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Survival Outcomes in the Patients of Ovarian Epithelial Carcinomas Treated with Fertility-Sparing Surgery: A Study from a Developing Country

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ABSTRACT

Objective: To assess the outcomes of fertility-sparing surgery in patients with ovarian epithelial carcinoma treated at our centre.

Study Design: Retrospective longitudinal study.

Place and Duration of Study: Shaukat Khanum Memorial Cancer Hospital & Research Center, Lahore Pakistan, from Jul 2001 to Aug 2015.

Methodology: We studied 31 patients with ovarian epithelial carcinoma who underwent fertility-sparing surgery at Shaukat Khanum Memorial Hospital. The detail regarding patients and tumour characteristics, along with outcomes of the intervention, was obtained from secondary data kept in the electronic hospital information system.

Results: A total of 132 patients with ovarian epithelial carcinoma were identified; 31 patients underwent fertility-sparing surgery (Stage-IA, n=19; Stage-IC, n=12). By histopathology, 14(45.0%) had mucinous cystadenocarcinoma, 7(22.6%) serous adenocarcinoma, 6(19.4%) endometroid, and 4(12.9%) with clear cell pathology. The mean duration of follow-up was 52.6±2.3 months (18-118 months) after fertility-sparing surgery. Five-year recurrence-free survival was 81.0%. (Three-year=89.0%), using the Kaplan-Meier graph. Three patients had successful pregnancies, with one having a twin pregnancy.

Conclusion: Fertility-sparing surgery should be considered for children of early-stage epithelial ovarian carcinoma patients as it preserves fertility and endocrine function while avoiding recurrence.

Keywords: Carcinoma, Fertility sparing surgery, Ovarian epithelial, Ovarian neoplasms, Pregnancy.

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INTRODUCTION

Ovarian carcinoma (OC) is the seventh most prevalent malignancy in females. Internationally 295 thousand new cases and 184 thousand causalities are reported annually due to ovarian cancer.[1] The five-year survival is 46% after diagnosis.[2] Ninety per cent of OC are ovarian epithelial carcinomas (EOC). Histologically EOCs are further classified into the serous, endometroid, mucinous, clear cell, squamous cell, transitional, mixed epithelial, undifferentiated, and unclassified tumours. These tumours widely vary in their risk factors and prognosis.[3,4]

EOC is commonly diagnosed in postmenopausal women, but 14% of patients are younger than 40 years. Most young females express eagerness to retain fertility, and at the same time, they are concerned about the therapy and its impact on survival. The standard conventional therapy for EOC is total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO), omentectomy with pelvic/para-aortic lymph node sampling and peritoneal washing followed by chemotherapy.[5,6]

Munnel was the first to describe Fertility Sparing Surgery (FSS) for EOC in 1960.[7] FSS aims to preserve the reproductive organs (uterus and contralateral ovary/fallopian tube) while performing unilateral salpingo-oophorectomy and optimal surgical staging.[5,6] Although standard conventional surgery in EOC has a good prognosis, FSS has remained a topic of discussion in women of child-bearing age.[5-7] Morgan *et al.* recommend considering FSS among women with early-stage (IA and IC) EOC, if technically feasible, and fertility preservation is desired.[8] A study published in Annals of oncology also suggests that FSS can be a possibility for females interested in fertility preservation with stage IA/IC favourable histology (non-clear cell carcinoma) having grade 1 or 2 tumours. However, the advantage of FSS in unfavourable histology (clear cell) and grade 3 tumours fertility preservation approach is still debatable.[9] Some authors found higher recurrence rates with FSS compared to conventional surgery.[10]

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Limited evidence is available on outcomes of FSS, and to our best knowledge, from our region, no published literature evaluates outcomes of FSS. Therefore, this study evaluates the oncological outcome of early-stage EOC following FSS in our local setting, which can guide patient selection for future FSS.

METHODOLOGY

In this retrospective longitudinal study single-centre study, a cohort of 132 patients having EOC was identified between July 2001 and August 2015 at Shaukat Khanum Memorial Cancer and Research Center, Lahore, Pakistan. We gathered data from the cancer registry of our hospital after acquiring Institutional Review Board approval [EX-03-05-19-02-A2].

