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ORIGINAL RESEARCH

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The effect of secondary cytoreductive surgery on survival in recurrent epithelial ovarian cancer

Goksu Goc[1,*], Cagatayhan Ozturk[2], Korhan Kahraman[3], Salih Taskin[2], İbrahim Yalcin[4], Batuhan Ozmen[2], Fırat Ortac[2]

[1]Department of Obstetrics and Gynecology, American Hospital, 10000 Prishtine, Kosova
[2]Department of Obstetrics and Gynecology, School of Medicine, Ankara University, 06100 Ankara, Turkey
[3]Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Private Office, 06510 Ankara, Turkey
[4]Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, School of Medicine, Dokuz Eylul University, 35220 Izmir, Turkey

***Correspondence**
goksu.goc@spitaliamerikan.com
(Goksu Goc)

Abstract

Background: The purpose of this research was to determine the key factors that can predict the outcomes of secondary cytoreductive surgery and the criteria for selecting patients that would result in improved survival rates. **Methods**: The retrospective study analyzed a cohort of 97 individuals who were diagnosed with platinum-sensitive epithelial ovarian cancer at the Gynecologic Oncology Unit from 1990 to 2012, and who had undergone surgery for recurrence following initial treatment, which included primary surgery and adjuvant chemotherapy. Surgical intervention was recommended for patients who had a median disease-free interval (DFI) of at least 6 months from their initial treatment to the recurrence, and who exhibited an Eastern Cooperative Gynecologic Oncology Group performance status of 2 or lower. All patients were treated with platinum-based chemotherapy or other chemotherapy regimens in the postoperative period. **Results**: The DFI was 24.5 months (95% confidence interval (CI): 18.2–30.7). Optimal secondary cytoreduction was achieved in 63 (64.9%) patients, with a significant increase in survival compared to patient groups with suboptimal cytoreduction (142.9 months *vs.* 42.2 months and 33.7 months) ($p < 0.001$). Survival was significantly increased in patients with a DFI >14 months ($p = 0.002$). Multivariate analysis revealed that disease-free interval (DFI) and the presence of residual disease following secondary surgery emerged as pivotal independent predictors of survival. **Conclusions**: Secondary cytoreductive surgery stands out as a secure and efficient therapeutic approach for recurrent epithelial ovarian cancer, leading to a decrease in complication rates. Employing maximal surgical interventions notably extends patients' survival times.

Keywords

Recurrent epithelial ovarian cancer; Secondary cytoreductive surgery; Disease-free interval (DFI); Overall survival (OS); Residual tumour; Complete cytoreduction; Optimal cytoreduction

1. Introduction

Ovarian cancer ranks second in terms of mortality among all gynaecological cancers [1]. More than 60% of cases are diagnosed at an advanced stage due to cavities in the pelvic area and asymptomatic findings. Especially in cases diagnosed at an early age, there may be problems with the preservation of fertility. The majority of malignant ovarian tumors, over 90 percent, stem from the ovaries and fallopian tubes. These tumors are predominantly composed of high-grade serous carcinoma when examined histopathologically. Nevertheless, there exists a less prevalent category comprising high-grade endometrioid, low-grade serous carcinoma, and clear cell carcinoma, which share comparable morphological and molecular characteristics [2, 3]. The combination of primary cytoreductive surgeries, interval cytoreduction following neoadjuvant chemotherapy, and various adjuvant therapies, along with several targeted treatments, collectively yield an overall survival rate of 40% or less for advanced stage 3 and beyond epithelial ovarian cancer [4].

Globally, 60% of individuals with ovarian cancer experience recurrent ovarian cancer (ROC) within a 5-year period following the initial treatment [5]. ROC is characterised by elevated cancer antigen 125 (CA 125) levels after primary treatment (initial surgery and chemotherapy) or by the findings of imaging studies performed in the presence of symptoms. Presently, radiological imaging methods, such as positron emission tomography (PET), lack the sensitivity required to detect peritoneal cancer when the tumors are smaller than a few millimeters in size. Therefore, the Gynecologic Cancer Intergroup recommends diagnosing ovarian cancer only in the presence of radiological imaging findings, along with elevated CA 125 levels [6]. Since ovarian cancer typically reoccurs within a disease-free interval (DFI) of 18–24 months following primary treatment, it is imperative to consider pretreatment prognostic factors [6]. The primary prognostic factors of ovarian can-

cer prognosis are the International Federation of Gynecology and Obstetrics (FIGO) staging, histologic type and residual size, while the secondary ones are the location and timing of recurrence, the existence of multiple recurrence sites and the treatment procedure. The DFI can be evaluated in three categories according to how long after primary chemotherapy the recurrence occurred: 12 months, 6 to 12 months and less than 6 months [6]. Approximately 50% of recurrences are identified within 12 months following the initial chemotherapy treatment, with a quarter occurring prior to the 6-month mark. Recurrences can be classified based on their location into two groups: primary (occurring in the pelvis and abdomen) and others. Similarly, the number of recurrences can be categorized as either single or multiple recurrences. Furthermore, patients' treatment approaches can be categorized as either surgical intervention or a combination of surgery and chemotherapy [6, 7].

Chemotherapy is the established therapy for platinum-sensitive ROC. Secondary surgical cytoreduction (SCS) refers to the surgical intervention aimed at removing recurrent tumours in patients who have achieved remission after primary treatment. The concept of SCS was first introduced by Berek *et al*. [8] in 1983, and extensive research on SCS has been carried out in numerous studies since its inception. Although SCS is a potentially valuable option for ROC, it is not yet an established standard of care due to its complexity and some concerns regarding its outcomes.

The surgical treatment of recurrent epithelial ovarian cancer is usually palliative and generally aims to improve the patient's survival and quality of life. A complete response to chemotherapy in ROC is rare, and tumour suppression does not always result in prolonged survival. Hence, surgical intervention is another frequently used method. After clinical detection of recurrence, SCS can be conducted, particularly in cases of persistent disease following chemotherapy. Factors such as DFI, the extent of recurrence sites, and residual tumour size post-SCS play a significant role in determining the postoperative prognosis. Sehouli *et al*. [9] found that the pattern of tumour invasion and its location significantly impacted survival. Patients with a prolonged DFI (>30 months) and a single site of recurrence constitute the patient group that may benefit most from SCS. Chi *et al*. [10] identified DFI and complete surgical resection as the most significant prognostic factors and stated that surgical outcomes depend on surgical skill, as well as the location and number of recurrences. By contrast, Onda and colleagues pinpointed four key prognostic indicators, which are progression-free survival (PFS) exceeding 12 months, lack of liver metastasis, presence of a single tumour, and tumour size less than 6 cm. They concluded that individuals with a minimum of three of these factors are the most likely to experience favourable outcomes from SCS [11]. Conversely, approximately 30% of patients require resection of the bowel or other organs during SCS, resulting in morbidity-inducing procedures, such as colostomy or pelvic exenteration [9–11]. Furthermore, it is crucial to carefully assess surgical and/or chemotherapy options for patients experiencing a recurrence, especially given the heightened effectiveness of second-line chemotherapy in individuals with prolonged DFI. An analysis of long-term studies highlights that maximal surgical cytoreduction and the administration of platinum-based chemotherapy continue to be the foremost prognostic indicators for survival in cases of recurrent ovarian cancer [6–8].

There is ongoing controversy about surgery for recurrent ovarian tumors. Retrospective and prospective studies indicate that secondary cytoreduction in recurrent ovarian cancer significantly improves survival rates, particularly in patients who are platinum sensitive and have a long interval since their last treatment, and that only complete cytoreductive surgery may be beneficial for survival. The degree of disease involvement is regarded as a stand-alone risk factor in secondary cytoreductive surgery conducted at specialized gynecological oncology centers, despite the fact that there is a possibility of elevated rates of morbidity, particularly in relation to gastrointestinal complications, both intraoperatively and postoperatively [12].

