

Original Article

Real-world Treatment Patterns and Outcomes after Fourth Recurrence in Epithelial Ovarian Cancer: A Single-center Retrospective Cohort Study

Eda Eylemer Mocan, Yüksel Ürün

Ankara University Faculty of Medicine, Department of Medical Oncology; Ankara University Cancer Institute, Ankara, Türkiye

ABSTRACT

Aim: Evidence guiding treatment beyond the third recurrence of epithelial ovarian cancer (EOC) remains limited because most prospective studies have focused on earlier relapse settings. We evaluated real-world treatment patterns, clinical outcomes, and prognostic factors in patients who reached a fourth documented recurrence.

Methods: This retrospective single-center cohort study included patients with EOC, fallopian tube, or primary peritoneal carcinoma who developed a fourth recurrence between January 2004 and July 2023. Treatment patterns, treatment response, overall survival (OS), and prognostic factors were evaluated using Kaplan-Meier survival analysis and Cox regression.

Results: Ninety-one patients reached their fourth recurrence; 72 (79.1%) received systemic therapy and 19 (20.9%) received best supportive care. The most common regimens were: irinotecan/topotecan (22.2%), carboplatin plus paclitaxel (16.7%), pegylated liposomal doxorubicin (13.9%), and platinum plus gemcitabine (11.1%). Among 62 evaluable patients, the objective response rate and disease control rate were 9.7% and 17.7%, respectively. Among patients receiving systemic therapy, median OS from the fourth recurrence was 13.8 months [95% confidence interval (CI), 8.4-19.1]. Platinum-containing therapy was associated with a numerically longer median OS than non-platinum therapy (18.4 vs. 12.7 months); this difference was not statistically significant ($p=0.446$). In univariable Cox analysis, higher serum albumin levels were associated with improved OS (hazard ratio 0.58, 95% CI 0.39-0.88; $p=0.010$).

Conclusion: Patients experiencing a fourth recurrence of EOC have limited therapeutic options and modest responses to treatment. Median survival after the fourth recurrence exceeded one year among patients receiving systemic therapy. Serum albumin may serve as a simple prognostic marker and warrants further evaluation in larger prospective studies.

Keywords: Ovarian neoplasms, fourth recurrence, treatment outcome, prognosis, survival analysis

Introduction

Epithelial ovarian cancer (EOC) remains a major cause of cancer-related mortality among women worldwide despite substantial advances in surgical management, systemic chemotherapy, maintenance therapies, and molecularly targeted therapies [1]. These therapeutic advances have prolonged survival for many patients, leading to a growing population of women living with recurrent disease who require multiple sequential lines of systemic therapy [2,3]. Consequently, recurrent disease

continues to account for the majority of ovarian cancer-related deaths [2].

Although most patients achieve an initial response to frontline therapy, recurrent disease develops within the first three years in nearly 70% of women with advanced high-grade ovarian cancer [2]. Therapeutic decision-making has therefore shifted from a treatment-line-based approach toward a more individualized strategy that considers disease biology, including prior platinum response and BRCA/homologous recombination deficiency status, together with previous exposure to antiangiogenic agents

Address for Correspondence: Eda Eylemer Mocan, MD, Ankara University Faculty of Medicine, Department of Medical Oncology, Ankara, Türkiye

E-mail: edaeylemer@gmail.com **ORCID ID:** orcid.org/0000-0003-0429-8142

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and PARP inhibitors, cumulative toxicities, performance status, symptom burden, and patient preferences, as recommended by current international guidelines [3,4].

The therapeutic landscape of recurrent ovarian cancer has largely been shaped by prospective clinical trials evaluating patients during earlier recurrences, particularly those with platinum-sensitive disease [5,6]. Subsequent randomized trials evaluating PARP inhibitor maintenance further expanded treatment options for selected patients with recurrent disease [7,8]. Nevertheless, patients receiving later lines of therapy remain a highly heterogeneous population because of repeated exposure to cytotoxic and targeted agents, cumulative treatment-related toxicities, and the continuous evolution of tumor biology [9,10].

