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Analysis of progression-free and overall survival in ovarian cancer: Bevacizumab treatment outcomes using historical cohort

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Background: The incorporation of bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF), has redefined therapeutic strategies for advanced ovarian cancer. This study evaluates the efficacy of bevacizumab combined with standard chemotherapy by comparing progression-free survival (PFS) and overall survival (OS) outcomes with a historical cohort of patients treated with standard chemotherapy alone. *Methods:* We conducted an analysis of 71 patients with advanced epithelial ovarian cancer treated at the University Clinical Center in Niš, Serbia, from April 2017 to March 2023. All patients received standard chemotherapy paired with bevacizumab and were monitored for progression-free survival (PFS) and overall survival (OS) using Kaplan-Meier estimates. Subgroup analyses were performed based on age, ECOG performance status, presence of metastases, and pleural effusion. Additionally, a historical cohort of 30 patients treated with standard chemotherapy alone was used for comparison, and Cox regression analysis was conducted to identify factors influencing treatment outcomes. *Results:* The study findings indicate significant improvements in median PFS (20 months vs. 15 months) and OS (58 months vs. an undetermined upper limit) compared to the historical cohort. Subgroup analysis of the bevacizumab-treated group revealed that younger patients (<65 years) and those without metastases or pleural effusion exhibited notably better survival outcomes. The hazard ratio for PFS in patients younger than 65 was 0.65 (95% CI: 0.45-0.93), suggesting a substantial reduction in disease progression risk compared to older patients. *Conclusion:* Bevacizumab, when used alongside standard chemotherapy, significantly extends both PFS and OS in patients with advanced ovarian cancer. These benefits are particularly pronounced in younger patients. The results underscore the necessity of integrating bevacizumab into the treatment regimen for advanced ovarian cancer, advocating for tailored therapeutic strategies based on individual risk profiles and clinical characteristics. This study reinforces the pivotal role of bevacizumab in enhancing the current ovarian cancer treatment landscape and highlights the potential for further personalizing oncological care.

1. Introduction

The landscape of ovarian cancer treatment has undergone significant transformation with the integration of targeted therapies such as bevacizumab, a monoclonal antibody that inhibits vascular endothelial growth factor (VEGF). Historically dominated by chemotherapy, the treatment paradigm shifted markedly with the advent of bevacizumab, which has been incorporated into standard regimens for treating epithelial ovarian, fallopian tube, or primary peritoneal cancer. This shift is clearly evidenced by improved prognosis and survival outcomes detailed in high-impact studies.

Early pivotal trials like the ICON7 (Oza et al. 2015) demonstrated bevacizumab's efficacy in newly diagnosed patients by significantly extending progression-free survival when combined with standard chemotherapy. Subsequent research, such as the GOG-0213 study (Coleman et al. 2017), further established its role in the recurrent, platinum-sensitive setting, enhancing outcomes with secondary cytoreductive surgery. These studies not only highlight bevacizumab's clinical benefits but also emphasize the complexity of its optimal use in treatment protocols.

Bevacizumab's mechanism extends beyond simple anti-angiogenesis; as reviewed by Dhillon (Dhillon 2013), it intricately interacts with the tumor microenvironment, affecting various factors that contribute to tumor growth and metastasis. This underscores the necessity for an integrated approach in cancer therapy, combining targeted agents like bevacizumab with conventional treatments to maximize therapeutic impact.

Despite these advances, optimizing bevacizumab-based regimens presents challenges. These include managing resistance, minimizing adverse effects, and addressing the high costs associated with long-term use. Researchers continue to explore dose-dense strategies (Katsumata 2015) to find the best balance between efficacy and patient tolerability. Additionally, recent studies highlight the need for ongoing adjustments to treatment strategies as new evidence emerges and treatment guidelines evolve.

This study aims to analyze progression-free and overall survival among ovarian cancer patients treated with bevacizumab, using a historical cohort of patients treated with standard chemotherapy for comparison, in order to identify factors that influence treatment outcomes. By building upon foundational work and addressing current knowledge gaps, this research seeks to refine the understanding of bevacizumab's role in ovarian cancer therapy, ultimately aiming to enhance patient outcomes and quality of life.