Newly released studies have shown that the DEAD (Asp-Glu-Ala-Asp)-box RNA helicase 1 (DDX1) marker may function as a valuable prognostic indicator for epithelial ovarian cancer. Specifically, these studies have shed light on its involvement in tumour growth as well as in the replication and transcription of mRNA/rRNA related to cancer advancement [13].

Apart from surgical treatments and chemotherapy, tocotrienols found in rice bran, palm oil, and achiote seeds have been suggested to inhibit the growth of tumour cells, particularly in patients with ROC [14].

Recent reviews have indicated that secondary cytoreductive surgery can be performed in recurrent ovarian cancer cases where complete cytoreduction is achieved during primary surgery. Moreover, when bevacizumab was not given but complete surgery was successfully performed, there was an enhancement in overall survival rates. Conversely, in instances of recurrence following incomplete surgery, studies have indicated elevated levels of morbidity and mortality linked to secondary surgical interventions [15].

Despite the advances in surgery and chemotherapy, OS in patients with advanced epithelial ovarian cancer has still not been sufficiently improved. Maximal surgical cytoreduction and platinum-based chemotherapy remain the most critical interventions for survival. Maximum resection with cytoreductive surgery has become the most significant step in the first-line treatment of primary and recurrent advanced ovarian cancer. The studies conducted to optimise the surgery and chemotherapy options for ROC reported DFI, complete surgical resection, amount of ascites before and after recurrence, and Eastern Cooperative Gynaecologic Oncology Group performance status (ECOG-PS) as the primary predictors for ROC. Sensitivity to chemotherapy, especially platinum-based chemotherapy, is another critical factor that has a significant impact on complete resection and survival.

A recent multicenter randomized trial revealed that incorporating platinum-based hyperthermic intraperitoneal chemotherapy (HIPEC) into cytoreductive surgery following the initial late recurrence in patients with epithelial ovarian cancer who had previously undergone platinum-based chemotherapy post primary or interval surgery led to a significant enhancement in overall survival rates. This

improvement was particularly notable among individuals diagnosed with high-grade serous and endometrioid-type ovarian cancers. These results indicate that the utilization of platinum-based HIPEC could potentially yield advantages in the management of recurrent ovarian cancers [16].

In light of the foregoing information, this study's primary objective is to evaluate the clinicopathologic factors affecting DFI and OS after SCS, and the secondary objective is to determine the prognostic factors that may predict the patients in whom optimal SCS can be achieved.

2. Materials and methods

The population of this retrospective study consisted of patients diagnosed with platinum-sensitive epithelial ovarian cancer in the Gynecologic Oncology Unit of the Department of Obstetrics and Gynecology, Faculty of Medicine, Ankara University, Ankara, Turkey, between 1990 and 2012 who underwent surgery for recurrence after primary treatment (primary surgery and adjuvant chemotherapy). The study protocol was approved by the ethics committee with the decision dated 07 May 2012 and numbered 08-230-12.

A total of 487 primary ovarian cancers were diagnosed in 22 years. Among these patients, 86 had poor performance scores (≤2), 63 were platinum-resistant, 79 were tumours with low malignant potential, 54 were non-epithelial tumours and 31 had no recurrence, and these patients were excluded from the study group. Out of the 174 patients with recurrence, 58 were excluded from the study group because they did not continue their follow-up, and 19 cases were excluded due to the unavailability of imaging data. A total of 97 patients were eligible for the study (Fig. 1).

Information regarding patients' conditions, such as the stage of the disease, grade of the tumour, histology of the tumour, the presence of any remaining tumour post-primary surgery, the utilization and type of adjuvant chemotherapy, DFI, size of recurrent lesions, level of CA 125, volume of ascites post-recurrence, residual disease following SCS, usage and type of salvage chemotherapy post-SCS, as well as morbidity and mortality rates post-SCS and survival outcomes, were collected from hospital archives and via telephone conversations. Written consent was obtained from all patients included in the study.

The chemotherapies administered were evaluated in three categories: platinum-based (cisplatin, carboplatin), taxane-based (paclitaxel and docetaxel), or platinum and nontaxane-based (cyclophosphamide, liposomal doxorubicin) chemotherapies. Recurrence sites with solid lesions were intraoperatively evaluated as single or multiple recurrence sites, and the maximum diameter of the largest lesion was recorded. Accordingly, residual tumours were evaluated in three categories: tumours >1 cm, tumours <1 cm (that is, between 0.1 and 1 cm), and tumours <0.1 cm (that is, no macroscopic (residual) tumour). The surgical intervention involved the resection of all visible lesions, including bowel resection, liver resection, modified anterior or posterior pelvic exenteration, retroperitoneal lymphadenectomy, peritoneal implant excision/ablation and splenectomy.

All patients included in the study were staged according to the FIGO surgical staging system. Patients with recurrent

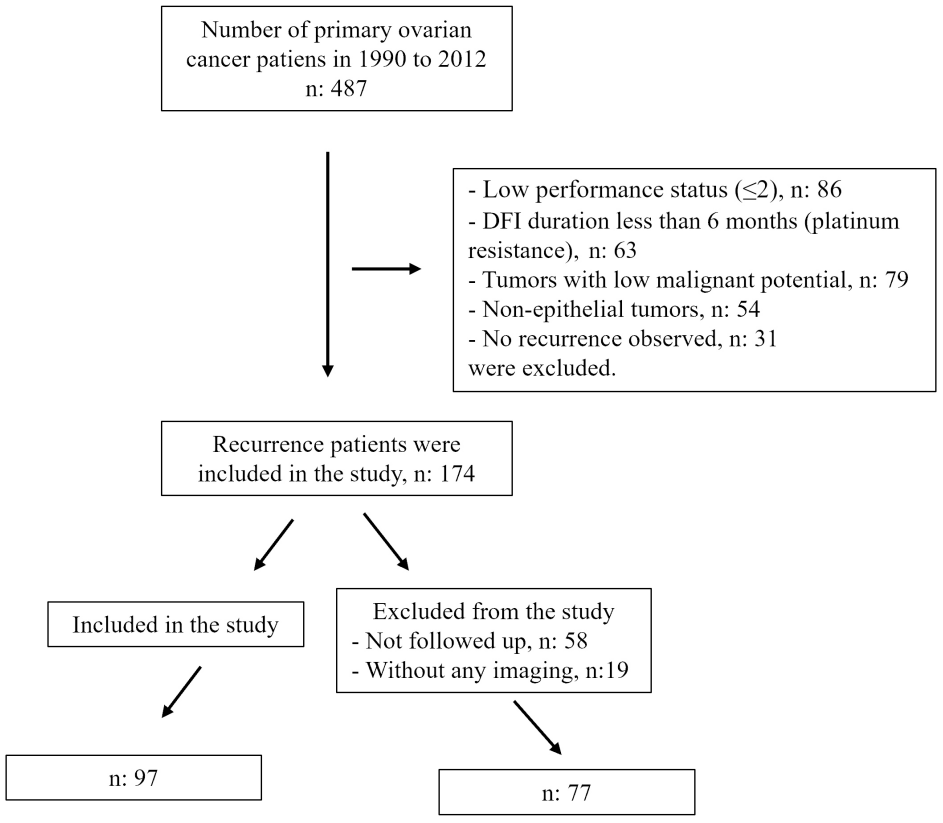

FIGURE 1. Flowchart of the inclusion criteria of patients in the study. DFI: disease-free interval.

epithelial ovarian cancer after completing primary treatment (primary surgery and adjuvant chemotherapy) and patients with a DFI of more than 6 months (that is, patients with a positive response to platinum-based chemotherapy) were included in the study. Patients with poor ECOG-PS (≤2), patients with a DFI of less than 6 months (that is, patients resistant to platinum-based chemotherapy), low malignancy potential, nonepithelial ovarian cancer, borderline ovarian tumours, second primary tumour, patients who received neoadjuvant chemotherapy and patients who were pregnant while experiencing ovarian cancer were excluded from the study. Additionally, 16 patients with missing FIGO staging data and three patients with missing residual tumour size data were excluded from the study. In the end, the study sample consisted of 97 patients.

