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ORIGINAL ARTICLE

The influence of cancer stage and surgery extent on long-term outcomes in ovarian cancer patients

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Summary

Introduction: Standard therapy for patients with ovarian cancer involves cytoreductive surgery followed by platinum-based chemotherapy. Factors such as the stage of the disease at diagnosis, the histological type of the tumor, the size of the tumor and the presence of residual disease after cytoreductive surgery influence the prognosis of patients.

Material and methods: This scientific paper presents a retrospective study in which the following parameters were analyzed by analyzing data obtained from the documentation of patients treated for ovarian cancer at the Institute of Oncology and Radiology of Serbia and the Institute of Oncology of Vojvodina: age of patients, period from last chemotherapy to disease progression, number of bevacizumab cycles received, disease stage, reasons for discontinuation of bevacizumab, type of surgery, and pathological verification of the disease.

Results: We have shown that PFS is longer in the operated group (suboptimal operation) compared to those who were not operated ($p < 0.05$, Log-Rank test). There is no statistically significant difference in PFS between stages IIIc and IV, as determined by Log-Rank test. Additionally, in our research, there was no significant difference in the number of operated patients based on disease stage IIIc or IV ($p = 0.361$).

Conclusions: Our data show that cytoreduction appears to confer a survival advantage in women with ovarian cancer treated with a combination of bevacizumab and chemotherapy. New studies should show whether the stage of the disease plays a significant role in the survival of patients with ovarian cancer.

Key words: ovarian cancer, progression-free survival, type of surgery, disease stage

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INTRODUCTION

Ovarian cancer is among the most common gynecologic malignancies, with over 300,000 cases diagnosed worldwide in 2020. Unfortunately, it is often detected at advanced stages due to non-specific symptoms and the absence of effective screening methods. Ovarian cancer is a very aggressive disease that, despite new therapies, does not increase the number of cured women. The standard treatment for ovarian cancer includes cytoreductive surgery followed by adjuvant platinum-based chemotherapy. Prognosis is influenced by clinical and biological factors such as tumor stage and grade at diagnosis, tumor size, and the presence of residual disease after cytoreductive surgery (1, 2).

Overall survival (OS) is considered the gold standard endpoint in cancer clinical trials because it is an objective measure, it can be accurately documented through the date of death, and is less prone to reporting bias. However, achieving statistically significant OS results typically requires large-scale clinical trials, which are costly, time-consuming, and require longer follow-up periods compared to studies using progression-free survival (PFS) as the primary endpoint. It is important to point out that PFS can provide evidence of the benefits of new therapies earlier because PFS cannot be affected by therapies after progression.

This study aimed to investigate the relationship between PFS and the type of surgery in our patients, as well as to analyze the impact of disease stage on long-term outcomes (3, 4).

MATERIALS AND METHODS

This scientific paper presents a retrospective study in which the following parameters were examined by analyzing the data obtained from the documentation of patients treated for ovarian cancer at the Department of Gynecology, Institute for Oncology and Radiology of Serbia (IORS) in Belgrade and the Institute of Vojvodina (IOV) in Sremska Kamenica: patient age, the period from the last chemotherapy to disease progression, the number of bevacizumab cycles received, disease stage, reasons for discontinuation of bevacizumab (disease progression/discontinuation due to complications), type of surgery, and pathological verification of the disease.

The patients were evaluated by the Tumor Oncology Board for Gynecological Tumors at IOV and IORS. The source of the material was archival data from IOV and IORS obtained through written records, Heliant, and the BIRPIS IOV system.

The study included patients over 18 years of age with histopathologically confirmed advanced ovarian cancer who were eligible for bevacizumab therapy. Patients with ovarian cancer without an indication for bevacizumab therapy or with concomitant other malignancies were excluded from the study. The patients were included in the study in the period from October 2017 to October 2020. The follow-up of the patients lasted 36 months. PFS is the time from the start of chemotherapy with bevacizumab to the onset of disease progression.