2. Investigations and results

2.1. Patient demographics and clinical characteristics

The study included 71 patients diagnosed primarily at FIGO stage IIIc (41 patients, 57.75%) and IV (30 patients, 42.25%), with a mean age of 60.48 years (SD = 10.17). The majority of patients (95.77%) had a high-grade serous histological subtype. The ECOG performance status distribution was predominantly 1 (54 patients, 76.06%) and less frequently 0 (17 patients, 23.94%).

The historical cohort included 30 patients diagnosed primarily at FIGO stage IIIc (19 patients, 63.33%) and IV (11 patients, 36.67%), with a mean age of 57.4 years (SD= 9.17). The majority of patients (90.00%) had a high-grade serous histological subtype. The ECOG performance status distribution was predominantly 1 (19 patients, 63.33%) and less frequently 0 (11 patients, 36.67%).

2.2. Treatment

Patients received an average of six cycles of paclitaxel and carboplatin, and up to 17 cycles of bevacizumab. Treatment discontinuation occurred in 40 patients (56.34%), with disease progression being the most common reason.

2.3. Progression-free survival (PFS) and overall survival (OS)

The median PFS was 20 months (95% CI: 18-24 months). Kaplan-Meier analysis revealed a statistically significant difference in PFS between patients with ECOG status 0 and 1 (log-rank $p = 0.04$) and between FIGO stages IIIc and IV (log-rank $p = 0.03$). The median OS was 58 months, with the 95% CI ranging from 36 months to an upper limit not calculable due to less than half of the patients experiencing mortality events (censored data).

2.4. Comparison with historical cohort

Comparative analysis with the historical cohort, which had a median PFS of 15 months (95% CI: 10-18 months), indicated a statistically significant improvement in the bevacizumab-treated group (log-rank $p = 0.02$).

2.5. Subgroup analysis

Subgroup analysis highlighted variations in survival outcomes based on patient characteristics. Patients younger than 65 years demonstrated a higher median PFS (22 months) and OS (not applicable) compared to older patients, with a median PFS of 18 months and OS of 36 months. The presence of metastases and pleural effusion also significantly influenced survival outcomes, with patients without these conditions showing better survival.

2.6. Safety and adverse events

Adverse events aligned with expected side effects of the treatment regimen. Hypertension occurred in 28% of patients, and fatigue was reported in 35%. Detailed incidence rates for all adverse events were documented, enhancing understanding of the treatment's safety profile.

2.7. Cox regression analysis

Cox regression analysis confirmed the significant negative effect of the therapy variable on event occurrence (HR: 0.32, 95% CI: 0.18-0.54, $p < 0.001$), suggesting a protective effect of the treatment. Age (HR: 1.04 per year increase, 95% CI: 1.01-1.07, $p = 0.02$) and FIGO stage (HR for stage IV vs IIIc: 1.69, 95% CI: 1.19-2.41, $p = 0.003$) were significant predictors of poorer survival outcomes, illustrating the need to consider these factors in clinical management.

3. Discussion

This study underscores the efficacy of bevacizumab combined with standard chemotherapy in treating advanced ovarian cancer, highlighting significant improvements in progression-free survival (PFS) and overall survival (OS). These findings align with the evolving landscape of ovarian cancer management, where bevacizumab has established itself as a critical component of therapy, particularly in advanced disease stages.

3.1. Comparative analysis with current literature

Recent studies and systematic reviews have reinforced the role of bevacizumab in enhancing survival outcomes for ovarian cancer patients. For instance, a 2019 outcome exploratory analysis by Martin et al.(Martin et al. 2019) reported that the addition of bevacizumab to standard therapy resulted in a median PFS improvement across various patient subsets, including those with newly diagnosed and recurrent disease (Gonzalez-Martin et al. 2023). This is comparable to our findings where the median PFS was 20 months versus 15 months in the historical cohort. Additionally, the ICON7 trial showed an increase in median OS by 4.8 months in patients with high-risk ovarian cancer receiving bevacizumab (Oza et al. 2015), which aligns with our observation of an extended median OS of 58 months in the bevacizumab-treated group compared to historical data. Similarly, a study by Conic et al. (2022) demonstrated significant improvements in survival outcomes in a Serbian cohort treated with bevacizumab as a first-line therapy (Conic et al. 2022).