The most used adjuvant chemotherapy protocol following primary surgery consisted of 3–6 cycles of paclitaxel (175 mg/m^2) and carboplatin (5–6 area under the curve (AUC), intravenous (IV)) administered every three weeks. Chemotherapy regimens included platinum-based treatments (cisplatin (75 mg/m^2), carboplatin (5–6 AUC, IV)), taxanes (paclitaxel (175 mg/m^2) and docetaxel (60–75 mg/m^2)). In platinum-resistant cases, nonplatinum and nontaxane regimens, such as cyclophosphamide (50 mg/m^2) and liposomal doxorubicin (40 mg/m^2), were administered for 2–6 cycles every three weeks.

Statistical analyses of the data were performed using SPSS Statistics 17.0 (Statistical Package for the Social Sciences for Windows, Version 17.0, SPSS Inc., Chicago, IL, USA, 2008). Descriptive statistics were used to express the results of the statistical analyses. For continuous variables, mean ± standard deviation values or median and minimum and maximum values according to whether they conform to normal distribution were used, and for categorical variables, numbers and percentages were used. Differences between independent groups of categorical variables were compared using chi-square tests and McNemar-Bowker tests in dependent groups. Survival analyses were performed using the Kaplan-Meier method. Survival analysis was performed for factors found to be statistically significant in the univariate analysis. A Type I error rate of 5% was taken as the basis for all tests, and all were two-tailed.

3. Results

3.1 Demographic and tumour characteristics of the sample

A total of 97 patients who underwent SCS for recurrent epithelial ovarian cancer were evaluated in this study. The median age of the sample was 55.5 years (range: 31–78). The histological analysis of the tumours revealed that 78.3% of the patients had serous, 7.2% had endometrioid, 4.1% had mucinous, 1.03% had clear cell and 9.3% had an undifferentiated type of ovarian cancer.

3.2 Primary staging surgery outcomes

An analysis of the residual tumour size after primary staging surgery revealed that 70.1% (n = 68) of the patients had a residual tumour size smaller than 1 cm, 26.8% (n = 26) had a residual tumour size larger than 1 cm and no data could be obtained from 3 (0.031%) patients. Maximum debulking was achieved in 48.5% (n = 47) of the patients, leaving no visible tumours behind.

The median and mean preoperative CA 125 levels of 70 patients with available data were 825 (range: 16–7702) U/mL and 378 ± 912.1 U/mL, respectively. Of these 70 patients with available data, 14.3% (n = 10) had CA 125 levels below 70 U/mL, 34.2% (n = 24) between 71 and 350 U/mL, and 51.5% (n = 36) above 350 U/mL. Consequently, it was determined that the majority (at least 75%) of the patients had stage III/IV disease, and approximately 8% (n = 8) had stage I/II disease.

Almost all patients were given chemotherapy following primary staging and recurrence surgeries. The majority (71.1%) of these patients received platinum/taxane-based primary treatment, and approximately 23% received second-line treatment before recurrence. Approximately 44.3% (n = 43) of the patients received platinum/taxane-based chemotherapy after SCS.

3.3 Secondary cytoreductive surgery outcomes

All patients included in the study underwent SCS for recurrence. The median and mean preoperative CA 125 levels of 49 patients with available data were 474 (range: 6–5678) U/mL and 112 U/mL, respectively. Of these 49 patients with available data, 42.9% (n = 21) had CA 125 levels below 70 U/mL, 36.7% (n = 18) between 71 and 350 U/mL and 20.4% (n = 10) above 350 U/mL.

Ascites was detected in 27.8% (n = 27) of 97 patients at the time of recurrence. In terms of intraoperative involvement, the vaginal cuff and rectosigmoid regions were the major sites of involvement. In terms of the number of recurrence sites, 52.5% (n = 51) of the patients had recurrence at a single site, while the remaining patients had recurrence at multiple sites, with the pelvic region being the most common (60.8%) site of recurrence (Table 1).

The most performed procedures during SCS were pelvic–para-aortic lymph node recurrence excision (21.6%) and rectosigmoid resection and colostomy/end-to-end anastomosis (20.6%), followed by pelvic tumour excision (13.4%), ileal resection and end-to-end anastomosis (13.4%), splenectomy (13.4%) and residual omentectomy (9.2%). Upper abdominal surgical procedures were among the most performed procedures during recurrence. Other recurrent surgeries included splenectomy, hepatic resection or mass excision (13.4%), diaphragmatic stripping or mass excision (9.2%), vaginal cuff mass excision (6.2%) and partial cystectomy and/or ureteroneocystostomy (6.2%). Implant excision/ablation from the intestinal surface, bladder, peritoneum, and cholecystectomy were also performed in decreasing order of frequency (Table 2).

Patients were operated on using SCS with a view to removing all visible areas of recurrence. Maximum debulking was achieved in approximately 65% (n = 63) of the cases, while the remaining (n = 34) patients were left with visible tumours. Of these 34 patients, 22 (22.6%) had tumours over 1 cm and 12 (12.3%) had tumours below 1 cm (0.1–1 cm). The mortality

TABLE 1. Clinical outcomes and procedures in cytoreductive surgery for ovarian cancer patients.

Characteristic	Cytoreductive Surgery	
	Number (N: 97)	Percentage (%)
Histological type:		
- Serous	76	78.3
- Endometrioid	7	7.2
- Mucinous	4	4.1
- Clear cell	1	1.1
- Undifferentiated	9	9.3
Primary surgical operation:		
- TAH + BSO + BPPLND + omentectomy	97	100.0
- Appendectomy	34	35.0
- Excision of the implant from the bowel surface	9	9.3
- Rectosigmoid colon resection + anastomosis	9	9.3
- Implant excision from the peritoneal surface	5	5.2
- Ileum resection + anastomosis	7	7.2
- Rectosigmoid colon resection + ostomy	5	5.2
- Splenectomy	4	4.1
- Cholecystectomy	4	4.1
- Liver resection/implant excision	3	3.1
- Umbilicus excision	2	2.1
- Diaphragm stripping	2	2.1
Residual tumour size:		
- No residue	47	48.5
- 0.1–1 cm	21	21.6
- 1 cm or above	26	26.8
- Missing data	3	3.1
FIGO stage at first diagnosis:		
- I	2	2.0
- II	6	6.1
- III	66	68.1
- IV	7	7.2
- Missing data	16	16.5
Previous first-line therapy:		
- Platinum + taxane	69	71.1
- Platinum + nontaxane	28	28.9
Previous second-line therapy:		
- Platinum + taxane	13	13.2
- Platinum + nontaxane	4	4.1
- Non-platinum	5	5.2
After secondary cytoreductive surgery:		
- Platinum + taxane	61	62.8
- Platinum + nontaxane	36	37.2
Site of relapse:		
- Pelvis	59	60.8
- Mid-abdomen (above pelvis)	37	38.1
- Upper abdomen	33	34.0

TAH: Total abdominal hysterectomy; BSO: Bilateral salpingo-oophorectomy; BPPLND: Bilateral pelvic and para-aortic lymph node dissection; FIGO: International Federation of Gynecology and Obstetrics. This table summarises the clinical outcomes and procedures of cytoreductive surgery for 97 ovarian cancer patients, detailing histological types, primary surgical operations performed, residual tumour sizes, FIGO stage at diagnosis, previous therapies, and site of relapse post-surgery.

TABLE 2. Surgical interventions and outcomes in secondary cytoreductive surgery for recurrent ovarian cancer.

