Impact of Types of Cytoreductive Surgery on Survival and Morbidity in Recurrent Epithelial Ovarian Cancer

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ABSTRACT

Objective: To evaluate the survival benefits and procedural morbidity associated with iterative cytoreductive interventions in recurrent epithelial ovarian cancer (EOC), comparing outcomes across secondary, tertiary, and quaternary surgical procedures.

Study Design: A descriptive analytical study.

Place and Duration of the Study: Department of Oncology, Azerbaijan Medical University, Narimanov, Azerbaijan, from 2014 to 2024.

Methodology: A total of 349 patients undergoing secondary cytoreduction, including subsequent tertiary (n = 155) and quaternary (n = 55) interventions, were analysed. Multivariate analysis assessed prognostic variables, such as residual disease burden, platinum sensitivity, disease-free interval (DFI), recurrence patterns, and histopathological characteristics. Survival analysis employed Kaplan-Meier estimates with Cox proportional hazards modelling.

Results: Complete macroscopic resection (R0) significantly improved survival across all surgeries, including secondary (36.6 *vs.* 15.3 months, HR 0.42, 95% CI 0.31-0.58; p <0.001), tertiary (22.2 *vs.* 6.4 months, HR 0.38, 95% CI 0.24-0.61; p <0.001), and quaternary (29.1 *vs.* 10.5 months, HR 0.29, 95% CI 0.17-0.51; p <0.001). A DFI of more than 12 months, platinum sensitivity, and isolated recurrence were identified as favourable prognostic factors. Platinum-sensitive patients with a DFI greater than 12 months demonstrated superior median overall survival (OS) in the following categories: secondary: 50.2 *vs.* 15.5 months (p <0.001), tertiary: 47.1 *vs.* 8.5 months (p <0.001), and quaternary: 50.6 *vs.* 9.2 months (p <0.001). Morbidity increased with successive interventions but remained clinically manageable. Intraoperative complication rates were as follows: secondary 9.1%, tertiary 15.5%, and quaternary 9%; postoperative complication rates were as follows: secondary 4.9%, tertiary 15.5%, and quaternary 9%.

Conclusion: Maximal-effort cytoreduction achieving R0 status significantly improves survival across multiple EOC recurrences when combined with platinum-based chemotherapy. DFI >12 months, isolated recurrence patterns, and platinum sensitivity emerge as critical selection criteria.

Key Words: *Tertiary cytoreduction, Ovarian cancer recurrence, Surgical oncology, Survival outcomes, Peritoneal carcinomatosis*.

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INTRODUCTION

Ovarian cancer remains the most lethal gynaecological malignancy, with a marked rise in incidence observed over the past five decades. According to projections by the American Cancer Society (2024), an estimated 19,680 new cases will be diagnosed in the United States, with 12,740 anticipated fatalities.[1] Prognosis varies significantly by disease stage; the five-year overall survival (OS) rate approaches 93% for localised tumours but decreases to 31% in cases with distant metastases, contributing to an average OS of 30-40%. Late-stage detection persists as a principal barrier to improved outcomes, as over 70% of patients present with advanced disease.[2] As a result, survival rates for ovarian cancer continue to be unacceptably low.

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Epithelial ovarian cancer (EOC) remains the most lethal gynaecologic malignancy, with a 70–80% recurrence rate despite primary cytoreduction and chemotherapy.[3] Over the past five decades, the surgical management of EOC has undergone significant progression, marked by increasingly radical approaches. This shift has centred on the integration of multiorgan resection strategies to achieve complete macroscopic tumour removal, guided by the principle that minimising postoperative residual disease is critical for improving survival outcomes in advanced-stage cases.[4]

The modern era of gynaecologic oncology is defined by personalised therapeutic strategies, optimisation of surgical quality through radical upper abdominal procedures, and *en bloc* tumour resections, all facilitated by advanced perioperative critical care systems.[5] This paradigm shift reflects an emphasis on surgical excellence, underscored by emerging prospective randomised controlled trials (RCTs) evaluating surgical outcomes through rigorous evidence-based frameworks. Examples include the LION trial, which investigates the role of systematic lymphadenectomy in ovarian neoplasms, and the AGO-DESKTOP III study, designed to

prospectively assess the efficacy of secondary cytoreductive surgery in EOC. These trials exemplify the field's commitment to refining surgical standards and validating therapeutic benefits within high-level clinical research.