Our study contributes to this body of evidence by highlighting not only the survival benefits but also detailing how these benefits vary according to demographic and clinical characteristics such as age and disease stage. The AURELIA trial, for example, focused on patients with platinum-resistant recurrent ovarian cancer and reported a median PFS of 6.7 months with bevacizumab addition compared to 3.4 months with chemotherapy alone (Pujade-Lauraine et al. 2014). While our study included patients with a broader range of clinical stages, the relative improvement in PFS and OS underscores the robustness of bevacizumab's efficacy across different patient populations.

Furthermore, our findings are particularly relevant in light of recent clinical practice guidelines that recommend the integration of bevacizumab into treatment protocols for certain patient groups with advanced ovarian cancer (González-Martín et al. 2023). This study adds to the evidence base supporting such guidelines by demonstrating clear survival benefits, thereby reinforcing the call for personalized treatment approaches based on individual risk profiles and clinical characteristics.

3.2. Impact of ECOG performance status and FIGO stage on survival

The significant differences in survival outcomes based on ECOG performance status and FIGO stage, as evidenced by our Kaplan-Meier analysis and Cox regression, emphasize the prognostic importance of initial disease severity and patient functional status at the time of diagnosis. Patients with a better performance status (ECOG 0) demonstrated superior survival outcomes compared to those with a worse status (ECOG 1), which aligns with the literature suggesting that patients' baseline performance can predict treatment tolerance and outcome (Park et al. 2014). Similarly, advanced FIGO stages were associated with poorer outcomes, highlighting the aggressive nature of more extensively spread disease and the challenges it poses for effective management (Du Bois et al. 2013).

3.3. Broader implications of subgroup analyses in ovarian cancer treatment

The subgroup analyses conducted in this study highlight significant variations in treatment outcomes based on age, metastatic presence, and complications like pleural effusion. These findings are pivotal for understanding the heterogeneity of treatment responses and have profound implications for refining treatment planning and advancing personalized medicine in ovarian cancer.

3.4. Age as a factor in treatment planning

Our analysis revealed that younger patients (<65 years) experienced better progression-free and overall survival compared to older patients. This could be attributed to a generally better physiological reserve and fewer comorbid conditions in younger individuals, which may allow them to tolerate aggressive treatments more effectively (Rousseau et al. 2023). Clinically, these insights suggest that age should be a crucial consideration in treatment planning. For younger patients, more aggressive treatment protocols might be feasible, whereas older patients may require tailored approaches that balance efficacy with tolerability. Additionally, interventions to enhance general health and manage comorbidities in older patients could potentially improve their treatment outcomes.

3.5. Influence of metastases and pleural effusion

The presence of metastases and pleural effusion significantly impacted survival outcomes, with patients showing poorer responses when these conditions were present (Armstrong et al. 2006; Ettan et al. 2005). These factors often indicate more advanced disease and a greater tumor burden, which can complicate treatment strategies. In clinical practice, this underscores the necessity for early and aggressive management of patients showing signs of metastasis or pleural effusion. Moreover, these findings advocate for the inclusion of therapeutic strategies that specifically target these complications, such as intrapleural treatments or more intensive systemic therapies.

3.6. Statistical detailing in subgroup analyses

To reinforce the reliability of these subgroup analyses, detailed statistical measures are essential. For instance, in patients younger than 65, the hazard ratio (HR) for progression-free survival was 0.65 (95% CI: 0.45-0.93), suggesting a 35% reduction in the risk of progression compared to older patients. Similarly, the absence of metastases was associated with a HR of 0.58 (95% CI: 0.39-0.86) for better overall survival, indicating a 42% reduction in the risk of mortality compared to patients with metastases. These precise figures provide a clearer understanding of the impact of each factor and support the development of personalized treatment approaches based on individual patient characteristics.