Surgical Procedures	Number (n)	%
Pelvic and para-aortic lymph node recurrence excision	21	21.60
Pelvic nodular mass excision	13	13.40
Ileum resection and end-to-end anastomosis	13	13.40
Splenectomy	13	13.40
Rectosigmoid resection and colostomy	12	12.40
Rectosigmoid resection and end-to-end anastomosis	8	8.20
Residual omentectomy	9	9.20
Diaphragm stripping/mass excision	9	9.20
Pelvic peritonectomy/implant excision	7	7.20
Hepatic resection	7	7.20
Hepatic mass resection	6	6.20
Mass excision from vaginal cuff	6	6.20
Partial cystectomy and/or ureteroneocystostomy	6	6.20
Tumour excision from the intestinal surface	6	6.20
Tumour excision through the bladder	6	6.20
Cholecystectomy	3	3.09
Appendectomy	3	3.09
Abdominal wall mass excision	3	3.09
Umbilicus excision	3	3.09
Inguinal lymph node excision	2	2.06
Posterior exenteration	2	2.06
Mass excision from the pancreas	2	2.06
Partial gastrectomy	2	2.06
Left hemicolectomy and sigmoidotransversostomy	1	1.03
Ileum resection and ileostomy	1	1.03
Vaginectomy	1	1.03
Mass excision from fascia scar	1	1.03
Right hemicolectomy, distal gastrectomy, ileotransversostomy, and gastroduodenostomy	1	1.03

This table presents the range of surgical procedures performed on patients undergoing secondary cytoreductive surgery for recurrent ovarian cancer. Key abbreviations include n: number of procedures; %: percentage of the total procedures; lymph node excision: removal of lymph nodes due to recurrence; mass excision: surgical removal of tumour masses; resection and anastomosis: cutting out a section of an organ or tissue and joining the ends; splenectomy: removal of the spleen; colostomy: creation of an opening from the colon to the surface of the abdomen; omentectomy: removal of the omentum; peritonectomy: removal of part or all of the peritoneum; hepatic resection: liver surgery; cystectomy: removal of the urinary bladder; ureteroneocystostomy: surgical attachment of a ureter to the bladder; gastrectomy: removal of part or all of the stomach; hemicolectomy: removal of one side of the colon; gastroduodenostomy: surgical formation of a direct connection between the stomach and the duodenum. Note: A total of 97 patients underwent secondary cytoreductive surgery. Since some patients underwent multiple procedures, it is not appropriate to calculate the overall total and percentage. Therefore, it is more appropriate to present the number and percentage of each individual procedure performed on the patients separately.

risk was the lowest in the group with maximum debulking, while it was statistically significantly higher in the group where the tumour was larger than 1 cm (45% *vs.* 66.7%, *p*: 0.017).

In 97 patients with epithelial ovarian cancer who had recurrence after primary surgery, residual tumour tissue sizes (no residue, 0.1–1 cm and more than 1 cm) remaining in the recurrence areas during secondary cytoreduction surgery were matched with the recurrence sites, number of recurrences, presence of ascites, FIGO stage, primary chemotherapy regimens, and residual tumour sizes remaining after primary surgery by McNemar's test, since it is the most important criterion for recurrence (Table 3).

Complete resection was achieved in 55.6% (n = 15) of 27 patients with ascites before SCS and in 68.6% (n = 48) of 70 patients without ascites. The rate of patients with complete resection was higher, albeit not significantly, in

TABLE 3. Association between residual tumour size, recurrence sites, and treatment outcomes in ovarian cancer patients.

	Residual Tumour (Recurrence)						Total		
	>1 cm		0.1–1 cm		No Residue				
	n	%	n	%	n	%	N	%	*p*-Value
Recurrence sites									
Pelvic	7	31.8%	5	41.7%	26	41.3%	38	39.2%	
Extrapelvic	8	36.4%	3	25.0%	26	41.3%	37	38.1%	NA
Pelvic + Extrapelvic	7	31.8%	4	33.3%	11	17.5%	22	22.7%	
Number of recurrence sites									
Plural	17	77.3%	6	50.0%	23	36.5%	46	47.4%	0.004
Only	5	22.7%	6	50.0%	40	63.5%	51	52.6%	
Ascites in recurrence									
(+)	8	36.4%	4	33.3%	15	23.8%	27	27.8%	0.476
(−)	14	63.6%	8	66.7%	48	76.2%	70	72.2%	
Stage (FIGO)									
≥3C	13	72.2%	8	80.0%	28	52.8%	49	60.5%	0.140
<3C	5	27.8%	2	20.0%	25	47.2%	32	39.5%	
Primary chemotherapy									
P/T	9	45.0%	7	53.8%	53	82.8%	69	71.1%	0.002
P/TD	11	55.0%	6	46.2%	11	17.2%	28	28.9%	
Residual size after primary surgery									
>1 cm	9	45.0%	6	54.5%	11	17.5%	26	27.7%	
0.1–1 cm	8	40.0%	3	27.3%	10	15.9%	21	22.3%	0.017*
No Residue	3	15.0%	2	18.2%	42	66.7%	47	50.0%	

*This table provides a detailed analysis of ovarian cancer recurrence based on residual tumour size post-surgery, recurrence site(s), presence of ascites at recurrence, FIGO stage at diagnosis, residual size after primary surgery, and type of primary chemotherapy received. Key abbreviations include FIGO: International Federation of Gynecology and Obstetrics, indicating the stage of cancer; P/T: Platinum plus taxane, a common chemotherapy regimen; P/TD: Platinum plus nontaxane drug, another chemotherapy regimen. The data are presented to understand the patterns of recurrence and the impact of initial treatment choices on recurrence characteristics. NA: Not Applicable. *McNemar-Bowker test.*

patients without ascites before SCS than in patients with ascites ($p = 0.476$). There was a significant difference in the presence of macroscopic residue between the patient groups created according to FIGO staging. Accordingly, while no macroscopic residue was detected after SCS in any of the 8 patients with FIGO stage IIIA and below disease, the macroscopic residue was detected in 7 (29.1%) of the 24 patients with FIGO stage IIIA/IIIB disease (R: 0.1–1 cm = 2, R >1 cm = 5) and 42.8% (n = 21) (R: 0.1–1 cm = 8, R >1 cm = 13) of 49 cases with FIGO stage IIIC/IV disease ($p = 0.140$, odds ratio (OR): 1.59, 95% CI: 1.02–2.48) (Table 3).

An analysis of patients with single or multiple recurrence sites evaluated intraoperatively during SCS revealed that maximum debulking was achieved in 78.4% (n = 40) of 51 (52.5%) patients with single-site involvement compared to only 50% (n = 23) of 46 (47.5%) patients with multiple-site involvement ($p = 0.004$).

In about 47.4% (n = 46) of the cases, the recurrence site was outside the pelvis. Of these sites, 38.1% were in the middle abdomen and 34% were in the upper abdominal region. There was no significant correlation between the location of the recurrence site and the complete resection. Since the rates of pelvic (local), extrapelvic (distant), and pelvic + extrapelvic (local + distant) recurrence cases were close to each other, statistical analysis revealed no significant difference ($p \geq 0.005$) (Tables 3 and 4).

Following the primary surgery, approximately 71% of the patients received platinum- and taxane-based chemotherapy, while the remaining 29% received nonplatinum- and nontaxane-based chemotherapy (liposomal doxorubicin + cyclophosphamide). The rate of patients with complete resection in SCS was 76.8% (n = 49) in patients receiving platinum- and taxane-based chemotherapy, compared to 39.3% (n = 11) in patients receiving nonplatinum- and nontaxane-based chemotherapy. Accordingly, the rate of patients with complete resection was significantly higher in the patient group that received platinum- and taxane-based chemotherapy ($p = 0.002$) (Table 4).

TABLE 4. Sites of recurrence before secondary cytoreduction.

	N	%
Locally		
Pelvis	59	60.80
Middle abdomen	37	38.10
Upper abdomen	33	34.00
Specific areas		
Pelvic or para-aortic lymph node	21	21.60
Rectosigmoid region	20	20.60
Small intestine	17	17.50
Vaginal cuff/Douglas	15	15.40
Liver	13	13.40
Pelvic peritoneum	11	11.30
Bladder	10	10.30
Diaphragm	9	9.20
Spleen	4	4.10
Abdominal wall	3	3.09
Umbilical region	3	3.09
Stomach	2	2.06
Pancreas	2	2.06
Inguinal lymph nodes	2	2.06

Note: The pelvic region is defined as the area extending from the umbilicus inferiorly, involving the pelvic bone, both ovaries, both tubules, uterus, vagina and the anal region. It also extends to the descending colon, bladder, both ureters extending from the promontorium and the soft tissue, lymph nodes and peritoneum within these regions. The extrapelvic area extends beyond the pelvic region and includes the small intestines, appendix, ascending colon, transverse colon, liver, spleen, both kidneys, and ureteral tracts, which extend from the umbilicus to the promontorium. Additionally, this region contains the mesentery of the intestines, the diaphragm, and all soft tissue, lymph nodes, and peritoneal areas extending from the pelvic region to the umbilicus.

