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Secondary cytoreduction in recurrent ovarian cancer- experience from a tertiary care centre in India

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ABSTRACT

Introduction: Ovarian cancer is a disease that presents in advanced stage, due to the absence of any specific or overtly dramatic symptoms. The standard of care is primary debulking surgery, followed by chemotherapy. Ovarian cancer recurrence treatment is very challenging and there is always a debate between cytoreduction vs chemotherapy.

Methods: The electronic medical records of all patients who underwent secondary cytoreductive surgery for recurrent ovarian cancer between January 2011 and December 2019 were retrieved the patients with platinum sensitive recurrent ovarian cancer who underwent secondary cytoreductive surgery in our department during this time period were included.

Results: A total of 52 patients underwent secondary cytoreductive surgery for recurrent ovarian cancer during the study period. Median treatment free interval after primary treatment was 20 months (range 6–132). The secondary cytoreductive surgery was highly complex in 4(8 %) patients,19 (37 %) had intermediate surgical complexity score, 29 (55 %) had low surgical complexity score according to the Aletti complexity score. Secondary cytoreductive surgery was complete (no macroscopic residual disease) in 31(60 %); Optimal (R1) in 17 (33 %) and suboptimal in only 4 (7 %) of the patients. Out of the 52 patients,8 expired, 16 had a second recurrence, and 10 were lost to follow up over time.

Conclusion: Successful surgery is possible in well selected patients, which in turn can lead to a meaningful progression free and overall survival benefit. Meticulous individualisation of cases should be done keeping in mind the patient's performance status, prior treatment history & toxicity; distribution & extent of disease, and the patient's overall life goals.

1. Introduction

Ovarian cancer is one of the most lethal gynaecological malignancies with over 207,000 deaths every year globally. According to Globocan's 2022 projections, the number of women diagnosed with ovarian cancer is expected to rise by over 55 % to 503,448 by 2050 (World Ovarian Cancer Coalition, 2023; de Bree et al., 2022). It also remains one of the most challenging to manage due to its high recurrence rate and poor overall survival (de Bree et al., 2022).

The standard of care is primary cytoreductive surgery followed by chemotherapy. In cases of extensive disease, neoadjuvant chemotherapy followed by interval debulking surgery is a reasonable option. Despite advances in these primary strategies, almost 80 % of patients experience disease recurrence with almost 15 % even with Stage 1 (de Bree et al., 2022; Dood et al., 2018).

Secondary cytoreductive surgery, first described by Berek et al in 1983 is defined as surgical resection of recurrent disease after initial treatment (Berek et al., 1983). Though recurrent ovarian cancer had mainly been treated by systemic chemotherapy, secondary cytoreduction has been emerging as a potential therapeutic option to improve outcomes in selected patients (de Bree et al., 2022). Many small retrospective studies as well as randomized trials have supported the clinical benefit of secondary cytoreductive surgery (SCS) in cases of platinum-sensitive recurrent ovarian cancer and recorded improved survival benefits (Munkarah et al., 2001; Eisenkop et al., 2000; Tay et al., 2002; Zang et al., 2004; Gronlund et al., 2005; Onda et al., 2005; Chi et al., 2006; Oksefjell et al., 2009; Du Bois et al., 2017; Harter et al., 2006; Harter et al., 2011). There have also been reports about the surging role

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of hyperthermic intraperitoneal chemotherapy (HIPEC) in the setting of secondary cytoreduction in recurrent ovarian malignancies (Conley et al., 2023; Zivanovic et al., 2021). While studies from Western populations have provided valuable insights into the role of secondary cytoreduction, data from Indian cohorts are limited and the scope of cytoreductive surgery in them has not been well defined.

Therefore, the primary aim of this study was to analyse data regarding secondary cytoreductive surgeries in the setting of recurrent ovarian malignancies operated at our institute. We also wanted to assess the survival outcomes of the patients undergoing secondary CRS as a secondary objective.

