Cormio:** Resources, Writing - original draft, Writing - review & editing. **N. Colombo:** Resources, Writing - original draft, Writing - review & editing. **A. Reinthaller:** Resources, Writing - original draft, Writing - review & editing. **I. Vergote:** Resources, Writing - original draft, Writing - review & editing. **A. Poveda:** Resources, Writing - original draft, Writing - review & editing. **P.B. Ottevanger:** Resources, Writing - original draft, Writing - review & editing. **L.C. Hanker:** Resources, Writing - original draft, Writing - review & editing. **A. Leminen:** Resources, Writing - original draft, Writing - review & editing. **J. Alexandre:** Resources, Writing - original draft, Writing - review & editing. **U. Canzler:** Resources, Writing - original draft, Writing - review & editing. **J. Sehouli:** Resources, Writing - original draft, Writing - review & editing. **J. Herrstedt:** Resources, Writing - original draft, Writing - review & editing. **B. Fiane:** Resources, Writing - original draft, Writing - review & editing. **M. Merger:** Resources, Conceptualization, Formal analyses, Writing - original draft, Writing - review & editing, Data curation. **A. du Bois:** Resources, Conceptualization, Formal analyses, Writing - original draft, Writing - review & editing, Data curation.

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