3.4 Prognostic variables related to ROC surgery

Of the factors investigated for their prognostic value in predicting complete resection in SCS, disease stage ($p = 0.04$), number of recurrence sites ($p = 0.003$), residual disease after primary surgery ($p < 0.001$), primary chemotherapy ($p = 0.002$), and DFI ($p = 0.001$) were found to be significantly associated with residual size after SCS, whereas the site of recurrence ($p = 0.244$), presence of ascites during recurrence ($p = 0.231$) and CA 125 level ($p = 0.154$) were not (Table 5).

The most common aetiologies of postoperative residual disease after recurrence surgery that were found to have a significant impact on the surgical technique were multiple involvements, diffuse tumour involvement in the intestinal mesentery, carcinomatous disease, diaphragmatic involvement and tumours associated with major vascular structures. The median DFI was 24.5 months, while the median duration of complete resection was 30.1 months (95% CI: 21.09–39.13). The log-rank test revealed that the DFI cutoff value of 14 months significantly predicted patients with complete resection (OR: 2.18, 95% CI: 1.24–3.83, $p = 0.001$). Accordingly, survival was significantly increased in patients with a DFI >14 months (OR: 0.395, 95% CI: 0.22–0.70, $p = 0.002$) (Fig. 2).

3.5 Survival-related variables

The median DFI following primary treatment was 24.5 months (95% CI: 18.2–22.7), while the median OS was 105 months (95% CI: 85.5–125.9). Approximately 52% of the patients died after recurrence. The 5-year survival rate was approximately 35% (n = 34). The development of residual disease following SCS emerged as a critical prognostic factor for OS. The median OS was approximately 143 months in patients with complete resection, compared to 42.2 months and 33.7 months in those with 0.1–1 cm and >1 cm residual tumours, respectively ($p < 0.001$). OS did not significantly differ between the groups with residual disease. Achieving maximum debulking emerged as a stronger predictor of disease-free survival ($p = 0.092$).

The optimal cytoreduction rate was 100% in patients with FIGO stage below IIIA disease. The median DFI and OS in patients with FIGO stages below IIIA, IIIA/IIIB, and IIIC/IV disease were 39.1 and 184 months, 21.5 and 94 months, and 20.9 and 93.4 months, respectively ($p = 0.052$). Conversely, the mortality risk increased approximately fourfold in patients with FIGO stage IIIA/IIIB disease and fivefold in FIGO stage IIIC/IV disease compared to patients with an FIGO stage below IIIA ($p = 0.061$ and $p = 0.028$, respectively) (Fig. 3).

Chemotherapy was administered to almost all patients following SCS. The median OS was 184.5 months for those who underwent platinum- and taxane-based chemotherapy (63%), while it was 94 months for those who received platinum- and non-taxane-based chemotherapy ($p = 0.001$). The mortality risk increased 1.7-fold in patients who received platinum- and nontaxane-based chemotherapy compared to those who received platinum- and taxane-based chemotherapy (95% CI: 0.88–3.46, $p = 0.04$).

Although the presence of ascites during recurrence was not found to be a significant variable in predicting complete resection, the median OS in patients with ascites was significantly shorter (114.5 months *vs.* 72.6 months) ($p = 0.059$), and the mortality risk was significantly (1.7 times) higher (95% CI: 0.97–3.22) compared to that in patients without ascites.

The major complication rate increased from 11.4% in primary surgery to 18.5% in SCS. Bowel resection, ileostomy, and colostomy were more frequently required in the SCS. The most common (21.6%) intraoperative complication during SCS was haemorrhage requiring erythrocyte transfusion. Other intraoperative complications included bladder injury (11.3%, n = 11), bowel injury (8.2%, n = 8) and large vessel injury (3.1%, n = 3). None of the 97 patients died intraoperatively, and all were monitored in the intensive care unit (ICU) for the first 24 hours. The mean length of stay in the ICU among the 31 patients who required intensive care for more than 24 h was 2.4 (range: 1–11) days.

The analysis of the short- and long-term complications re-

TABLE 5. Risk factors for recurrence in ovarian cancer: statistical analysis of stage, ascites volume, CA 125 levels, and surgical outcomes.

	Number (n)	OR	95% CI	*p*-Value
Stage (FIGO)				
<IIIA	8	-	-	
IIIA/IIIB	24	1.00	-	0.040
IIIC/IV	49	1.59	1.02–2.48	
Preoperative ascites in recurrence (mL)				
(−)	70	1.00		0.231
(+)	27	1.74	0.70–4.30	
CA 125 (U/mL)				
<70	21	-	-	
71–350	18			0.154
>350	10			
Recurrence sites				
Pelvic	51	-	-	0.244
Extrapelvic	46	-	-	
Number of recurrence sites				
Single	51	1.00	-	0.003
Multiple	46	3.63	1.50–8.79	
Residual size after primary surgery				
0 cm	47	1.00	-	
0.1–1 cm	21	9.24	2.61–32.60	<0.001
>1 cm	26	11.45	3.41–38.40	
Disease-free interval (mon)				
<14	50	1.00	-	0.001
>14	47	2.18	1.24–3.83	

This table presents a comprehensive analysis of potential risk factors for recurrence in ovarian cancer patients, including FIGO stage, preoperative ascites volume, CA 125 level, location and number of recurrence sites, residual tumour size after primary surgery and disease-free interval. "OR" stands for odds ratio, indicating the likelihood of recurrence under various conditions compared to a reference group; "95% CI" refers to the 95% confidence interval, providing a range within which the true value of the OR is expected to fall; "p-value" indicates the statistical significance of the findings, with values less than 0.05 considered statistically significant. "FIGO" refers to the International Federation of Gynecology and Obstetrics staging system for ovarian cancer. CA: cancer antigen.

vealed no deaths within the first 24 hours postoperatively. The most common (28.8%) complication encountered in this period was haemorrhage requiring erythrocyte transfusion, as in the intraoperative period. The most common complication within the first postoperative month was ileus, while lymphocele (17.5%, n = 17) and ileus (11.3%, n = 11) were the most common complications encountered during the first postoperative year. Postoperative fever was observed in 12.3% of the cases. In approximately half of these cases, fever occurred within the first 48 hours without a detectable source of infection and resolved without complications within an average of two days. In the remaining cases, fever developed secondary to urinary infection, lung infection, abscess or deep vein thrombosis. Five patients required surgery for pain due to lymphocele, and two patients were operated on for hydronephrosis. Four patients received broad-spectrum antibiotics for fever. One of these patients died in the fourth month, possibly due to antibiotic toxicity-associated renal dysfunction. Among the seven patients who developed acute kidney failure within the first week, none died. The earliest cases of intra-abdominal abscesses were identified on the 12th day following surgery. Reoperation was required in almost all patients. There were no mortalities in the early period. However, two patients died in the 5th and 7th months, possibly due to abscess complications. Of the seven patients treated medically for ileus, four required reoperations. Three of these patients required ileostomies, and one patient, who was suffering from an anastomotic leak and subsequent deterioration, died. Two patients developed short bowel syndrome and died from nutritional deficiencies at the 12th and 17th weeks. Of the patients with wound infections, three required debridement and secondary suturing, while another three were referred for plastic surgery. Lastly,