2. Methods

This is a retrospective study conducted at a tertiary care institute in South India. After obtaining permission from the Institutional Review Board (No 13350), the electronic medical records of all patients who underwent secondary cytoreductive surgery for recurrent ovarian cancer between January 2011 and December 2019 at the department of Gynaecologic Oncology were retrieved. Consent was waived off as it was a retrospective design.

Inclusion criteria:All patients with platinum-sensitive recurrent ovarian cancer including both epithelial and non-epithelial histologies who underwent secondary cytoreductive surgery at our institute were included.Exclusion criteria: Low-grade tumors and those undergoing palliative surgeries for any cause were excluded. Pertinent demographic, clinical, operative details and follow-up data were extracted from the records. Recurrence was defined as definite evidence of disease on imaging (CT scan) prompted either by symptoms suggestive of recurrence or raised tumor markers.

In most cases, patient selection for secondary cytoreduction was based on Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) scoring which was first recorded by the AGO OVAR Group (Harter et al., 2006). The AGO score is a combination of PS (performance status), early FIGO stage initially or no residual tumor after first surgery, and absence of ascites which could be helpful in predicting complete resection for cytoreduction (Harter et al., 2006; Harter et al., 2011). Computed tomography (CT) scan was done as a baseline investigation for all patients. Disease operability was further confirmed including a positron emission tomography CT (PET CT) to rule out any metastatic focus. Cases were further discussed in a multi-disciplinary team meeting and a decision of secondary cytoreductive surgery was taken. Patients were then counselled regarding the extent of the surgery including the use of HIPEC intraoperatively if feasible. Some patients with a negative AGO score but disease amenable to resection were also operated based on the surgeon's discretion as well as her preoperative/ intraoperative assessment. Aletti's Surgical complexity score was used to grade the complexity of surgeries intraoperatively (Aletti et al., 2007). Major morbidity was defined as perioperative massive bleeding, deep vein thrombosis, pulmonary embolism, or having a relaparotomy. Post operative data including duration of ICU/ Hospital stay following surgery and any other major events were also taken into consideration.

2.1. Statistical analysis

Data was entered using the EPIDATA software. All categorical variables were calculated using frequencies and percentages, and continuous variables were reported using the mean and standard deviation or Median (IQR). The log-rank test was used to compare the survival probabilities over time. Prognostic factors for overall survival (OS) and progression-free survival (PFS) were determined via Cox proportional hazards regression analysis. OS (overall survival) was calculated as the time (in months) from secondary cytoreductive surgery till death, while PFS (Progression free survival) was from surgery to the next documented recurrence. If there was no recurrence following secondary cytoreduction, PFS was calculated to the last follow-up or death. Kaplan-Meier curves were used to plot survival probabilities for different variables. Statistical significance was considered at a p-value < 0.05. All analyses were completed using Statistical Package for Social Services (SPSS) software Version 25.0 (Armonk, NY; IBM Corp).

3. Results

A total of 52 patients underwent secondary cytoreductive surgery for recurrent ovarian cancer during the study period. Supplementary Table 1 shows the patient demographics at initial treatment. Among the participants, 48 (92 %) patients had epithelial histology while 4(8 %) were sex cord stromal tumors. At initial diagnosis, 26 (50 %) of the patients had been diagnosed with Stage III/IV and rest were stage I/II.

In terms of initial surgery, primary cytoreduction was complete in 10 (19 %) patients, optimal (</= 1 cm residual disease) in 19 (37 %) and sub-optimal in 23 (44 %). Most patients (85 %) had completed six cycles of chemotherapy postoperatively. The mean age of the patients at recurrence was 49.21(±11.85) years. The median treatment-free interval after primary treatment was 20 months (range 6–132).

Of all 31 patients who had primary surgery elsewhere, only two were optimal. Remaining 21 patients had primary surgery at our center, and 17 of them were adequate. Median CA125 at recurrence was 30.50 (range 7.13–218.25) IU/L. The ECOG performance status was 0–1 in 50 (96 %) patients. The patient characteristics at recurrence are recorded in Table 1. Ascites of 500 ml or less was present in 49 (95 %) patients. Only 11 (21 %) patients had a single-site disease while 41(79 %) had disease at multiple sites/carcinomatosis.