Descriptive statistical methods were applied in data analysis, including the calculation of measures of central tendency (arithmetic mean, median) and measures of dispersion (standard deviation). The Student's T-test was used to compare arithmetic means of parametric measurement values. The $\chi 2$ test was applied to assess statistical associations between the variables. A p-value of less than 0.05 was considered statistically significant. Survival was evaluated with Kaplan-Meier product-limit method. Median with corresponding 95% CI and Log-Rank test were used for progression-free survival (PFS) and overall survival (OS). Reported p-values were not corrected for multiple testing. Analyses were performed with Statistical Package for Social Sciences, Version 11.5 (SPSS, Inc., Chicago, IL, USA).

RESULTS

The study analyzed 111 patients treated with combined chemotherapy carboplatin/paclitaxel and biological therapy with bevacizumab. The full therapy with bevacizumab included 18 cycles.

The patients were between 36 and 84 years old, with an mean age of 60 years. Seventy-one patients completed the full bevacizumab therapy, representing 64% of the total number. In 37 patients, or 33.3%, therapy was discontinued due to disease progression. Adverse effects requiring therapy discontinuation occurred in 3 patients, accounting for 2.7% **(Table 1)**. In our study, two cases of deep vein thrombosis were observed, along with one case of grade 3 hypertension that was not adequately controlled with antihypertensive therapy.

Table 1. Treatment outcomes of patients

	n	%
Complete remission	71	64.0
Progression during therapy	37	33.3
Discontinuation due to therapy complications	3	2.7
Total	111	100.0

The minimum number of bevacizumab cycles administered was 4, the maximum was 18, with an mean of 15.3 ± 2.98 SD **(Table 2)**.

In all patients, an advanced stage of epithelial ovarian carcinoma was confirmed. According to the FIGO classification, 78 patients (70.3% of the total) were in stage IIIc, while the remaining 33 patients (29.7%) were in stage IV **(Table 3)**.

The patients were divided into two groups:

Group 1: Non-operated patients in whom pathological verification of the disease was obtained through core biopsy, exploratory surgery with biopsy, or aspiration of

Table 2. Number of administered bevacizumab cycles

	Mean	Standard deviation	Median	Minimum	Maximum
Number of bevacizumab cycles administered	15.3	2.98	11	4	18

ascites/pleural effusion. The total number of patients is 40 (36%) of all patients.

Group 2: Previously operated patients where cytoreductive surgery was performed. The total number of patients is 71 (64%) of all patients. These were suboptimal operated patients with residual disease after surgery **(Table 4)**.

Table 3. Distribution of FIGO stages among analyzed patients

Stage	n	%
IIIc	78	70.3
IV	33	29.7
Total number of ptc	111	100.0

Table 4. Operated vs. non-operated patients

	n	%
Non-operated patients	40	36.0
Operated patients	71	64.0
Total number of ptc	111	100.0

The median follow-up period was 30 months. The median overall progression-free survival (PFS) was 12.9 months (95% CI: 11.8- 13.9) for operated patients and 10.7 months (95% CI: 9.8-11.2) for non-operated patients. Using the Log-Rank, statistical significance (p =0.048) was demonstrated, indicating a statistically better PFS in the group of operated patients (suboptimal surgery) compared to those who were not operated **(Figure 1)**.

The median overall progression-free survival (PFS) for IIIc patients was 11.9 months (95% CI: 10.8- 12.3) and 10.9 months (95% CI: 10.2-11.2) for non-operated patients. There is no statistically significant difference in PFS between stages IIIc and IV, as determined by the Log-Rank, with p=0.261 **(Figure 2)**.

There was no statistically significant difference in the number of operated patients between disease stages IIIc and IV (p = 0.363) **(Figure 3)**.