Robust evidence underscores residual tumour burden, following cytoreductive surgery, as the most influential prognostic determinant in this context, a correlation consistently demonstrated across foundational studies.[6] The presence of residual tumour tissue following surgery remains a critical prognostic factor across multiple phases of EOC management, including primary cytoreduction, delayed surgery after neoadjuvant chemotherapy, and secondary tumour debulking. However, its prognostic relevance in the tertiary cytoreductive setting remains uncertain, as highlighted in prior studies.[7,8]

Existing literature on tertiary cytoreductive surgery (TCS) is sparse, predominantly derived from single-centre studies with limited patient cohorts.[9] Given the logistical and ethical challenges of conducting RCTs comparing TCS to non-surgical interventions, a large-scale, retrospective analysis offers the most viable approach to elucidating the role of surgical management in recurrent EOC.[7,10] While secondary cytoreduction is established in platinum-sensitive recurrence, the role of tertiary or quaternary surgeries remains debated.[11,12]

To address this gap, this study aimed to provide robust evidence on the outcomes and feasibility of TCS in the context of a second relapse. The objective of the study was to assess the survival benefit and morbidity of repeated cytoreductive surgeries, emphasising prognostic factors and patient selection.

METHODOLOGY

An analytical study was conducted retrospectively on patients undergoing surgical intervention for recurrent EOC at the Department of Oncology, Azerbaijan Medical University, Narimanov, Azerbaijan, from 2014 to 2024. Inclusion criteria comprised histologically confirmed primary EOC, complete primary cytoreduction, and subsequent secondary, tertiary, or quaternary surgeries for recurrence. Patients with non-epithelial histology or incomplete primary cytoreduction were excluded. A total of 349 patients underwent secondary cytoreduction, while 155 and 55 received tertiary and quaternary procedures, respectively.

The International Federation of Gynaecology and Obstetrics (FIGO) staging system was utilised for disease classification. Optimal cytoreduction (no macroscopic residual tumour) was uniformly pursued. Preoperative evaluations by anaesthesiologists and informed consent were mandatory. Adjuvant chemotherapy regimens were administered postoperatively. Disease-free survival (DFS) was defined as the interval from primary surgery completion (or final chemotherapy cycle) to recurrence confirmed *via* clinical, radiological (PET-CT, MRI, and ultrasound), or serological (CA-125) assessment. Intraoperative complications (*e.g.*, organ injury and Haematoma) and postoperative complications (such as those occurring during hospitalisation) were documented. The study adhered to the institutional ethical standards, with informed consent obtained from all patients and families prior to procedures.

The data collected from the study cohort were analysed using SPSS version 22.0 statistical software (SPSS *Inc.*, Chicago, IL, USA). Continuous variables were summarised as mean values with standard deviation ± SD, while categorical variables were expressed as numerical counts and percentages. Survival rates were assessed *via* Kaplan-Meier survival analysis, and between-group comparisons were conducted using a log-rank test. For all statistical evaluations, a p-value of <0.05 was considered statistically significant.

Cox proportional hazards modelling was employed for multivariate analysis. The variables included in the multivariate model were residual disease burden (R0 *vs.* suboptimal), platinum sensitivity (sensitive *vs.* resistant), DFI (≤6 months, 6-12 months, or ≥12 months), recurrence patterns (localised, multifocal, or disseminated carcinomatosis), and histopathological characteristics (serous, endometrioid, mucinous, clear cell, mixed epithelial, and undifferentiated). Missing data for the stage of primary surgery (4.3%), tumour grade (16.6%), and recurrence site (12.8%) were handled by analysing only patients with complete information for each specific variable, meaning those with missing data were excluded from the analysis for that variable. The potential impact of missing data on the results is acknowledged as a limitation of this retrospective study. For all statistical evaluations, a two-sided p-value of <0.05 was considered statistically significant.