Secondary cytoreductive surgery was highly complex in 4(8 %) patients, 19(37 %) had intermediate, and 29 (55 %) had a low surgical complexity score according to the Aletti complexity scoring system. The surgical outcomes are presented in Table 2.

Secondary cytoreduction was complete (no macroscopic residual disease) in 31(60 %), Optimal (R1) in 17 (33 %), and suboptimal in only 4 (7 %) of the patients. Though these terminologies have been replaced by the recent CC (completeness of cytoreduction) classification, since our study period had patients from 2011 to 2019, we have followed the previous classification in our study. Rectosigmoid/large bowel resection was done in 16 patients. Ten patients underwent diaphragm stripping/ resection. Ureteric resection/reimplantation was done in 5 patients. Splenectomy was done in 5 patients while one patient had distal pancreatectomy along with splenectomy. Major morbidity occurred in 12 (23 %) patients. The mean ICU stay was 1.06 +/− 2.73 days. The mean hospital stay was 9.1 +/− 4.82 days. Most of the patients (85 %) completed chemotherapy after secondary surgery. On univariate analysis,the duration of hospital stay and ICU stay were the two factors that were significantly associated with survival. Multivariate analysis could

Table 1
Characteristics at recurrence.

Characteristics at recurrence	N(%)
Age	49.21 +/− 11.85
Histology	
High grade serous carcinoma	34(65.3 %)
Mucinous carcinoma	5(9.6 %)
Endometroid carcinoma	7(13.5 %)
Mixed	2(3.8 %)
Adult granulosa cell tumor	4(7.7 %)
ECOG*	
0–1	50(96.2 %)
2	2(3.8 %)
Ascites	
<500 ml	49(94.2 %)
>500 ml	3(5.8 %)
Sites of disease	
Single	11(21.2 %)
Multiple	37(71.2 %)
Carcinomatosis	4(7.7 %)

* ECOG – Eastern Co operative Oncology Group.

Table 2
Surgical outcomes.

HIPEC*	
Yes	11(21.2 %)
No	41(78.8 %)
Surgical complexity score	
Low	29(55.8 %)
Intermediate	19(36.5 %)
High	4(7.7 %)
Secondary surgery	
Optimal	48(92.3 %)
Suboptimal	4(7.7 %)
Major morbidity	
Yes	12(23.1 %)
No	40(76.9 %)
Chemotherapy (2nd line)	
Yes	39(84.8 %)
No	7(15.2 %)
Bevacizumab	
Yes	2(4.2 %)
No	46(95.8 %)
Survival status	
Alive	44(84.6 %)
Dead	8(15.4 %)

* HIPEC- Hyperthemic Intraperitoneal Chemotherapy.

not be done due to small effective size.

Primary chemotherapy was with carboplatin and paclitaxel in 41(79 %) patients while 8 (15 %) did not receive any adjuvant after primary surgery. 5 Fluorouracil was given in one patient, one received Cyclophosphamide, Adriamycin, and Cisplatin while Cisplatin with Etoposide was administered in another. Most of the patients had received the first cycle of chemotherapy within 2 to 4 weeks. In 8 (15 %) patients, there was a delay in the initiation of the first cycle of chemotherapy being at 6–8 weeks post surgery. At the completion of our study, second recurrence was detected in 16 (30.76 %) of our patients and 8(15 %) expired.

Median follow-up was 19.5 months(range 0–105 months). Median PFS was 19 (95 % CI 13.62–24.37, p = 0.31) months (Fig. 1) and median OS 22 (95 % CI 15.84–28.15, p = 0.41) months (Fig. 2) for all the participants. Median PFS in the optimal cytoreduction group was 19 (95 % CI 13.81–24.18) months and 7 (95 % CI 0.00–25.94) months in the suboptimal cytoreduction group,p = 0.51 (Fig. 3). Median OS was 22 (95 % CI 15.1–28.81) months and 7 (95 %CI 0.00–22.68) months in the optimal and suboptimal surgery groups respectively, p = 0.23 (Fig. 4).