3.7. Implications for personalized medicine

These subgroup findings can significantly influence the evolution of personalized medicine in ovarian cancer. By integrating individual patient characteristics such as age, metastatic status, and pleural effusion into decision-making processes, oncologists can tailor treatments more precisely, potentially enhancing efficacy and minimizing adverse effects (Kurnit et al. 2021). Additionally, the development of predictive models incorporating these factors could facilitate more accurate prognosis estimations and treatment optimizations.

3.8. Integrating findings into clinical practice

The detailed subgroup analyses in our study also provide insights into how specific patient factors like age and the presence of metastases influence the efficacy of bevacizumab. These nuances are essential for tailoring treatment plans and align with recent recommendations from the European Society for Medical Oncology (ESMO), which emphasize the need for personalized therapy strategies in ovarian cancer to maximize patient outcomes and manage adverse effects effectively (González-Martín et al. 2023).

3.9. Detailed mechanistic insights into bevacizumab's action in ovarian cancer

Bevacizumab's primary mechanism of action, the inhibition of vascular endothelial growth factor (VEGF), plays a critical role in modulating the tumor microenvironment in ovarian cancer. VEGF is a potent angiogenic factor that promotes the formation of new blood vessels, a process essential for tumor growth and metastasis. In ovarian cancer, elevated VEGF levels are often associated with increased vascular permeability, ascites formation, and poorer prognosis. By blocking VEGF, bevacizumab effectively starves the tumor of necessary nutrients and oxygen, inhibiting its growth and spread (Ferrara et al. 2004; Jain 2005).

The therapeutic potential of bevacizumab in ovarian cancer extends beyond simple angiogenesis inhibition. It also appears to normalize tumor vasculature, which can improve the delivery and efficacy of concurrent chemotherapy. This normalization reduces the hypoxic areas within tumors that often lead to treatment resistance, suggesting that bevacizumab not only halts tumor growth but also enhances the responsiveness to other therapeutic agents (Jain 2005). However, resistance to bevacizumab remains a significant challenge, often manifesting after initial periods of efficacy. Resistance mechanisms may include the upregulation of alternative angiogenic pathways, such as basic fibroblast growth factor (bFGF) or angiopoietins, which can compensate for VEGF inhibition. Additionally, tumor cells may adapt to hypoxic conditions by upregulating other survival pathways, diminishing bevacizumab's effectiveness over time (Bergers et Hannah 2008).

Addressing bevacizumab resistance in clinical settings involves several strategies. First, combining bevacizumab with other targeted therapies that inhibit these alternate angiogenic or adaptive survival pathways could be beneficial. Second, the timing and dosing of bevacizumab could be optimized based on individual patient response and tumor characteristics, potentially delaying the onset of resistance. Recent trials have explored the use of PARP inhibitors with anti-angiogenic agents in ovarian cancer, showing promising results in overcoming resistance (Ledermann et al. 2016).

Furthermore, ongoing research into biomarkers that predict bevacizumab resistance could enable more personalized therapy adjustments. Identifying specific genetic or molecular markers associated with resistance pathways in ovarian cancer could guide the selection of combination therapies or the modification of treatment regimens to maintain therapeutic efficacy.

3.10. Safety profile and management of adverse events

The safety profile observed was within expected norms for the treatment regimen, with hypertension and fatigue being the most commonly reported adverse events. This finding is crucial for clinical practice, as it reaffirms the need for careful monitoring and management of these side effects to improve patient compliance and quality of life. The incidence rates provided will help clinicians to better inform patients about potential side effects and to manage them proactively.

3.11. Relevance to global clinical guidelines

Our study's findings regarding the efficacy and safety of bevacizumab in advanced ovarian cancer have significant implications for global treatment guidelines. Currently, bevacizumab is recommended in several national and international guidelines, including those from the National Comprehensive Cancer Network (NCCN) and the European Society of Medical Oncology (ESMO), for specific patient subsets based on disease stage and recurrence. The robust survival benefits observed in our study support these recommendations and suggest potential expansions of current guidelines to wider patient populations (Armstrong et al. 2019).