Historically, the platinum-free interval (PFI) has been a key determinant of treatment selection in recurrent ovarian cancer [11]. While platinum-based combinations remain the preferred option for appropriately selected patients with platinum-sensitive relapse, patients with platinum-resistant disease are generally treated with sequential single-agent therapies, including pegylated liposomal doxorubicin, weekly paclitaxel, gemcitabine, or topotecan, with or without bevacizumab [5,12,13].

Despite these established treatment principles, evidence guiding therapeutic decision-making for patients with multiple recurrences remains limited. Given the limited evidence available for patients treated after multiple recurrences, additional real-world data are needed to better characterize treatment patterns and clinical outcomes in this setting. This study aimed to evaluate treatment strategies, survival outcomes, and prognostic factors in patients with EOC, fallopian tube, or primary peritoneal carcinomas who had reached a fourth documented recurrence.

Methods

Study Design

This retrospective, single-center cohort study was conducted at the Department of Medical Oncology, Ankara University Faculty of Medicine. Medical records of consecutive patients diagnosed and treated between January 2004 and July 2023 were retrospectively reviewed. The study was designed to evaluate real-world treatment patterns and clinical outcomes of patients with a fourth recurrence of EOC.

Patient Selection

Patients were eligible if they met all of the following criteria: Age ≥ 18 years, histologically confirmed EOC, fallopian tube, or primary peritoneal carcinoma, diagnosis and treatment at Ankara University Faculty of Medicine, development of recurrent disease and survival until the fourth documented recurrence during the study period.

Patients with borderline ovarian tumors, non-epithelial ovarian malignancies, germ cell tumors, sex cord-stromal tumors, or incomplete clinical records were excluded.

The study cohort comprised all patients who experienced a fourth recurrence, regardless of whether they subsequently received systemic therapy or were managed with best supportive care (BSC).

Data Collection

Clinical and pathological data were extracted from the institutional electronic medical records. The following variables were collected: demographic characteristics; primary tumor origin; histopathological subtype; FIGO stage at diagnosis; primary treatment strategy; surgical approach; Eastern Cooperative Oncology Group (ECOG) performance status at the fourth recurrence; laboratory parameters at the fourth recurrence, including serum CA-125, hemoglobin, albumin, lactate dehydrogenase, C-reactive protein, neutrophil, lymphocyte, monocyte, and platelet counts, and neutrophil-to-lymphocyte ratio (NLR); systemic therapy after the fourth recurrence; platinum sensitivity status; concomitant bevacizumab administration; number of treatment cycles; best treatment response; reason for treatment discontinuation, and survival outcomes.

Definitions

The fourth recurrence was defined as the fourth documented episode of disease recurrence after completion of prior anticancer treatment.

Systemic therapy after the fourth recurrence was defined as any systemic anticancer treatment initiated following documentation of that recurrence. This designation refers to the time point of recurrence rather than to the numerical line of systemic treatment. Patients who received no systemic anticancer treatment after the fourth recurrence and were managed with symptom-directed supportive care were classified as the BSC group.

The PFI was defined as the time from the last dose of first-line platinum-based chemotherapy to the first documented recurrence. PFI was analyzed as both a continuous and a categorical variable. Patients were classified as platinum-resistant (PFI < 6 months) or platinum-sensitive (PFI ≥ 6 months) at first recurrence. Given the heavily pretreated study population, this classification was used to characterize the initial platinum response phenotype rather than platinum sensitivity at the fourth recurrence.

Treatment responses were extracted from contemporaneous clinical records documenting radiologists' assessments of computed tomography scans according to RECIST version 1.1; the images were not retrospectively reassessed for this study. In routine clinical practice, serial serum CA-125 measurements were also used to support the assessment of disease recurrence and treatment monitoring, but not as the sole criterion for response evaluation.