4. Discussion

4.1. Summary

Recurrent ovarian cancer is a challenging disease with various therapeutic entities. In this study on secondary cytoreduction for recurrent ovarian malignancies, we found an improved survival outcome for optimally cytoreduced cases. This also highlights the importance of appropriate patient selection and surgical expertise in optimizing outcomes.

4.2. Comparison with existing literature

Berek et al retrospectively identified a relatively heterogeneous group of 32 patients with a median interval between primary and secondary surgery of 12 months (range 6–48 months) in one of the earliest reports about secondary cytoreduction. Optimal cytoreduction was found to improve survival and also increased the interval between primary and secondary surgery (Berek et al., 1983). Another significant study of secondary cytoreduction for recurrent ovarian cancer had recruited 789 patients, out of which 217 had secondary cytoreduction followed by chemotherapy while 572 who had only chemotherapy. The median OS was 4.5 years, 2.3 years, and 0.7 years in patients who underwent secondary cytoreduction with residual tumors 0 cm, ≤ 2 cm, and > 2 cm, respectively (p < 0.001) which again pointed towards achieving a complete/optimal cytoreduction, directly improving the survival (Oksefjell et al., 2009).

The AGO OVAR Group carried out the DESKTOP trial to identify patients who would most likely achieve complete cytoreduction and hence would achieve a significant survival benefit from secondary cytoreduction. They evaluated the AGO score for predicting complete gross resection (R0) at secondary cytoreductive surgery (Harter et al., 2006). In the prospective DESKTOP II trial, complete gross resection (R0) was achieved in 76 percent of patients with a positive AGO score.

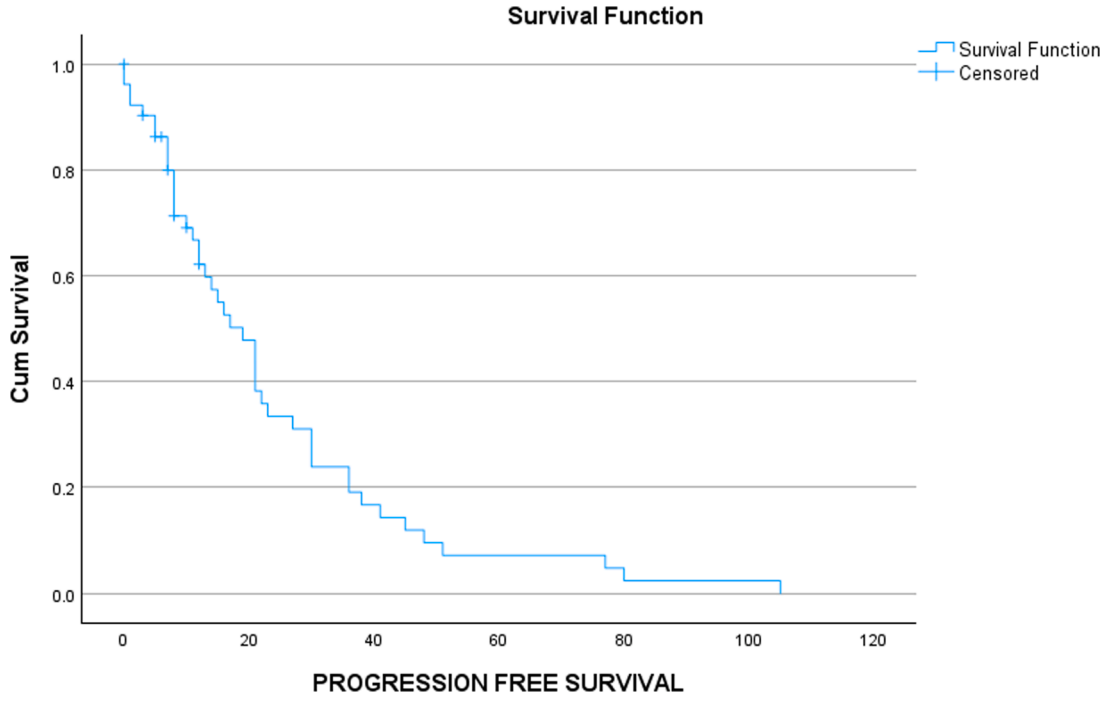

Fig. 1. Progression free survival for all patients.