Given the observed benefits in progression-free and overall survival, especially in patients under 65 and those without extensive metastases or pleural effusion, our findings could advocate for earlier integration of bevacizumab in treatment regimens. This could particularly influence guidelines to lower the threshold for bevacizumab inclusion in first-line treatment scenarios, potentially setting a new standard for care that maximizes patient outcomes early in the disease course.

3.12. Ethical considerations and management of side effects

Ethical considerations play a crucial role in cancer treatment, especially concerning patient selection and the management of adverse

effects. In clinical trials and subsequent clinical practice, ensuring informed consent is paramount, particularly when discussing the potential risks and benefits of a relatively aggressive treatment such as bevacizumab. Patients must be made aware of the possible side effects, including hypertension and fatigue, as observed in our study, and the measures taken to manage these effects should be clearly outlined.

Furthermore, ethical treatment practices should also consider the equity of access to bevacizumab, given its cost and the resource settings of different regions. Strategies to ensure that all eligible patients have access to such therapies are essential, requiring collaboration between healthcare providers, insurance companies, and pharmaceutical entities to navigate the financial aspects of cancer care.

3.13. Patient quality of life outcomes

Integrating patient quality of life outcomes into the clinical assessment process is vital to understand the holistic impact of bevacizumab treatment. While our study highlights significant improvements in survival rates, the real-world impact of these outcomes must also consider how the treatment affects patients' daily lives. Future studies should incorporate validated quality of life metrics to assess the physical, emotional, and social well-being of patients undergoing treatment. This approach not only ensures a more comprehensive evaluation of the treatment's benefits but also aligns with patient-centered care principles, emphasizing the importance of the patient's overall well-being and satisfaction with their treatment (Lheureux et al. 2019).

3.14. Potential confounders and limitations

While this study provides valuable insights into the efficacy of bevacizumab combined with standard chemotherapy in treating advanced ovarian cancer, several potential confounders and limitations must be acknowledged to fully interpret the findings.

One of the primary concerns in our study is the potential for selection bias, particularly in the historical cohort. The selection criteria for the historical cohort, while rigorous, may have inherent biases due to the retrospective nature of the data collection. We attempted to mitigate this by carefully matching patients based on age, FIGO stage, and ECOG performance status. However, unmeasured confounders, such as differences in comorbidities or variations in supportive care practices over time, could still influence the outcomes. Future prospective studies with randomized control designs are essential to eliminate this bias.

Although we performed rigorous data verification through cross-referencing hospital records and follow-up interviews, some data inconsistencies and missing information could not be entirely ruled out. This limitation emphasizes the need for prospective data collection to ensure high-quality and comprehensive datasets.

The generalizability of our findings is another critical limitation. The study was conducted at a single institution, the University Clinical Center in Niš, Serbia, which may limit the applicability of the results to other populations and healthcare settings. The patient population in this study may differ from those in other regions regarding genetic, environmental, and healthcare system factors.

Several potential confounding variables could impact the study outcomes. While we adjusted for known confounders such as age, FIGO stage, and ECOG performance status using multivariable Cox regression analysis, other factors such as genetic mutations, tumor biology, and differences in follow-up care could influence the survival outcomes. The lack of data on molecular characteristics and genetic profiling of the tumors is a significant limitation that could affect the interpretation of our results.

The follow-up duration varied among patients, which could impact the observed survival outcomes. Longer follow-up periods are necessary to capture late recurrences and long-term survival benefits fully. In this study, some patients had relatively short follow-up times, which might lead to underestimating the true survival benefits of bevacizumab.

By explicitly addressing these potential confounders and limitations, we aim to provide a balanced and transparent interpretation of our findings. Acknowledging these factors underscores the complexity of real-world clinical research and highlights areas for improvement in future studies to enhance the robustness and applicability of the results.

3.15. Future directions

Future research should focus on multicenter trials to confirm these findings and explore the interactions between bevacizumab and newer biological agents or immunotherapies. Further studies are also needed to investigate the long-term effects of bevacizumab beyond the initial treatment cycles, particularly in patients who show initial positive responses. Additionally, research into the genetic markers that may predict response to bevacizumab could refine patient selection, leading to personalized treatment approaches.