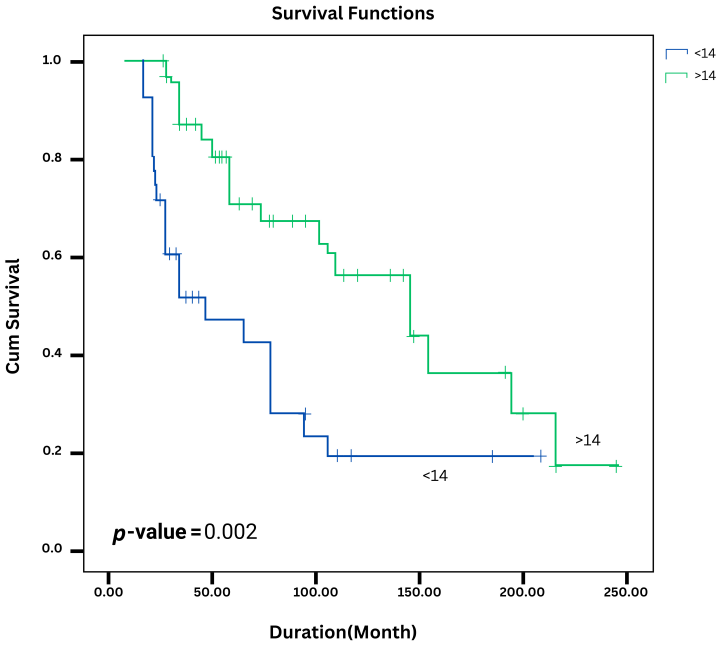

FIGURE 2. Relationship between DFI duration and OS.

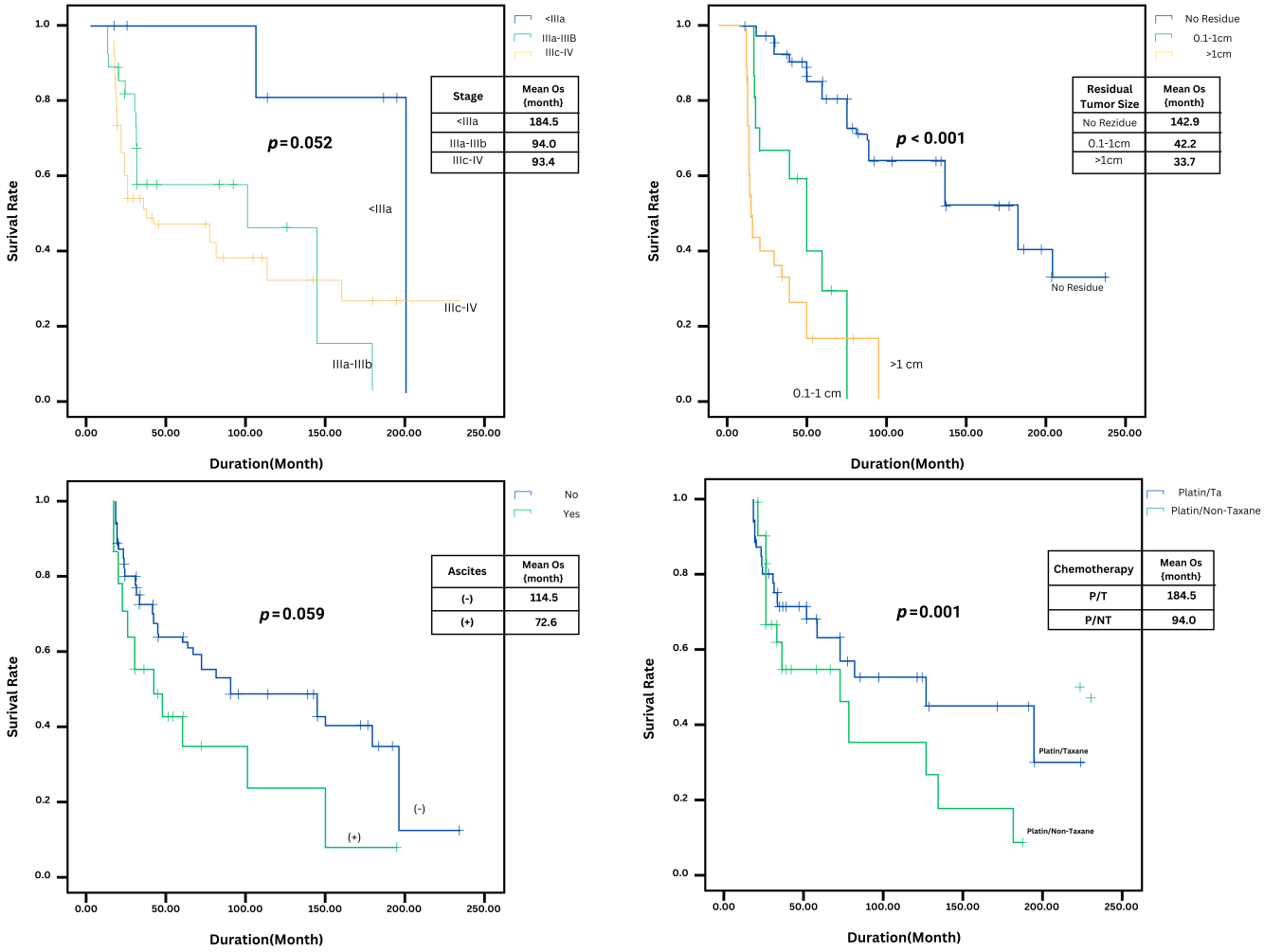

FIGURE 3. The impact of residual tumor size, FIGO stage, chemotherapy regimens used and the presence of ascites on mean survival in recurrent ovarian cancer. OS: Overall survival; P/T: Platinum plus taxane, a common chemotherapy regimen; P/TD: Platinum plus nontaxane drug, another chemotherapy regimen.

of the two patients with pulmonary thromboembolism, one was successfully treated with low-molecular-weight heparin, and follow-up data were not available for the other. In brief, the major complication rate increased from 11.4% in primary surgery to 18.5% in SCS. Compared to primary surgery, SCS requires more bowel resections, ileostomies and colostomies (Table 6).

4. Discussion

Our analyses identified platinum/taxane-based primary chemotherapy, single-site recurrence, complete resection at primary surgery, and DFI >14 months as the significant prognostic factors for complete resection, ascites <1000 mL at primary diagnosis, platinum/taxane-based chemotherapy, DFI, and complete surgical resection as the significant prognostic factors for survival in ROC.

In most advanced cases of ovarian cancer, recurrence is a common occurrence despite the significant progress made in primary treatment. Research indicates that 22% of cases experience recurrence within 6 months, with the majority of platinum-sensitive cases seeing a recurrence after the 6-month mark. While there is a lack of clear guidelines on the surgical management of recurrent ovarian cancer, an expanding body of research has highlighted the advantages of secondary cytoreductive surgery in specific cases of recurrent ovarian cancer. According to a meta-analysis of 6885 patients with advanced ovarian cancer, maximal cytoreductive surgery was identified as the most efficacious treatment strategy for enhancing survival outcomes [17]. Along these lines, in a prospective study conducted by Eisenkop *et al*. [18], complete SCS performed on 83% of patients with first-time ROC between 1990 and 1994 resulted in significant improvements in the prognosis of symptomatic patients and a significant increase in survival.