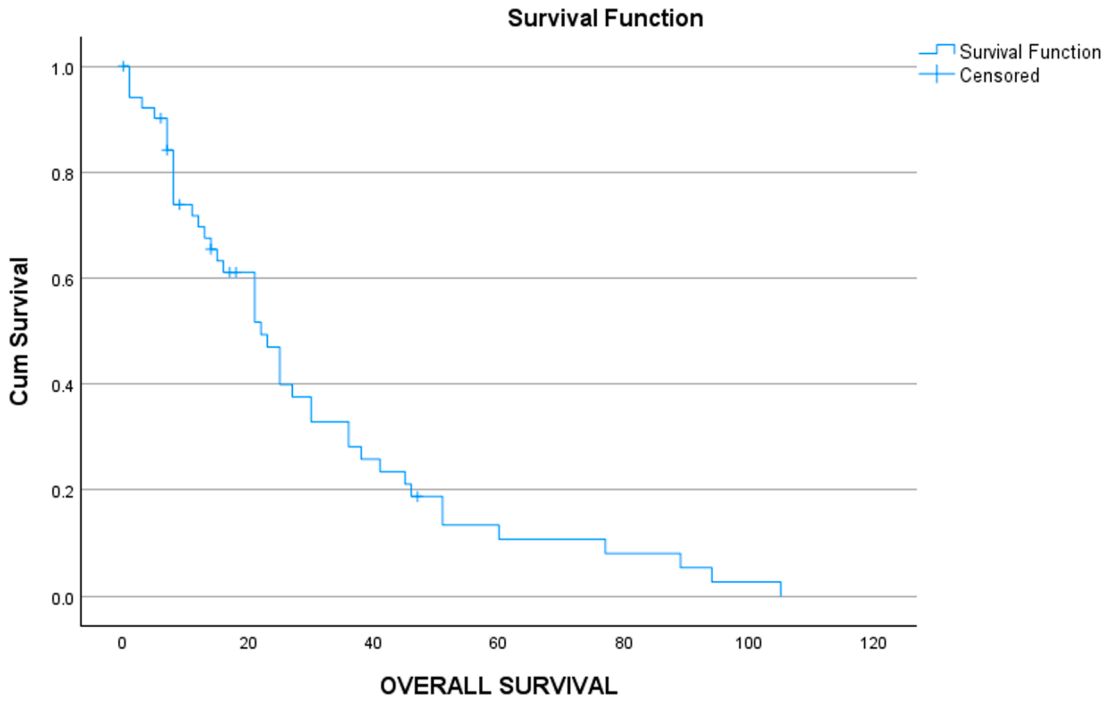

Fig. 2. Overall survival for all patients.

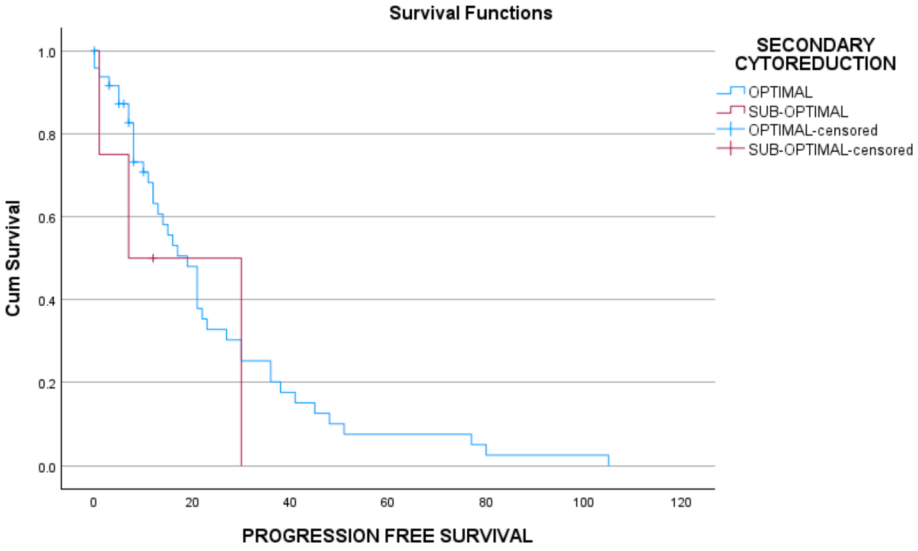

Fig. 3. Progression free survival of optimal vs suboptimally cytoreduced patients.