The objective response rate (ORR) was defined as the proportion of patients achieving a complete or partial response, while the disease control rate (DCR) included complete response, partial response, and stable disease.

Study Outcomes

The primary objective of the study was to describe real-world treatment patterns among patients who experienced a fourth recurrence. Secondary objectives included evaluation of treatment distribution following the fourth recurrence, comparison of platinum-containing and non-platinum treatment strategies, treatment response, and overall survival (OS).

OS was defined as the time from the date of the fourth documented recurrence to death from any cause or to the date of the last follow-up. Death from any cause was considered the event. Patients who were alive at the last documented follow-up were censored on the date of their last clinical assessment. Survival analyses were restricted to the 72 patients who received systemic therapy after the fourth recurrence. The 19 patients managed with BSC were included in the descriptive characterization of the overall cohort, but excluded from the survival analyses.

Ethics

The study was approved by the Ankara University Ethics Committee (date: 25.04.2024; decision no: I03-277-24) and was conducted in accordance with the Declaration of Helsinki. Given the retrospective nature of the study, the ethics committee waived the requirement for written informed consent.

Statistical Analysis

Continuous variables were expressed as medians and interquartile ranges (IQRs), whereas categorical variables were summarized as frequencies and percentages.

Comparisons between categorical variables were performed using the chi-square test or Fisher's exact test, as appropriate. Continuous variables were compared using the Mann-Whitney U test.

OS was estimated using the Kaplan-Meier method and compared using the log-rank test. Prognostic factors associated with survival were evaluated using Cox proportional hazards regression analysis. Variables with a *p* value <0.10 in univariable analyses were considered eligible for inclusion in a multivariable model. Only serum albumin met this criterion; therefore, no multivariable model was fitted. Median follow-up duration was estimated using the reverse Kaplan-Meier method.

All statistical analyses were performed using IBM SPSS Statistics version 30.0 (IBM Corp., Armonk, NY, USA). All tests were two-sided, and a *p* value <0.05 was considered statistically significant.

Results

Study Cohort and Baseline Characteristics

A total of 91 patients with EOC, fallopian tube, or primary peritoneal carcinoma reached a fourth documented recurrence during the study period. Among them, 72 patients (79.1%)

received systemic therapy, whereas 19 patients (20.9%) were managed with BSC.

Baseline demographic and clinicopathological characteristics are summarized in Table 1. The median age at diagnosis was 55 years (IQR, 48-65). Median serum CA-125 levels were 1210 U/mL (IQR, 434-2732) at diagnosis and 518 U/mL (IQR, 203-1924) at the fourth recurrence. The median albumin level at the fourth recurrence was 4.0 g/dL (IQR, 3.5-4.2), and the median NLR was 2.15 (IQR, 1.30-3.39). Most patients had serous histology (91.2%) and FIGO stage 3-4 disease (84.6%). PFI data at the first recurrence were available for 82 patients, of whom 10 (12.2%) were classified as platinum-resistant and 72 (87.8%) were platinum-sensitive. This classification reflects the initial platinum-response phenotype and does not represent platinum sensitivity at the fourth recurrence (Table 1).

Among the 72 patients who received systemic therapy after the fourth recurrence, all had documented prior exposure to platinum-containing chemotherapy, and 47 (65.3%) had previously received bevacizumab. One patient (1.4%) had received a PARP inhibitor as active treatment for the second recurrence rather than as maintenance therapy.

Treatment Patterns after the Fourth Recurrence

The distribution of systemic therapy after the fourth recurrence is presented in Table 2. The most frequently administered regimens were irinotecan/topotecan (22.2%), carboplatin plus paclitaxel (16.7%), pegylated liposomal doxorubicin (13.9%), platinum plus gemcitabine (11.1%), and oral etoposide (9.7%).