In research involving patients from the ROC who received SCS treatment, Tian *et al*. [19] discovered that individuals with a DFI exceeding 24 months exhibited markedly higher rates of success following complete tumor removal (R0, 48.9%) and when dealing with smaller tumors (0.1–1 cm, R1, 47.8%) as opposed to cases involving residual or unmeasurable tumors (>1 cm, R2, 21.8%). However, several recent studies have reported that there is no significant difference in survival between residual tumour sizes of 0.1–1 cm or >1 cm. In comparison, we found a median OS of 142.9, 42.2, and 33.7 months in the residual tumour-free, residual tumour size of 0.1–1 cm, and residual tumour size >1 cm groups, respectively (p = 0.001). However, although we found a significant difference between the complete resection group (33.3%) and residual tumour groups in terms of the rate of patients with a DFI >24 months (p = 0.001), we did not find any difference between the residual groups (8.2% *vs.* 9%) (p = 0.33). Complete removal of any visible remaining tumours is a crucial determinant of patient prognosis. Specifically, overall survival rates showed a significant increase in individuals who underwent surgical cytoreduction with thorough debulking (≤1 cm) as opposed to those with incomplete debulking (16 to 61 months versus 8 to 27 months) [8]. Generally, patients with a prolonged recurrence period (12–36 months) after completion of chemotherapy benefit more from SCS. For instance, a notable increase in OS was observed in instances where the time gap between diagnosis and recurrence exceeded 18 months, as compared to cases with shorter intervals (49 months versus 3 months) [20]. According to the same study, it was also mentioned that patients who showed recurrence in just one or two areas in

TABLE 6. Intraoperative and postoperative complication rates in secondary cytoreductive surgery.

	Intraoperative	Postoperative
	N (%)	N (%)
Need for erythrocyte transfusion	21 (21.6)	28 (28.8)
Bladder injury	11 (11.3)	-
Intestinal injury	8 (8.2)	-
Major vascular injury	3 (3.1)	-
Lymphocele	-	17 (17.5)
Ileus	-	11 (11.3)
Post-operative fever	-	12 (12.3)
Incision site infection	-	11 (11.3)
Acute renal failure	-	7 (7.2)
Intra-abdominal abscess	-	4 (4.1)
Pulmonary thromboembolism	-	5 (5.1)
Deep vein thrombosis	-	3 (3.1)
Hydro-ureteronephrosis	-	3 (3.1)
Death	-	-

The incidence of major complications during or following secondary cytoreduction surgery was 18.5%.

the preoperative radiologic assessment tended to gain greater benefits from the treatment. In comparison, we found that the rate of patients with complete resection was significantly higher in patients with a DFI >14 months (OR: 2.18, 95% CI: 1.24–3.83, $p = 0.001$).

In a meta-analysis of 40 studies, Bristow *et al*. [21] reported a significant increase in OS in 2019 patients who underwent SCS. Various studies have identified DFI, the number of recurrent sites, and the feasibility of complete resection as key factors in determining patient eligibility for SCS, based on their demonstrated correlation with survival rates [10]. In comparison, we found the median DFI to be 24.5 months (CI: 18.2–30.7) and the OS to be significantly increased in patients with a DFI >14 months (OR: 0.395, 95% CI: 0.22–0.70, $p = 0.002$).

Patients eligible for repeat surgery are reportedly those with localised recurrent disease, a DFI >6 months and adequate ECOG-PS. Detecting persistent cancer in ovarian cancer patients poses a significant challenge, largely attributable to its correlation with peritoneal carcinomatosis. Recurrence occurs in about 70–80% of cases of advanced ovarian cancer following initial treatment, with a majority of these individuals succumbing to the disease after experiencing a second recurrence, despite receiving effective therapy [19].

Preoperative evaluation for optimal cytoreduction is very complicated. In the DEScriptive Evaluation of Preoperative Selection C(K)riteria for OPerability in recurrent OVARian cancer (DESKTOP OVAR) study (n = 276), the criteria for successful surgery were defined as good ECOG-PS, early FIGO stage or no residual tumour after surgery and the absence of ascites [22]. Successful surgical resection was achieved in 79% of the patients who fulfilled the criteria. Diagnostic laparoscopy is a valuable tool for identifying patients for optimal cytoreduction. Accordingly, patients with minimal pathology can have an intraperitoneal catheter inserted and receive chemotherapy.

At the second International Ovarian Cancer Consensus Conference 1998, the criteria to identify the most suitable candidates for SCS were determined as follows: (i) DFI >12 months, (ii) positive response to first-line therapy, (iii) potential for complete resectability based on preoperative evaluation, (iv) good ECOG-PS, (v) relatively young age, (vi) amount of ascites ≤500 mL, (vii) CA 125 levels less than 10 times the upper limit, (viii) absence of peritoneal carcinosis on radiological imaging, (ix) and presence of local recurrent lesions [23]. The rate of complete resection after SCS was significantly higher in patients who met these criteria compared to those who did not.

Keeping the residual lesion size below 1 cm after primary surgical debulking was first introduced as an objective in 1990. However, recent analyses have shown that macroscopically complete resection is associated with a significantly better prognosis in advanced-stage patients. Similarly, a number of case series reported that complete surgical resection is an independent prognostic factor for OS in the ROC [24]. The AGO DESKTOP OVAR I (Arbeitsgemeinschaft Gynäkologische Onkologie Descriptive Evaluation of preoperative Selection of (K)Criteria for OPerability in recurrent OVARian cancer) study, the most comprehensive of these case series, reported that complete resection was the most significant prognostic factor for SCS [20]. In the AGO DESKTOP I study, the median OS was reported as 45 months in patients who underwent complete debulking, compared to 19 months in patients with incomplete resection. In addition, they reported good ECOG-PS, *i.e.*, "0," macroscopic complete resection at the primary surgery, and amount of ascites ≤500 mL as independent factors for complete resection. The more recent AGO DESKTOP OVAR III study also featured a prospective evaluation of the prognostic value of the AGO scoring system.

Following the development of criteria that can be used to identify the residual tumour size and patients suitable for the surgical treatment of platinum-sensitive ROC, SCS started to be included in the guidelines as a treatment method. In parallel, prospective randomised studies were conducted worldwide, particularly in the centres that publish major guidelines, to address the question of whether surgery or chemotherapy is better for patients eligible for SCS.

The Gynecologic Oncology Group (GOG) 0213 study, the second study of its kind, involved 485 platinum-sensitive ROC patients who were considered suitable for surgery. These patients had a median Disease-Free Interval (DFI) of 20.4 months. Rather than applying a specific scoring system to determine eligibility for surgery, the decision was made by the gynaecologic oncologists carrying out the procedure based on a thorough evaluation of imaging and physical examination data. Among the 225 patients who underwent surgery, 150 (68%) successfully underwent complete resection. The incidence of intraoperative morbidity was 9%, and there was one postoperative fatality. Chemotherapy was administered for a median duration of 40 (28–51) and 7 (4–11) days in the surgical and nonsurgical groups, respectively. As a chemotherapy regimen, platinum-based therapy combined with paclitaxel was preferred in 69% (337/485) of the patients. Additionally, bevacizumab was used in 84% (408/485) of the patients, both as adjunctive and as maintenance therapy. Consequently, OS and DFI were found to be longer in the surgical group than in the nonsurgical group, but not significantly. Three main critiques have been raised concerning this research. Initially, it is acknowledged that ensuring impartiality in patient selection for surgery poses difficulties. The gynaecologic oncologists predominantly opted to operate on patients with recurrent tumors confined to one or two locations for comprehensive removal. Moreover, the study's inclusion of platinum-sensitive patients (average DFI: 20.4 months) could have potentially masked the impact of the surgical intervention. Second, bevacizumab, which has been proven to have an impact on progression-free survival (PFS) and OS, was used in 84% of cases. Third, the actual OS was approximately three times longer than the one they predicted would occur when the study was designed. The exact reason why such a large difference between predicted OS and actual OS occurred is still unknown, but it is thought to be related to improvements in clinical practice and the use of more effective therapies, *e.g.*, *poly* (*ADP-ribose*) *polymerase* (*PARP*) inhibitors in *BReast CAncer gene 1* (*BRCA1*)- or *BReast CAncer gene 2* (*BRCA2*)-positive patients. Moreover, prolonged OS might have masked the effect of PFS. Given that the percentage of patients achieving complete cytoreduction in those with a positive AGO score

can exceed 78%, it was noted that the actual rate of complete cytoreduction (68%) fell below expectations due to the absence of utilization of a designated scoring system [25].