This study provides valuable evidence supporting the use of bevacizumab in combination with chemotherapy for advanced ovarian cancer, demonstrating clear benefits in progression-free survival (PFS) and overall survival (OS). Our findings indicate that patients receiving bevacizumab alongside standard chemotherapy exhibit significantly improved survival outcomes compared to those treated with chemotherapy alone, particularly among younger patients and those without metastases or pleural effusion. However, several limitations must be considered when interpreting these findings. The potential for selection bias and the retrospective nature of the study highlight the need for cautious interpretation. The single-institution setting may limit the generalizability of our findings, and variations in data completeness and follow-up duration could impact the robustness of our results. Future prospective, multicenter studies with standardized protocols and comprehensive data collection are essential to validate our findings. Integrating molecular and genetic profiling into future research will help elucidate the interactions between tumor characteristics and treatment efficacy. Investigating the long-term benefits and safety of bevacizumab in diverse patient populations will be crucial for optimizing treatment strategies and ensuring broad applicability. By acknowledging these limitations and suggesting areas for further investigation, we aim to contribute to the ongoing efforts to refine and personalize therapeutic approaches, ultimately enhancing patient well-being and survival outcomes.

4. Experimental

4.1. Participant recruitment and eligibility criteria

Between April 2017 and August 2023, patients diagnosed with ovarian cancer and receiving treatment at the Oncology Clinic of the University Clinical Center in Niš, Serbia, were prospectively enrolled in this study. Eligibility was based on histopathological confirmation of epithelial ovarian cancer. To qualify, patients were required to have undergone extensive surgical intervention, including total abdominal hysterectomy, bilateral salpingo-oophorectomy, and omentectomy. Eligible participants were over 18 years of age, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and demonstrated adequate hepatic, renal, and bone marrow function. Inclusion was limited to those with International Federation of Gynecology and Obstetrics (FIGO) stages IIIc and IV.

4.2. Exclusion criteria

Exclusion criteria encompassed individuals with a history of bowel obstruction or subocclusive disorders, abdominal fistulas, gastrointestinal perforations, intra-abdominal abscesses, or rectosigmoid involvement as identified by pelvic examinations, colonoscopy, CT imaging, or clinical symptoms suggestive of bowel involvement. Patients with recent thrombotic or hemorrhagic events, uncontrolled hypertension, significant cardiovascular diseases, or non-healing wounds were also excluded from the study.

4.3. Treatment protocol

The treatment protocol involved administering a chemotherapy regimen comprising 175 mg/m^2 of paclitaxel and carboplatin dosed to an area under the curve (AUC) of 6, delivered over the first six cycles. In addition, patients received bevacizumab at a dosage of 7.5 mg/kg every three weeks, for up to 17 cycles, depending on disease progression, intolerable toxicity, or withdrawal of consent. Chemotherapy dose adjustments adhered to established clinical guidelines, while the bevacizumab dosage remained fixed throughout the treatment course.

4.4. Assessment and monitoring

Tumor evaluations were performed using computed tomography (CT) or magnetic resonance imaging (MRI) in patients with contrast allergies, at baseline and subsequently every nine weeks. Safety assessments were conducted before each treatment cycle and within 30 days following the last treatment, utilizing the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Monitored clinical and pathological parameters included histological subtype, ECOG performance status, FIGO stage, ovarian cancer grade, and the presence of pleural effusion and ascites.