RESULTS

This study included 349 patients who underwent surgery for recurrent EOC at the institution between 2014 and 2024. The median follow-up duration was 111 months (range: 90.4-131.6 months). The mean age at diagnosis was 52.4 ± 11.6 years (range: 22-82 years). Histopathological evaluation of the primary surgical specimens revealed the following tumour subtypes: serous papillary carcinoma in 283 (81.1%) patients, endometrioid carcinoma in 27 (7.7%) patients, mucinous carcinoma in 10 (2.9%) patients, clear cell carcinoma in 16 (4.6%) patients, mixed epithelial carcinoma in 9 (2.6%) patients, and undifferentiated carcinoma in 4 (1.1%) patients.

According to the FIGO staging criteria, 77 (22.1%) patients were diagnosed with stage 1-2 disease at primary surgery, while 257 (73.6%) patients presented with stage 3-4 disease. The stage of primary surgery could not be determined for 15 (4.3%) patients. Tumour grading revealed grade 1 in 16 (4.6%) patients, grade 2 in 65 (18.6%) patients, and grade 3 in 210 (60.2%) patients. Tumour grade data were unavailable for 58 (16.6%) patients.

During primary cytoreduction, intraoperative complications were documented as full-thickness bladder wall defects in 3 patients, full-thickness bowel wall defects in 4 patients, bowel serosal injuries in 8 patients, and major vascular injuries in 2

patients. In the postoperative period, 332 patients (93.2% of the cohort) experienced no complications. Among the remaining cases, postoperative ileus was noted in 4 (1.1%) patients, deep vein thrombosis (DVT) in 4 (1.1%) patients, lymphocele and acute renal failure in two (0.5%) patients each, and surgical site infection in one (0.3%) patient. Additionally, rare complications included rectovaginal fistula, ileovaginal fistula, pneumonia, and concurrent ileus with gastrointestinal bleeding in one case (0.3%, each).