Furthermore, no statistically significant difference was found in the treatment outcome with bevacizumab between non-operated and operated patients. Among the non-operated patients, 41% experienced progression during bevacizumab therapy, while in the operated (suboptimal) group, 30.4% experienced progression. A trend toward better out-

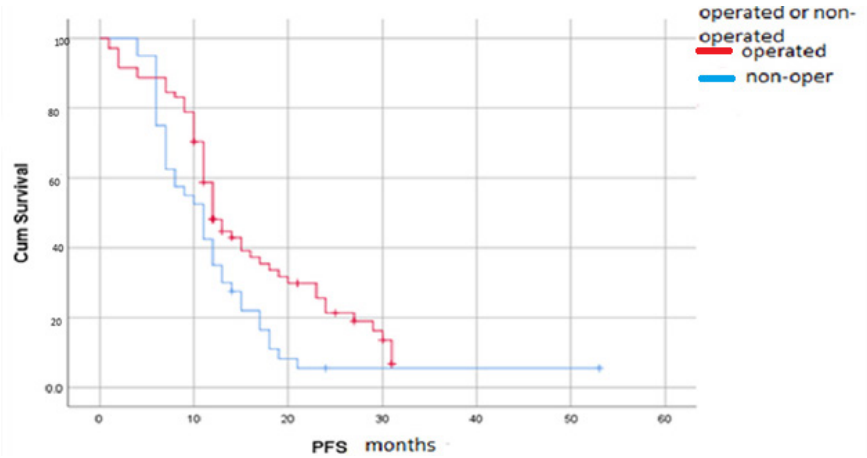

Figure 1. Kaplan-Meier Curves of PFS (Operated vs. Non-Operated Patients)

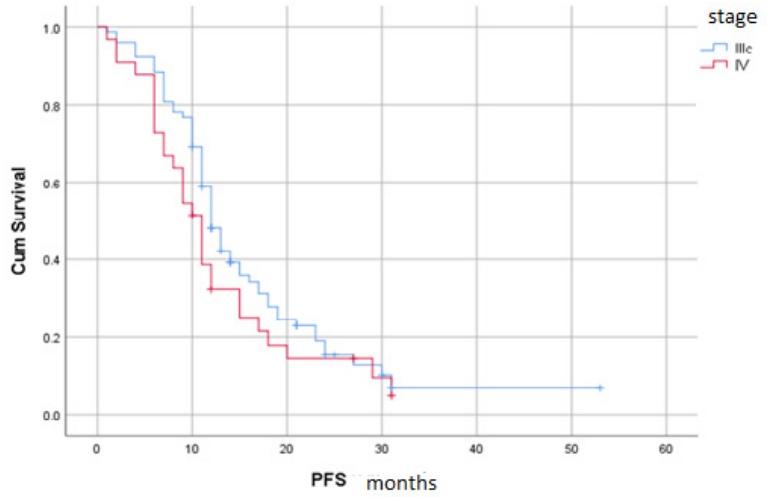

Figure 2. Kaplan-Meier Curve of PFS (FIGO IIIc vs. IV)

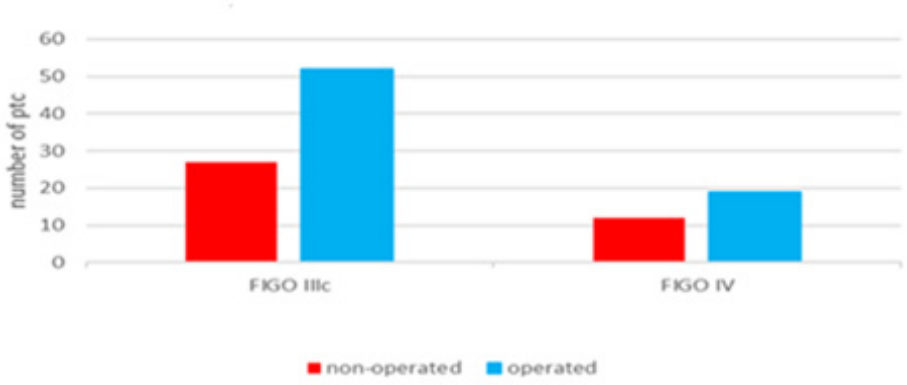

Figure 3. Number of operated patients by disease stage (IIIc vs. IV)