Among the 72 treated patients, 24 (33.3%) received platinum-containing regimens, whereas 48 (66.7%) received non-platinum therapy. Concomitant bevacizumab was administered to 7 patients (9.7%) (Table 3).

Treatment Response

Treatment response is summarized in Table 3. The best overall response was a partial response in 6 patients (8.3%), stable disease in 5 (6.9%), and progressive disease in 51 (70.8%); response assessment was unavailable for 10 patients (13.9%).

Among the 62 patients with an evaluable radiological response, the ORR was 9.7% and the DCR was 17.7%.

Survival Outcomes

Among the 72 patients who received systemic therapy after the fourth recurrence, the median follow-up, estimated using the reverse Kaplan-Meier method, was 47.8 months [95% confidence interval (CI), 35.9-59.7]. During follow-up, 62 patients (86.1%) died, and 10 (13.9%) were censored at their last follow-up. In this treated population, median OS from the fourth documented recurrence was 13.8 months (95% CI, 8.4-19.1).

Patients receiving platinum-containing systemic therapy after the fourth recurrence had a median OS of 18.4 months (95% CI, 15.5-21.2), compared with 12.7 months (95% CI, 7.3-18.2) for those receiving non-platinum systemic therapy. However, this

Table 1. Baseline characteristics

	All patients, n (%)
Age, years, median (IQR)	55 (48-65)
CA-125 at diagnosis, median (IQR)	1210 (434-2732)
CA-125 at fourth recurrence, median (IQR)	518 (203-1924)
Albumin at fourth recurrence, median (IQR), (n=80)	4.0 gr/dL (3.5-4.2)
NLR at fourth-recurrence, median (IQR), (n=82)	2.15 (1.30-3.39)
ECOG performance status at fourth recurrence	
1-2	22 (24.2)
3-4	13 (14.3)
Unknown	56 (61.5)
BRCA status	
Mutated	8 (8.8)
Non-mutated	22 (24.2)
Unknown	61 (67.0)
Primary tumor localisation	
Ovarian	55 (60.4)
Fallopian tube	7 (7.7)
Peritoneum	9 (9.9)
Unknown	20 (22.0)
Pathology	
Serous (high or low grade)	83 (91.2)
Other (endometrioid, clear cell, mucinous, or mixed type)	8 (8.8)
Clinical stage at diagnosis	
Stage 1-2	9 (9.9)
Stage 3-4	77 (84.6)
Unknown	5 (5.5)
Ascites at diagnosis	
Present	49 (53.8)
Absent	35 (38.5)
Unknown	7 (7.7)
Surgery	
Primary cytoreductive surgery	56 (61.5)
NACT + interval cytoreductive surgery	30 (33.0)
No surgery	5 (5.5)
Platinum-free interval, months, median (IQR)	12.1 (8.2-20.4)
Platinum sensitivity at first recurrence*	
Platinum-resistant (<6 months)	10 (12.2)
Platinum-sensitive (≥6 months)	72 (87.8)

*PFI data were available for 82 of the 91 patients.
 NLR: Neutrophil-to-lymphocyte ratio, IQR: Interquartile range, ECOG: Eastern Cooperative Oncology Group, PFI: Platinum-free interval

difference was not statistically significant (log-rank $p=0.446$; Figure 1).