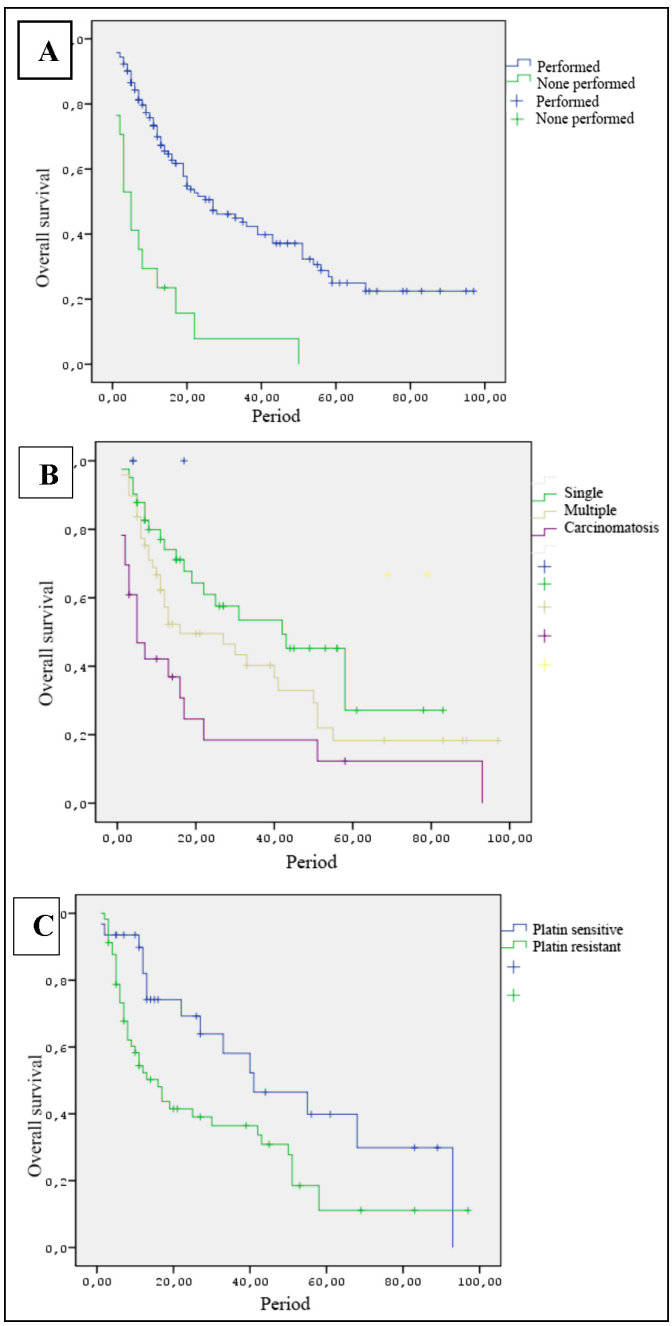

Figure 1: (A) OS of patients with second relapse who underwent optimal *vs*. suboptimal tertiary cytoreduction. (B) OS of patients undergoing tertiary cytoreduction stratified by site of recurrence. (C) OS of patients undergoing tertiary cytoreduction stratified by platinum sensitivity.

All 349 patients received platinum-based chemotherapy following primary surgery. The DFI was defined as the period from the completion of postoperative chemotherapy to the first clinical, radiological, or laboratory confirmation of disease recurrence. Analysis revealed distinct stratification of recurrence patterns as follows: 93 (26.6%) patients experienced disease recurrence within <6 months, 44 (12.6%) patients demonstrated DFI of 6-12 months, and 212 (60.7%) patients maintained DFI ≥12 months. Among patients with first recurrence, secondary cytoreductive surgery was performed in 349 to achieve optimal tumour reduction. Eighty (22.9%) patients received single- or multi-agent chemotherapy prior to secondary cytoreduction (Figure 1 and 2).