4.5. Historical cohort

This study utilized a historical cohort of patients with advanced epithelial ovarian cancer treated at the University Clinical Center in Niš, Serbia, from April 2013 to March 2017. This cohort was selected to evaluate the outcomes associated with standard chemotherapy. The cohort consisted of patients with advanced disease (FIGO stages IIIc and IV), ensuring a homogeneous population for assessing the efficacy and safety of the treatment regimen. All patients had undergone standard surgical procedures, including total abdominal hysterectomy, bilateral salpingo-oophorectomy, and omentectomy, prior to initiating systemic therapy. Demographic and baseline characteristics, such as age, ECOG performance status, histological subtype, and the presence of metastatic features (e.g., pleural effusion and ascites), were meticulously documented to provide a comprehensive profile of the patient population. This historical cohort facilitated a detailed real-world evaluation of treatment effects and served as a benchmark for assessing the long-term benefits and risks of standard chemotherapy, thereby offering valuable insights into optimal therapeutic strategies for managing advanced ovarian cancer. To ensure a valid comparison and minimize selection bias, we employed the following rigorous criteria for selecting patients for the historical cohort: Patients received standard chemotherapy, specifically paclitaxel and carboplatin, without the addition of bevacizumab. Patients aged between 18 and 80 years at the time of diagnosis. Patients with an ECOG performance status of 0-2 to ensure comparability with the treatment group. Patients with a history of other malignancies, were excluded to avoid confounding effects. Patients with incomplete medical records or insufficient follow-up data for progression-free survival (PFS) and overall survival (OS) analysis were excluded. Patients with severe comorbid conditions that could significantly affect survival independently of ovarian cancer (e.g., severe cardiovascular diseases, end-stage renal disease) were excluded. For each patient in the bevacizumab-treated group, a matching patient from the historical cohort was selected based on age (±5 years) and FIGO stage to ensure comparable baseline characteristics. Patients were also matched based on their ECOG performance status to control for differences in functional status at baseline. Comprehensive data were collected from the patients' medical records, including demographic information, clinical characteristics, treatment details, and follow-up outcomes. Data accuracy was verified by cross-referencing with hospital databases and follow-up interviews with patients or their families where necessary. The sample size for the historical cohort was determined based on the availability of eligible patients within the specified timeframe and was aimed at providing sufficient statistical power for comparative analysis. Multivariable Cox regression analysis was performed to adjust for potential confounders, including age, FIGO stage, and ECOG performance status, to ensure robust comparison between the two cohorts.

4.6. Ethical considerations

All participants provided written informed consent before any study-specific procedures were performed. The study adhered to the ethical principles outlined in the Declaration of Helsinki, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice, and the European Union Clinical Trials Directive.

4.7. Endpoints and statistical analysis

The primary endpoint was progression-free survival (PFS), defined as the interval from the date of initial surgery to the date of disease progression as determined by RECIST 1.1 criteria. Overall survival (OS) was defined as the time from the initial surgery to death from any cause, with surviving patients censored at their last known contact date. Survival analyses were conducted using the Kaplan-Meier method, and statistical analyses were performed using the Stata software package (release 17). Differences between subgroups were evaluated using the log-rank test, and Cox proportional hazards regression models were employed to determine the impact of clinical variables on PFS and OS, with hazard ratios (HRs) and 95% confidence intervals (CIs) reported.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy restrictions.

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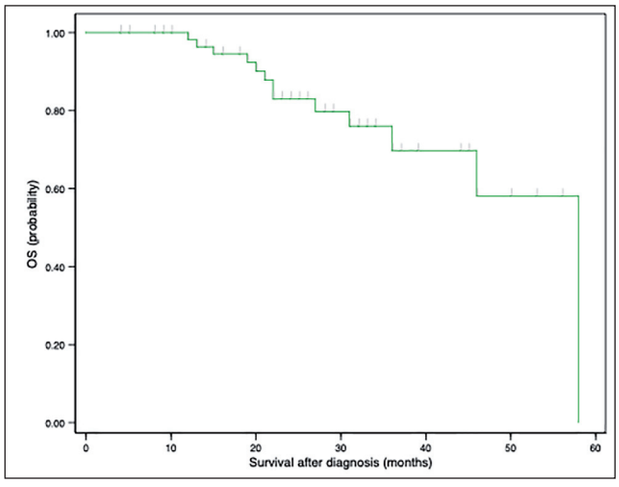

Fig. 1: Kaplan-Meier curve for overall survival (OS) probability.