Prognostic Factors

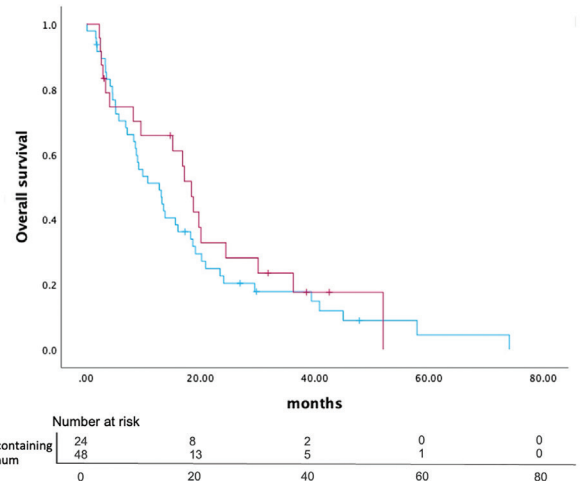


Figure 1. Overall survival (OS) according to treatment type in patients receiving systemic therapy after fourth recurrence of epithelial ovarian cancer. Kaplan-Meier curves comparing OS between patients treated with platinum-containing and non-platinum regimens

Table 2. Treatment regimens after fourth recurrence

	n (%)
Irinotecan/topotecan	16 (22.2)
Carboplatin+paclitaxel	12 (16.7)
PLD	10 (13.9)
Platinum+gemcitabine	8 (11.1)
Oral etoposide	7 (9.7)
Oral cyclophosphamide	5 (6.9)
Weekly paclitaxel	3 (4.2)
Tamoxifen	3 (4.2)
Aromatase inhibitor	2 (2.8)
Others	6 (8.3)

Irinotecan and topotecan were grouped into a single treatment category for descriptive reporting. Others included carboplatin plus pegylated liposomal doxorubicin (n=1), gemcitabine monotherapy (n=1), carboplatin plus docetaxel (n=1), melphalan (n=1), platinum plus irinotecan (n=1), and intraperitoneal cisplatin (n=1).
 PLD: Pegylated liposomal doxorubicin

The results of the univariable Cox proportional hazards regression analysis are presented in Table 4. Serum albumin level at the fourth recurrence was significantly associated with OS in univariable Cox analysis; higher levels were associated with a lower mortality [hazard ratio (HR) 0.58, 95% CI, 0.39-0.88; $p=0.010$].

Age at diagnosis (HR 1.00, $p=0.99$), NLR at fourth recurrence (HR 1.05, $p=0.36$), receipt of platinum-containing therapy (HR 0.81, $p=0.44$), platinum sensitivity at first recurrence (HR 1.05, $p=0.91$), and FIGO stage (HR 2.45, $p=0.11$) were not significantly associated with OS.

Discussion

In this retrospective cohort study, we evaluated treatment patterns and outcomes in patients with EOC who experienced a fourth documented recurrence, a population that remains

Table 3. Treatment characteristics and response to systemic therapy after fourth recurrence

	n (%)
Platinum-containing therapy	24 (33.3)
Non-platinum therapy	48 (66.7)
Bevacizumab-containing therapy	7 (9.7)
Complete response	0
Partial response	6 (8.3)
Stable disease	5 (6.9)
Progressive disease	51 (70.8)
Unknown	10 (13.9)
ORR*	6 (9.7)
DCR*	11 (17.7)
*ORR and DCR were calculated among patients with evaluable response data (n=62). ORR: Objective response rate, DCR: Disease control rate	

poorly represented in prospective clinical trials. Despite extensive prior treatment exposure, nearly 80% of patients received systemic therapy after the fourth recurrence, highlighting that active treatment remains feasible in a substantial proportion of them. Median OS among the 72 treated patients was 13.8 months; among the 62 response-evaluable patients, ORR and DCR were 9.7% and 17.7%, respectively. Although platinum-containing regimens were associated with a numerically longer median OS than non-platinum therapy (18.4 vs. 12.7 months), this difference was not statistically significant. Serum albumin was the only variable significantly associated with OS in the univariable analyses.