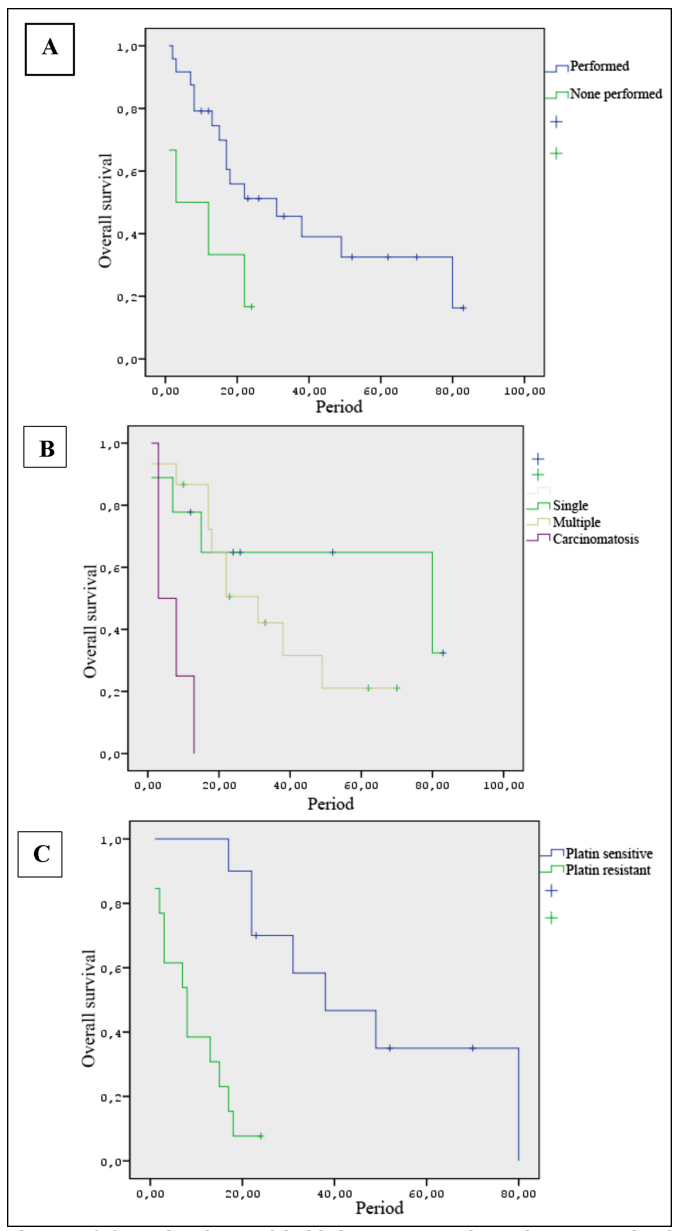

Figure 2: (A) OS of patients with third recurrence who underwent optimal *vs*. suboptimal quaternary cytoreduction. (B) OS of patients undergoing quaternary cytoreduction stratified by site of recurrence. (C) OS of patients undergoing quaternary cytoreduction stratified by platinum sensitivity.

Table I: Names of surgical operations.

Performed	Patients (n)
Tertiary cytoreduction	139
Tumoural debulking	49
+BPPLND+omentectomy	6
+Splenectomy	13
+Mass excision from liver	5
+Mass excision from ureter	2
+Segmental ileum resection+ileostomy	5
+Segmental ileum resection+end-to-end anastomosis	5
+Segmental small intestine and colon resection + ileocolostomy	10
+Rectosigmoid colon resection + colostomy	14
+Segmental colon resection+end-to-end anastomosis	3
+Splenectomy+segmentaal colon resection + colostomy	3
+Partial gastrectomy+distal pancreatectomy + splenectomy	1
+ Partial gastrectomy +jejunostomy + splenectomy	3
+Small intestine perforation repair	2
+Vaginal cuff mass excision	10
+Vesicovaginal fistula repair	1
Brain tumour excision	2
Inguinal lymph node dissection	4
VATS (*video-assisted thoracic surgery*)	1
None performed	16
Quaternary operations	55
Mass excision by laparotomy	21
Vaginal cuff mass excision	7
Rectosigmoid colon resection and colostomy	8
Splenectomy + rectosigmoid colon resection and colostomy	2
Ileum resection and ileostomy	4
Intestinal perforation repair	2
Mass excision + vesicovaginal fistula repair	1

Table II: Complications of cytoreductive procedures.

Parameters	Patients n (%)
Intraoperative complications (primary surgery)	**17 (4.8%)**
Intestinal serosal defect	8 (2.4 %)
Full-thickness intestinal defect	4 (1.1%)
Full-thickness bladder defect	3 (0.8%)
Major vessel injury	2 (0.5%)
Postoperative complications (primary surgery)	**17 (4.9%)**
Postoperative ileus	4 (1.1%)
Deep vein thrombosis (DVT)	4 (1.1%)
Lymphocele	2 (0.6%)
Acute renal failure	2 (0.6%)
Injury site infection	1 (0.3%)
Rectovaginal fistula	1 (0.3%)
Ileovaginal fistula	1 (0.3%)
Pneumonia	1 (0.3%)
Ileus + gastrointestinal bleeding	1 (0.3%)
Intraoperative complications (secondary cytoreduction)	
Intestinal serosal defect	13 (3.7%)
Intestinal full wall defect	8 (2.2%)
Ureteral full wall incision	3 (0.8%)
Major vessel ınjury	3 (0.8%)
Bladder full-thickness defect	4 (1.1%)
Diaphragmatic perforation	1 (0.2%)
Total	**32 (9.1%)**
Intraoperative complications (tertiary cytoreduction)	
Intestinal serosal defect	10 (6.4%)
Intestinal full wall defect	10 (6.4%)
Ureteral injury	1 (0.6%)
Bladder full wall defect	3 (1.9%)
Total	**24 (15.5%)**
Intraoperative complications (quaternary cytoreduction)	
Intestinal serosal defect	2 (3.6%)
Intestinal full wall defect	2 (3.6%)
Bladder full-thickness defect	1 (1.8%)
Total	**5 (9%)**

Table III: Recurrence patterns.