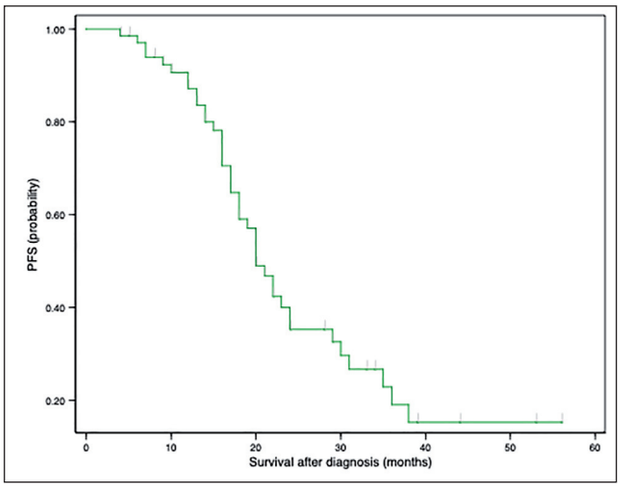

Fig. 2: Kaplan-Meier curve for progression-free survival (PFS) probability.

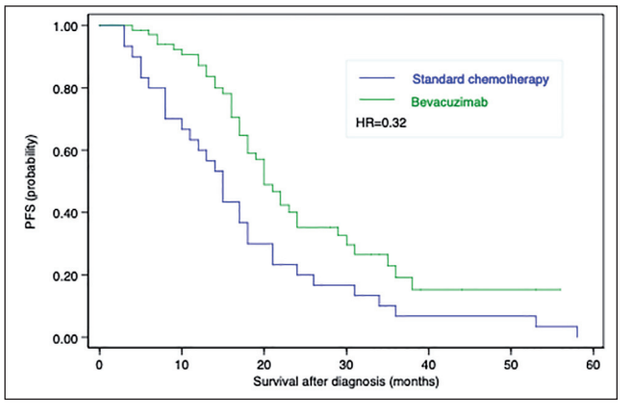

Fig. 3: Comparison of PFS probability between standard chemotherapy of historical cohort and recruited cohort.

Table 1: Demographic and clinical characteristics of bevacizumab treated group and historical cohort

Clincal ch.	Bevacizumab treated group N=71	%	Historical cohort N=30	%
Age (Mean, SD)	60.48 , 10.17		59.40, 9.17	
Histological subtype				
Seruous	68	95.77	27	90.00
Mucinous	1	1.41	1	3.33
Clear cell	1	1.41	0	0.00
Endometrioid	1	1.41	2	6.67
ECOG Performance status				
0	17	23.94	11	36.67
1	54	76.06	19	63.33
FIGO stage				
III	41	57.75	19	63.33
IVa	24	33.80	8	26.67
IVb	6	8.45	3	10.00
Gradus				
Low	4	5.63	1	3.33
High	67	94.37	29	96.67
Metastases				
Yes	15	21.13	3	10.00
No	56	78.87	27	90.00
Pleural effusion				
Yes	23	32.39	8	26.67
No	48	67.61	22	73.33
Ascites				
Yes	32	45.07	13	43.33
No	39	54.93	17	56.67
Operation type				
HTABO and omentectomy	33	46.48	14	46.47
Adnexectomy with omentum biopsy	7	9.86	2	6.67
Exploratory laparotomy with tumor biopsy	31	43.66	14	46.47
Secondary operation				
Yes	21	29.58	10	33.33
No	50	70.42	20	66.67
Lymph nodes				
Yes	11	15.49		
No	60	84.51		
Peritoneal carcinoma				
Yes	26	36.62		
No	45	63.38		

Table 2: Subgroup analysis results for bevacizumab treated group

Subgroup	Number of Patients	Median PFS (months)	Median OS (months)
Age < 65	43	22	NA
Age ≥ 65	28	20	36
Metastases	15	17	58
No metastases	56	22	NA
Pleural effusion	23	23	NA
No pleural effusion	48	18	58

Table 3: Cox regression analysis results

Covariate	HR	Standard Error	z-value	p-value	95% CI Lower	95% CI Upper
Therapy	0.32	0.09	-4.18	0.00	0.18	0.54
Age	1.03	0.01	2.33	0.02	1.01	1.06
FIGO	1.70	0.30	2.98	0.00	1.20	2.41