Data on patients experiencing a fourth recurrence remain scarce because most randomized trials have enrolled patients with first or second relapse. Consequently, later-line treatment decisions are largely based on retrospective studies and physician experience rather than high-level evidence. The ORWIC consortium demonstrated considerable heterogeneity

in treatment sequencing after repeated recurrences across different countries, reflecting the absence of a universally accepted standard [9]. Similarly, the sixth Gynecologic Cancer InterGroup consensus identified heavily pretreated recurrent ovarian cancer as one of the major unmet areas in ovarian cancer research, emphasizing the need for additional real-world data to guide clinical practice [10]. Therefore, our study contributes clinically relevant information from a population frequently encountered in routine oncology practice but rarely investigated systematically.

The median OS of 13.8 months observed in our cohort is comparable to those reported in several contemporary real-world studies, despite the advanced treatment setting. Wang et al. [14] reported a median OS of 15.9 months with platinum-containing regimens and 13.0 months with non-platinum chemotherapy in platinum-resistant recurrent ovarian cancer, whereas Sharma et al. [15] achieved a median OS of 13.3 months using dose-dense weekly carboplatin and paclitaxel in heavily pretreated patients. In contrast, Taylor et al. [16] recently reported a median OS of only 4 months in patients treated with single-agent gemcitabine after a median of four previous treatment lines. These differences probably reflect variations in patient selection, treatment availability, and disease biology. In our cohort, nearly 88% of patients were platinum-sensitive at first recurrence, suggesting relatively favorable underlying disease biology despite subsequent treatment resistance.

Treatment efficacy was modest, with an ORR of 9.7% and a DCR of 17.7%, consistent with the progressive decline in chemotherapy responsiveness after multiple recurrences. In the randomized trial by Gordon et al. [12], pegylated liposomal doxorubicin and topotecan achieved response rates of approximately 20% and 17%, respectively, whereas Mutch et al. [13] reported ORRs of 6.1% for gemcitabine and 8.3% for pegylated liposomal doxorubicin in platinum-resistant disease. More recently, the AURELIA trial demonstrated that adding bevacizumab to single-agent chemotherapy increased ORR

Table 4. Univariable cox regression analysis of overall survival

	Hazard ratio	95% CI	p
Age	1.00	0.97-1.02	0.99
NLR at fourth recurrence (n=67)	1.05	0.94-1.15	0.36
Albumin at fourth recurrence (n=66)	0.58	0.39-0.88	0.01
Treatments after fourth recurrence			
Platinum-based therapy (n=24)	0.81	0.47-1.40	0.44
Non-platinum therapy (n=48)	1		
Platinum sensitivity at first recurrence			
PFI ≥6	1.05	0.44-2.47	0.91
PFI <6	1		
Stage			
Stage 3-4	2.45	0.80-7.50	0.11
Stage 1-2	1		

The survival analysis population comprised 72 patients who received systemic therapy after the fourth recurrence.
NLR: Neutrophil-to-lymphocyte ratio, CI: Confidence interval, PFI: Platinum-free interval

from 11.8% to 27.3%, supporting antiangiogenic therapy as an effective option for platinum-resistant recurrence [17]. The lower response rates observed in our study were therefore expected, given that all patients had already experienced their fourth recurrence and only 9.7% had received bevacizumab-containing therapy; this illustrates the limited therapeutic efficacy currently achievable in this heavily pretreated population.

This comparison was exploratory and should not be interpreted as evidence of a causal treatment benefit. This finding should be interpreted cautiously. Only one-third of treated patients received platinum-based therapy, limiting statistical power, while treatment allocation was determined by clinical judgement rather than randomization. Previous toxicities, cumulative platinum exposure, performance status, and patient preference inevitably influenced treatment selection. Furthermore, the prognostic value of the initial PFI is likely to diminish after multiple sequential therapies because repeated exposure to cytotoxic agents and evolving tumor biology progressively alter treatment responsiveness. Importantly, platinum sensitivity in this study was classified at the first recurrence and should not be interpreted as a measure of platinum sensitivity at the fourth recurrence. The interval between the most recent platinum exposure and the fourth recurrence was not evaluated, which further limits interpretation of this comparison. Recent real-world evidence supports platinum rechallenge in carefully selected patients but emphasizes that therapeutic decisions after multiple recurrences should integrate previous treatment history, cumulative toxicities, and patient fitness rather than relying solely on platinum sensitivity at first relapse [2]. Therefore, our results support the current trend toward individualized treatment selection in heavily pretreated ovarian cancer.