(Harter et al., 2011). The DESKTOP III randomized control trial results have further provided much needed clarity. Median OS benefit of 7.7 months and progression-free survival (PFS) benefit of 4.4 months was found in the surgery group. Notably, the median OS for the subgroup of patients in the surgery arm who achieved complete resection (CR) versus an incomplete resection was 61.9 months and 28.8 months, respectively (Du Bois et al., 2017).

GOG-0213 was another landmark phase 3 randomized control trial of secondary cytoreductive surgery followed by platinum chemotherapy with or without bevacizumab which showed no significant PFS or OS benefit of secondary debulking surgery. In an exploratory analysis for PFS and OS, surgical patients with a complete gross resection were compared with all patients receiving chemotherapy without surgery. As in DESKTOP III, PFS was improved by complete gross resection. However OS was the same in both groups (Coleman et al., 2019).

In our study, we found that although half of the patients were stage I/II at initial diagnosis, 44 % had a suboptimal primary surgery. Many primary surgeries were carried out elsewhere and referred to our institution. A higher stage at initial diagnosis conferred a hazard ratio of 4.24 for survival. Regarding histology, it was a more or less homogenous group, with 92 % being high-grade epithelial histology and most had completed the first line of chemotherapy.

Patient selection is crucial to outcomes. Existing data suggests that secondary cytoreduction is likely to be most effective when there is a single isolated relapse, a long disease-free interval, when the patient is reasonably healthy, and when resection to no/minimal residual disease can be achieved. In contrast, women with symptomatic ascites, carcinomatosis, early relapse and poor performance status were least likely to benefit (de Bree et al., 2022; Baek et al., 2022).

The patients selected for surgery were relatively young, but we found

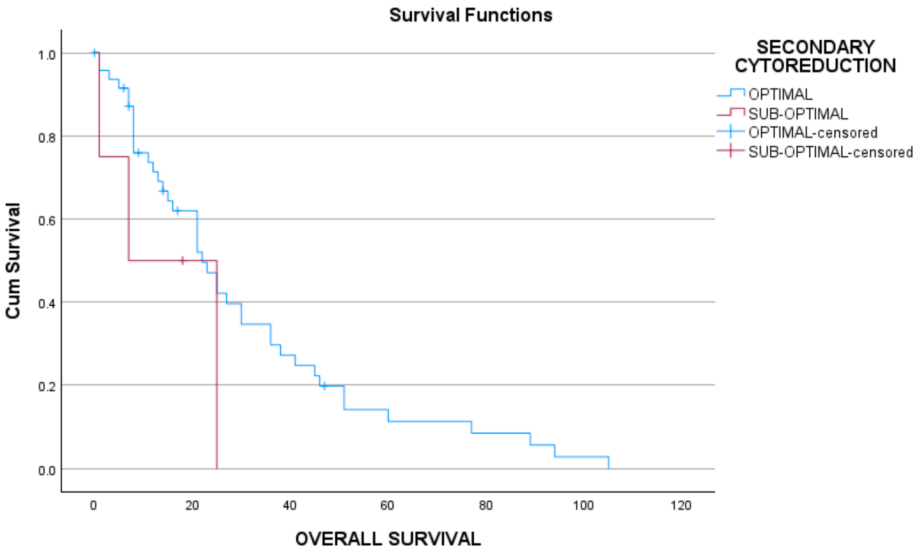

Fig. 4. Overall survival for optimal vs suboptimal cytoreduced patients.

that the mean age of those who died was three years older. The patients chosen for secondary debulking surgery had good performance status, with ECOG of 0–1, and had no or minimal ascites. Although 44 % of our patients did not have an optimal primary surgery, it is more likely due to inadequate surgical effort rather than disease load. Patient selection was mostly at the surgeon's discretion. In most cases, though, two of the three criteria were present.The median treatment-free interval between the primary treatment and the recurrence was 20 months. However, the range was wide, and most, but not all, patients were platinum-sensitive by definition.