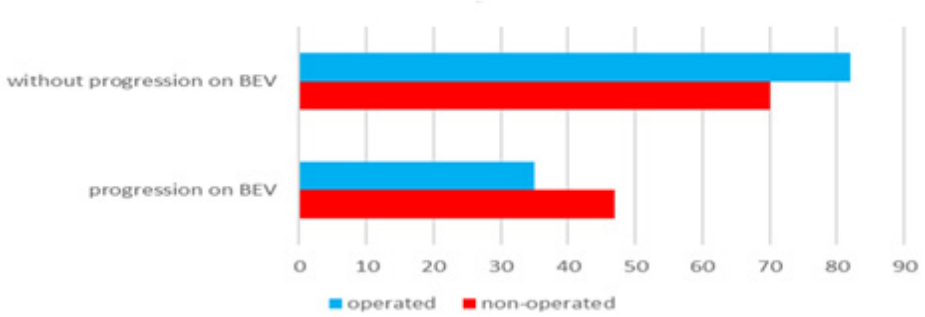

Figure 4. Progression during bevacizumab therapy

comes was observed in the operated group, though it did not reach statistical significance **(Figure 4)**.

There were no statistically significant differences in patient age between groups with different disease stages ($p = 0.201$), in disease outcome during the follow-up period (progression vs. no progression) ($p = 0.150$), or in the outcome of bevacizumab treatment (completion of 12-month therapy vs. discontinuation due to progression) ($p = 0.060$).

A statistically significant difference in patient age was observed between the operated and non-operated groups ($p = 0.037$). Operated patients were significantly younger (mean age 59.28 years) compared to non-operated patients (mean age 64.25 years).

DISCUSSION

In our retrospective analysis, we demonstrated the importance and statistical significance of surgical extensiveness for long-term outcomes, showing that progression-free survival (PFS) was significantly better in patients who underwent suboptimal surgery compared to those who did not have surgery. This aligns with the current literature, where the standard management of advanced epithelial ovarian cancer involves correct surgical staging and optimal tumor cytoreduction, followed by chemotherapy with platinum and taxane-based agents. Standard surgical staging includes peritoneal washings, total hysterectomy, bilateral salpingo-oophorectomy, inspection of all abdominal organs and the peritoneal surface, biopsies of suspicious or random areas, omentectomy, and para-aortic lymphadenectomy. Achieving complete tumor cytoreduction has been shown to improve survival (5). Importantly, optimal surgical cytoreduction is one of the strongest predictors of outcomes in patients with high-grade serous carcinoma (HGSOC) treated with primary cytoreductive surgery (6, 7).

Our results indicated that there is no statistically significant difference in long-term outcomes between stages IIIc and IV, which aligns with previous data. This correlation between progression-free survival (PFS) and overall survival (OS) following primary treatment for ovarian cancer underscores the validity of using PFS as a primary endpoint. Most of the data come from observational studies, which have limited information on disease stage and histology. Patients with advanced stage (III or IV) ovarian cancer generally have a poor prognosis. The standard treatment options of surgery and chemotherapy extend survival beyond diagnosis for five years or more in only about 45% of patients, with little difference observed between stage IIIc with residual disease and stage IV (2, 3). There was no statistically significant difference in the number of patients who underwent surgery based on the disease stage, whether stage IIIc or IV, which aligns with previous data where comparison of surgical extensiveness revealed no difference in tumor stage between IIIc and IV (8).

Additionally, no statistically significant difference was found in the treatment outcomes with bevacizumab between operated and non-operated patients. Although there was a trend towards better outcomes in the operated group, it was not sufficient to reach statistical significance.