The second of these studies is the AGO DESKTOP OVAR III study, in which the effect of SCS on ROC was compared with the impact of chemotherapy in terms of OS. A total of 408 platinum-sensitive patients (≥6 months platinum-free period) with positive AGO scores with ovarian, tuba, or peritoneal cancer that recurred for the first time after primary treatment were included in the study. The AGO scoring system was used to assess complete respectability. The mean age of the sample was over 60 years. The platinum-free period was 12 months or more in 75% of the patients. Bevacizumab was used in 23% of the patients. The rate of patients in whom complete resection was achieved was 74.2%, which is closer to the target rate compared to 68% achieved in the GOG 213 study. The mean OS was significantly higher in the surgical group than in the nonsurgical group (53.7 months *vs.* 46 months, $p = 0.02$), as was DFI ($p < 0.001$). A subgroup analysis of the surgical group revealed that patients in whom complete resection was achieved had a longer OS. Approximately 50% of the patients with ROC who had a DFI over six months had a positive AGO score. Surgical procedures resulted in complete removal of tumors in 75% of patients who scored positively on AGO. Following SCS, those patients who underwent complete resection were found to have a survival rate exceeding 12 months. As a result, it is recommended that individuals with platinum-sensitive ROC, determined by AGO scores, imaging techniques, and specific patient and tumor traits, should be pinpointed for potential SCS and directed to specialized medical facilities as needed [26].

The third study in this category is the Shanghai Gynecologic Oncology Group Surgery or Chemotherapy in Recurrent Ovarian Cancer (SGOC SOC-1) trial, which aimed to evaluate the PFS and OS outcomes between SCS and chemotherapy for 357 patients with ROC. The patients included in the study had recurrent ovarian, tuba, or peritoneal cancer with a platinum-free period ≥6 months and an international model (iMODEL) score ≤4.7, and were evaluated using positron emission tomography-computed tomography (PET-CT) by two specialists to jointly decide whether complete resection could be achieved because of surgical treatment. The mean age (54 years) of the patients included in the SGOC SOC-1 study was younger than in other comparable studies. Preoperative imaging techniques were utilized to pinpoint the recurrence sites in patients, which were subsequently validated for accuracy during surgical procedures. These imaging modalities have shown efficacy in detecting widespread conditions effectively. Interestingly, patients initially diagnosed with localized diseases (1–3 sites) exhibited recurrences across a broader spectrum during surgical interventions. Moreover, the feasibility of achieving total resection declined with an increase in the distribution areas of the tumours. Nevertheless, successful complete cytoreductive surgery was feasible, even in cases of carcinomatosis. Complete resection was achieved in approximately 76% of the patients. The DFI was significantly more prolonged (5.5 months) in the R0 surgical group than in the nonsurgical group (17.4 months *vs.* 11.9 months, $p < 0.001$). As in comparable studies, the PFS was significantly more prolonged in patients with complete resection (R0). Moreover, the DFI in the surgical patient group with small residual tumours (R1) was also more prolonged, although not significantly, than in the nonsurgical group (12.6 months *vs.* 11.9 months, $p = 0.65$). In the group that underwent surgery, the OS was slightly longer, but not significantly, compared to the group that did not have surgery, with durations of 58.1 months and 53.9 months, respectively. The percentage of patients receiving bevacizumab was 1% [27].

The results of the three abovementioned large-scale prospective randomised studies show that the success rate of SCS depends on many variables, including the characteristics of the ROC patient (*e.g.*, age, ECOG-PS score, whether they are willing to accept surgical treatment), the characteristics of the disease (*e.g.*, DFI, whether complete resection was achieved after the first surgical treatment, the initial stage of diagnosis, the presence of ascites), and the characteristics of the centre where the surgery will be performed (*e.g.*, whether it is an experienced centre in this field, the competence of the surgeon and the presence of cooperation during the surgical intervention, and the availability of appropriate conditions for postoperative care and chemotherapy). Overall, the research indicates that SCS enhances the overall survival (OS) of patients with recurrent ovarian cancer (ROC), particularly when complete resection is possible. Likewise, our study revealed that the most influential predictor of survival among ROC patients receiving primary or recurrent surgery was the successful achievement of complete resection. We categorised the ROC patients undergoing surgical treatment into three groups based on the size of the residual tumour: R0 (complete resection, no visible tumour), R1 (small tumours: 0.1–1 cm), and R2 (residual tumour: >1 cm or unevaluable tumour). Accordingly, complete resection was achieved in 48.5% and 63% of the patients after primary and recurrence surgery, respectively. Furthermore, it is worth noting that achieving optimal cytoreduction, defined as a residual tumour size <1 cm, was observed in around 70% of patients following primary surgery and approximately 77% following recurrent surgery. This suggests that patients who have a small residual tumour after primary surgery, although present, are more inclined to undergo complete resection in secondary surgery due to their heightened chemosensitivity. Early recurrence (short DFI) is often associated with a poor response to chemotherapy, limiting the benefit of repeat cytoreduction. Therefore, we excluded patients with a DFI (platinum-resistant) of less than 6 months from our study.

In 2009, the National Comprehensive Cancer Network (NCCN) recommended that primary evaluation and debulking surgery should be performed by well-trained gynaecologic oncologists. SCS is often not the preferred initial treatment option for ROC, primarily because of the challenges associated with assessing recurrence and determining the appropriateness of SCS. Factors such as residual tumour thresholds and less-than-ideal results are closely connected. Therefore, the primary goal of surgical intervention for patients with ROC is the complete removal of all detectable lesions [28].

This study had several limitations, such as its retrospective design, relatively small sample size and selection bias.

In our study on recurrent ovarian cancer, data on factors such as patient age, the addition of genetic analysis to histopathological evaluations, familial genetic mutations, and the use of PARP inhibitors or bevacizumab in second-line treatments were missing. However, a review of the literature suggests that these factors may affect survival outcomes in recurrent ovarian cancer.

Furthermore, individual analyses were conducted on all cases based on factors such as FIGO stages, preoperative ascites levels, CA 125 levels, sites of recurrence, recurrence numbers, residual tumor sizes post-primary surgery, and durations of disease-free interval. However, due to missing data on FIGO stage in 16 cases, CA 125 levels in 48 cases, and residual tumor size after primary surgery in 3 cases, a multivariate analysis could not be carried out, highlighting the potential constraints of our study. These limitations were countered by excluding factors that could potentially affect survival from our analysis to ensure a homogeneous sample. For this purpose, individuals with a DFI less than 6 months, such as those who were responsive to platinum treatment and those with non-epithelial tumors who underwent neoadjuvant chemotherapy, were not considered in the research. Moreover, the profiles of initial surgery, chemotherapy, and subsequent surgery were quite similar across the participants in the study. Most of these patients received platinum-based chemotherapy as a primary and secondary therapy (76.2% and 81.5%, respectively).

In both our sample and the samples of relevant studies in the literature, patients who underwent SCS were relatively younger, had better ECOG-PS, and responded well to chemotherapy. Surgery and chemotherapy are used in combination in both primary and recurrent ROC patients. However, in ROC patients with poor response to chemotherapy, the surgical benefit will also be reduced, since recurrence will develop quite rapidly.

5. Conclusions

In conclusion, SCS is a safe procedure with low complication rates for platinum-sensitive epithelial ovarian cancer patients, significantly improving OS if optimal surgery can be achieved. Nevertheless, there is a need for further large-scale, prospective, multicentre studies and/or randomised trials targeting specific patient groups to fully assess the short- and long-term outcomes of SCS in ROC patients.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available upon request from the corresponding author.

AUTHOR CONTRIBUTIONS

GG—Conceptualisation; writing original draft; writing review and editing. CO—Methodology. KK—Validation. ST—Formal analysis. İY—Resources and designed the research study. BO—Visualisation. FO—Supervision and analysed the data. All authors have read and agreed to the published version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Gynecologic Oncology Unit of the Department of Obstetrics and Gynecology, Ankara University Faculty of Medicine ethics committee (date: 07 May 2012; approval #: 08-230-12). Data were collected retrospectively from hospital records and through telephone interviews. The patients provided written informed consent for the publication of anonymised data and any accompanying images, as specified in the Declaration of Helsinki.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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