Recurrence Patterns	Patients n (%)	p-values
Secondary cytoreduction organ involvement	76 (21.8%)	<0.001
Single organ		
Multiple organ	164 (47.1%)	
Carcinomatosis	64 (18.3%)	
Unknown	45 (12.8%)	
Status of secondary cytoreduction	-	-
Operations	-	-
Optimal cytoreduction (<1 cm)	342 (98%)	<0.001
Suboptimal cytoreduction (>1 cm)	7 (2%)	
Total	**349**	-
Tertiary cytoreduction organ involvement	-	-
Single organ	50 (32.2%)	0.004
Multiple organ	68 (43.8%)	
Carcinomatosis	30 (19.3%)	
Unknown	7 (4.7%)	
Status of tertiary cytoreduction	-	-
Operation	-	-
Optimal cytoreduction (<1 cm)	139 (89.7%)	<0.001
Suboptimal cytoreduction (>1 cm)	16 (10.3%)	
Total	**155 (100%)**	
Quaternary cytoreduction organ involvement		
Single organ	24 (43.6%)	<0.001
Multiple organ	19 (34.6%)	
Carcinomatosis	12 (21.8%)	
Status of quaternary cytoreduction		
Optimal cytoreduction (<1 cm)	45 (81.8%)	<0.001
Suboptimal cytoreduction (>1 cm)	10 (18.2%)	
Total	**55 (100%)**	

Intraoperative documentation of recurrence patterns included localised single-site recurrence in 76 (21.8%) patients, multifocal recurrence (≥2 sites) in 164 (47%) patients, and disseminated carcinomatosis in 64 (18.3%) patients. Recurrence site data (single *vs.* multifocal) were unavailable for 45 (12.8%) patients due to incomplete operative records. The objective of secondary cytoreductive surgery was to achieve complete resection of visible tumour implants, leaving no residual disease. Optimal secondary cytoreduction (defined as residual tumour <1 cm) was accomplished in 342 (98%) cases, while suboptimal cytoreduction (residual tumour >1 cm) was performed in 7 (2%) patients (Table III). During secondary cytoreduction, intraoperative complications were documented as follows: intestinal serosal defects in 13 (3.7%) patients, transmural intestinal defects in 8 (2.2%) patients, transmural ureteral injury in 3 (0.8%) patients, major vascular injury in 3 (0.8%) patients, transmural bladder defects in 4 (1.1%) patients, and diaphragmatic perforation in 1 (0.2%) patient (Table I and II).

Complete macroscopic resection (R0) was identified as the most significant prognostic factor for improved OS across all surgical interventions. Cox proportional hazards modelling revealed that achieving R0 status was associated with substantial reductions in mortality risk across successive cytoreductive procedures. For secondary cytoreduction, patients achieving R0 demonstrated a hazard ratio (HR) of 0.42 (95% confidence interval [CI]: 0.31-0.58; p <0.001) compared to those with suboptimal resection. The median OS for patients with R0 resection was 36.6 months *vs.* 15.3 months for those with residual disease (p <0.001). In tertiary cytoreduction, R0 status yielded an HR of 0.38 (95% CI: 0.24-0.61; p <0.001). The median OS for patients with R0 resection was 22.2 months *vs.* 6.4 months for

suboptimal resection (p <0.001). For quaternary cytoreduction, achieving R0 was associated with an HR of 0.29 (95% CI: 0.17-0.51; p <0.001). The median OS for complete resection was 29.1 months *vs.* 10.5 months for incomplete resection (p <0.001).

DFI emerged as another critical prognostic factor across all surgical interventions. Patients with DFI ≥12 months consistently demonstrated superior survival outcomes compared to those with shorter intervals. In secondary cytoreduction, the median OS was 50.2 months for DFI ≥12 months *vs.* 15.5 months for DFI ≤6 months (p <0.001). Similar patterns were observed in tertiary (47.1 *vs.* 8.5 months, p <0.001) and quaternary procedures (50.6 *vs.* 9.2 months, p <0.001). Platinum sensitivity significantly influenced survival outcomes across all surgical interventions. In secondary cytoreduction, platinum-sensitive patients had a median OS of 40.4 months compared to 15.3 months for platinum-resistant cases (p <0.001). This survival advantage was maintained in tertiary (27.2 *vs.* 17.5 months, p = 0.001) and quaternary procedures (40.4 *vs.* 9.2 months, p <0.001).