Among the evaluated variables, serum albumin was the only factor significantly associated with OS in univariable analysis. The unadjusted association between albumin and survival may partly reflect overall patient fitness, which could not be adequately assessed because ECOG data were substantially missing. Hypoalbuminemia has consistently been associated with inferior survival in advanced malignancies because it reflects the combined effects of cancer-related inflammation, malnutrition, cachexia, and declining physiological reserve [18]. In contrast, although inflammatory biomarkers such as NLR have shown prognostic value in some ovarian cancer series, results remain inconsistent across different disease settings and treatment lines [19]. The absence of a significant association between NLR and survival in our cohort may be explained by the limited sample size and marked biological heterogeneity among patients who had undergone multiple lines of systemic therapy.

Bevacizumab was administered to 7 of the 72 treated patients (9.7%) after the fourth recurrence, whereas 47 (65.3%) had received it previously. This distinction and the long study period should be considered when interpreting treatment patterns. Randomized studies have demonstrated improved response rates and progression-free survival with

bevacizumab-containing regimens in platinum-resistant disease, while PARP inhibitor maintenance has substantially prolonged disease control in appropriately selected patients with platinum-sensitive relapse [6-8]. Therefore, although our survival outcomes remain clinically informative, they should be interpreted within the historical context of changing therapeutic standards.

The principal strength of this study is its evaluation of a clinically relevant but rarely investigated population that survived until a fourth documented recurrence. Unlike randomized clinical trials, which predominantly include patients treated during earlier relapses, our cohort reflects routine clinical practice and the complexity of therapeutic decision-making after multiple sequential treatments.

Study Limitations

This study has several limitations. First, its retrospective single-center design introduces an inherent risk of selection bias and limits the generalizability of the findings. Second, the relatively small sample size and substantial heterogeneity in systemic treatment regimens administered after the fourth recurrence limited the statistical power for treatment-specific and subgroup analyses. In addition, some clinically relevant variables, particularly ECOG performance status and molecular characteristics such as BRCA status, were unavailable for a substantial proportion of patients, precluding their comprehensive evaluation as prognostic factors. The long study period (2004-2023) encompasses substantial changes in ovarian cancer management; therefore, the reported treatment patterns and outcomes reflect a heterogeneous historical treatment era and may not fully represent contemporary practice. Finally, treatment allocation was based on physician judgment rather than randomization; therefore, comparisons between platinum-containing and non-platinum regimens are susceptible to confounding by indication and should not be interpreted as evidence of comparative treatment efficacy.

Conclusion

Patients with a fourth recurrence of EOC continue to represent a population with limited therapeutic options and modest treatment responses. Among patients receiving systemic therapy, the median survival after the fourth recurrence exceeded one year. Higher serum albumin was associated with better survival in univariable analysis, but this finding requires validation with adjustment for potential confounders. Larger multicenter real-world studies incorporating contemporary targeted therapies and molecular biomarkers are warranted to optimize treatment strategies for this increasingly prevalent patient population.

Ethics

Ethics Committee Approval: The study was approved by the Ankara University Ethics Committee (date: 25.04.2024; decision no: 103-277-24) and was conducted in accordance with the Declaration of Helsinki.

Informed Consent: Given the retrospective nature of the study, the ethics committee waived the requirement for written informed consent.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.E.M., Concept: E.E.M., Y.Ü., Design: E.E.M., Y.Ü., Data Collection or Processing: E.E.M., Analysis or Interpretation: E.E.M., Y.Ü., Writing: E.E.M.

Conflict of Interest: No conflict of interest was declared by the authors.

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