Several studies have demonstrated that women with advanced high-grade serous carcinoma (HGSOC) who underwent primary cytoreductive surgery (PCS) had better survival outcomes compared to those who received neoadjuvant chemotherapy (NAC) followed by interval surgery, regardless of the number of NAC cycles administered. Furthermore, achieving optimal cytoreduction did not confer a survival advantage in the NAC group, whereas patients who underwent primary surgery exhibited a clear survival benefit (9, 10). Overall, the use of neoadjuvant chemotherapy as a first-line treatment for women with newly diagnosed HGSOC remains controversial (10).

A statistically significant difference in the age of patients was found between the operated and non-operated groups. Operated patients were significantly younger (mean age 59.28 years) compared to non-operated patients. Patients treated with neoadjuvant chemotherapy were significantly older than patients treated with PCS according to the results of Stewart's Canadian study (8).

Studies have shown that operative treatment has an impact on all prognostic groups in all FIGO stages of the disease, regardless of the different preoperative tumor burden (10). Of course, tumor biology itself remains one of the most important prognostic factors contributing to the poor outcome of patients. A meta-analysis including 6885 patients with stage III and IV ovarian cancer and examining the effect of surgery on PFS showed that overall cytoreduction affects survival (12, 13).

CONCLUSION

Our data indicate that surgical factors, such as the extent of surgery and the rate of optimal cytoreduction, appear to confer a survival advantage for women with ovarian cancer treated with a combination of bevacizumab and chemotherapy. New studies will show whether the stage of the disease plays a significant role in the survival of patients with ovarian cancer, since stages IIIc and IV represent advanced disseminated disease with almost equally poor outcomes. Also, the dilemma remains whether the significantly higher percentage of operated on younger patients is due to the willingness of the surgeon to operate and the lower risk of complications from such procedures.

Author contributions

The conception or design of the work: SR, MMK, and SSR.
The acquisition, analysis, or interpretation of data: MMK, SM and MM.
Preparing the draft of the manuscript or interpretation of revised version of manuscript SR.

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UTICAJ STADIJUMA BOLESTI I HIRURGIJE NA DUGOROČNE ISHODE KOD PACIJENTKINJA SA KARCINOMOM JAJNIKA

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Sažetak

Uvod: Standardna terapija za pacijente sa karcinomom jajnika uključuje citoreduktivnu operaciju praćenu hemoterapijom na bazi platine. Faktori kao što su stadijum bolesti pri postavljanju dijagnoze, histološki tip tumora, veličina tumora i prisustvo rezidualne bolesti posle citoreduktivne operacije utiču na prognozu pacijenata.

Materijal i metode: Ovaj naučni rad predstavlja retrospektivnu studiju u kojoj su analizirani sledeći parametri analizom podataka dobijenih iz dokumentacije pacijenata lečenih od karcinoma jajnika na Institutu za onkologiju i radiologiju Srbije i Institutu za onkologiju Vojvodine: godine starosti pacijenata, period od poslednje hemoterapije do progresije bolesti, broj primljenih ciklusa bevacizumaba, stadijum bolesti, razlozi za prekid bevacizumaba, vrsta hirurgija i patološka verifikacija bolesti.

Rezultati: Pokazali smo da je PFS duži u operisanoj grupi (suboptimalna operacija) u odnosu na one koji nisu operisani ($p < 0,05$, Log-Rank test). Ne postoji statistički značajna razlika u PFS između stadijuma IIIc i IV, što je utvrđeno Log-Rank testom. Takođe, u našem istraživanju nije bilo značajne razlike u broju operisanih pacijenata na osnovu IIIc ili IV stadijuma bolesti ($p = 0, 361$).

Zaključci: Naši podaci pokazuju da se čini da citoredukcija daje prednost u preživljavanju kod žena sa karcinomom jajnika lečenih kombinacijom bevacizumaba i hemoterapije. Nove studije treba da pokažu da li stadijum bolesti igra značajnu ulogu u preživljavanju pacijenata sa karcinomom jajnika.

Ključne reči: karcinom jajnika, preživljavanje bez progresije bolesti, tip operacije, stadijum bolesti

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