DISCUSSION

The findings of this large, single-centre retrospective study confirm that maximal cytoreduction, achieving no macroscopic residual disease (R0) is the most significant prognostic factor for improved OS in patients with recurrent EOC, regardless of whether the procedure is secondary, tertiary, or quaternary. The survival benefit associated with R0 status was consistently observed across all iterative surgeries, with the most pronounced effect seen in quaternary cytoreduction (HR 0.29).

This observation supports the ongoing paradigm shift in gynaecological oncology, which prioritises surgical quality and the achievement of R0 status in the recurrent setting. The study also reinforces the established role of DFI and platinum sensitivity as crucial selection criteria. Patients with a DFI of 12 months or more, and those who were platinum-sensitive, demonstrated significantly superior OS following cytoreduction, aligning with the results of key randomised trials such as DESKTOP III and AGO-OVAR.[12] However, the study extends these findings by demonstrating that this survival advantage is maintained even in the setting of tertiary and quaternary cytoreduction, which are areas of ongoing debate and limited high--level evidence. The data suggest that patient selection based on these criteria remains valid even for multiple recurrences.

While morbidity increased incrementally with successive interventions, the complication rates remained clinically acceptable, particularly when compared to the substantial survival gains achieved with R0 resection. This suggests that in carefully selected patients, the risk-benefit ratio remains favourable for aggressive surgical management. The complexity of these procedures, coupled with the need for advanced perioperative care, highlights the necessity for centralised management in high-volume centres. The consistent and robust survival benefit observed in this cohort, despite the increasing technical difficulty of repeated surgeries, underscores the therapeutic potential of cytoreduction beyond the second recurrence.

A critical aspect of the evolving management of recurrent EOC is the integration of surgical outcomes with novel systemic therapies and the role of molecular profiling. Recent literature has highlighted the importance of poly (ADP-ribose) polymerase (PARP) inhibitors, particularly in patients with germline or somatic *BRCA* mutations, which often correlate with platinum sensitivity and longer DFI, thus overlapping with the favourable prognostic factors identified in this study.[13,14]

Furthermore, the incorporation of bevacizumab into chemotherapy regimens has demonstrated progression-free survival benefits in the recurrent setting.[15] The decision to proceed with tertiary or quaternary cytoreduction must now be considered within this multidisciplinary framework, where surgical feasibility is balanced against the potential benefit of targeted agents. Molecular markers, such as homologous recombination deficiency (HRD) status, are increasingly used to refine patient selection for non-surgical treatments.[16,17] Future research should focus on prospective studies that integrate these molecular and systemic factors with the surgical outcomes of iterative cytoreduction to further personalise treatment algorithms and confirm the long-term benefit of aggressive surgical management in the era of targeted therapy.[18-20]

CONCLUSION

Maximal cytoreduction to R0 status significantly improves OS in patients with recurrent EOC, extending the survival benefit to tertiary and quaternary procedures. DFI >12 months and platinum sensitivity are confirmed as critical selection criteria. While procedural morbidity increases with successive interventions, the risk-benefit ratio remains favourable in appropriately selected patients managed in specialised, high-volume oncological centres.

ETHICAL APPROVAL:

The study was approved by the Ethics Committee of the Department of Oncology, Azerbaijan Medical University, Narimanov, Azerbaijan (Reference. 2024/AMU/0108; No. 113). The study was conducted in accordance with the ethical standards of the Institutional and National Research Committee and with the Helsinki Declaration 1964.

PATIENTS' CONSENT:

Informed consent was obtained from al l individual participants included in the study.

COMPETING INTEREST:

The author declared no conflict of interest.

AUTHOR'S CONTRIBUTION:

AI: Conceptualisation, methodology, data curation, editing, and review, resources, supervision, validation, and approval of the final version of the manuscript to be published.

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