A high surgical complexity score conferred a hazard ratio of 8.26 for subsequent death. Complete or optimal cytoreduction was achieved in 93 % of patients, and those who had suboptimal debulking (residual disease $>$ 1 cm) were twice as likely not to survive. Significant post-operative morbidity in almost one-fourth of the patients also conferred a hazard ratio of 4.59. The patients who did not receive HIPEC had a hazard ratio of 0.84. Duration of ICU stay was found to be significantly associated with survival on univariate analysis.

Data from randomized control trials have shown a median PFS of about 18 months which is similar to ours (Shi et al., 2021) but the overall survival rates were lower (Shi et al., 2021; Felsinger et al., 2018). But as previous reports, both the OS and PFS were higher in participants who had a complete/optimal cytoreduction than in those who had a suboptimal surgery (de Bree et al., 2022). In a retrospective analysis, the optimal resection rate had been 100 % (Takahashi et al., 2017) while it was 93 % in another (Baek et al., 2022); The optimal resection rate in our study is 93 % which is similar to the data mentioned above. Newer scores like the Tian/iMODEL Scores as per the SOC1 trial (Felsinger et al., 2018) have been put forward to predict the resectabilty in secondary cytoreduction but warrant further evaluation. Achieving optimal cytoreduction is of prime importance. However, the evidence provided by the randomized trials suggests complete resection rate of 67 % in GOG 0213 (Coleman et al., 2019); 74 % in DESKTOP III (Du Bois et al., 2017), and 76 % in the SOC 1 trial (Felsinger et al., 2018). Our difference with these studies could be due to the different selection criteria used.

Regarding the role of HIPEC in the setting of secondary cytoreduction, opinions are divided as some studies have shown a survival benefit (Spiliotis et al., 2015; Zhang et al., 2021) while others have not (Zivanovic et al., 2021; Lee et al., 2023). In our study, HIPEC failed to demonstrate a survival benefit among the participants stressing the fact that a successful cytoreductive surgery depends on a combination of factors.

Among other factors, surgeries done in specialised centres might have a better outcome in terms of improved survival as have been reported previously (Cummings et al., 2022).

4.3. Strengths and limitations

In our study we looked at the survival outcomes of recurrent ovarian cancers as a whole including all the histology groups. Though it is a single institutional study, our study population was heterogenous which added to the practicality. Limitations were the small sample size and absence of control groups for comparison. Also due to the retrospective study design, there may have been some inherent selection bias.

4.4. Implications for future practice and research

Meticulous individualization of cases should be done considering the patient's performance status, prior treatment history, disease extent as well as an optimal resectibility even in primary cytoreduction cases. Multicentric randomized prospective data is needed to assess the actual value added benefit of surgery. Morbidity, however, can be significant in highly complex surgeries which also needs to be a part of patient counselling.

5. Conclusion

Secondary cytoreductive surgery plays a crucial role in the management of recurrent ovarian carcinoma, with favorable survival outcomes observed in selected patients. Optimal cytoreduction remains a key determinant of survival outcomes, emphasizing the importance of meticulous surgical technique and patient selection.

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CRediT authorship contribution statement

Priya Bhati: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Anitha Thomas:** Writing – review & editing, Resources, Data curation. **Rachel George Chandy:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Amrita Datta:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Dhanya Susan Thomas:** Writing – review & editing, Visualization, Resources. **Vinotha**

Thomas: Writing – review & editing, Supervision, Resources, Formal analysis, Conceptualization. **Abraham Peedicayil:** Writing – review & editing, Supervision, Resources, Methodology, Formal analysis, Conceptualization. **Ajit Sebastian:** Writing – review & editing, Writing – original draft, Supervision, Resources, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gore.2024.101463.

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