Inclusion Criteria: Patients with ovarian epithelial carcinoma who underwent fertility-sparing surgery at Shaukat Khanum Memorial hospital were included in the study.

Exclusion Criteria: Patients underwent fertility-sparing surgery, but did not get back after surgery were excluded from the study.

We studied all patients who presented during the mentioned duration and maintained active follow-up. Forty-one patients underwent FSS, and ten of them did not get back after surgery. Hence, we evaluated thirty-one cases in our study, which completed a median of five years of follow-up after successful FSS. The patients were classified according to histopathology, including serous, mucinous, endometroid, and clear cell carcinoma. We used the World Health Organization (WHO) criteria for grading and histopathology.[4] In addition, the staging system drawn by the International Federation of Gynecology and Obstetrics (FIGO) was applied.[11]

All studied cases were below 40 years of age, having established stage IA or IC, with Grade 1-2 EOC and desired to retain fertility. Patients signed a consent form for FSS after understanding the associated risks and benefits. All patients registered in this research underwent unilateral salpingo-oophorectomy on the side of the tumour with appendectomy, peritoneal lymph node biopsy, and omentectomy. Cytologic examination of ascites and peritoneal washing was also performed.

Postoperatively Platinum and Taxane-based chemotherapy was given to 21 patients. The follow-up plan comprised three monthly clinical examinations, radiological studies (ultrasound), and CA 125 level. The research team used SPSS software (version 23.0; SPSS, Chicago, IL, USA) for statistical data analy-sis. The mean and standard deviation were used for continuous variables, while frequencies and percentages were used for categorical variables. We used the Kaplan-Meier method to calculate survival as a function of time. The overall survival (OS) was defined as the time between FSS and the last follow-up or death due to EOC. Recurrence-free survival (RFS) was the time between surgery and the date of recurrence or last clinic visit.

RESULTS

After carefully reviewing the data acquired from the cancer registry, we studied thirty-one patients for analysis. Table-I showed detail of patient characteristics. After FSS, the patients were followed for the mean of 52.6±2.3 months (range from 18 to 118 months).

Table-I: Characteristics of Patients undergoing Fertility Sparing Surgery (n=31)

Characteristics	Frequency (%)
Age (years)	
Mean±SD	28.0±6.4 years
Range	18-43
Eastern Cooperative Oncology Group-Performance Status (ECOG-PS)	
0	5 (16.0)
1	26 (84.0)
Co-morbidities	
No comorbidities	28 (90.3)
Hypertension	2 (6.5)
Diabetes	1 (3.2)
Pre Fertility Sparing Surgery-Parity	
Nulliparous	22 (71.0)
Parous	9 (29.0)
Pre Fertility Sparing Surgery-Menstruation	
Regular	11 (35.5)
Irregular/Amenorrhea	13 (42.0)
Unknown	7 (22.5)

Twenty-two patients were nulliparous upon diagnosis, while nine had a previous successful pregnancy. Regarding tumour characteristics, nineteen patients were diagnosed with stage IA, while twelve were in stage IC; remaining parameters were in Tables-II & III.

Five-year RFS was 81% and three-year was 89%, using the Kaplan-Meier graph. The recurrence rate after FSS was 12.9% (4 out of 31). Recurrence occurred once in each histopathology type; clear cell type had a higher recurrence rate.According to histopathology recurrence rate was Mucinous 7%(1 in 14), Endometroid 16% (1 in 6), Serous 14% (1 in 7), Clear cell (1 in 4) 25%. After FSS, three patients had successful pregnan-

cies, with one having a twin pregnancy. No congenital abnormality was reported. Recurrence occurred in four patients. Recurrence sites were residual ovary in three patients and uterus in one patient (Table-IV). Recurrence-free survival (RFS) and overall survival (OS) were illus-trated in Figure.

Table-II: Tumor Related Characteristics (n=31)

Characteristics	Frequency (%)
Histopathology	
Serous	7 (22.6)
Endometroid	6 (19.4)
Mucinous	14 (45.1)
Clear Cell	4 (12.9)
International Federation of Gynecology and Obstetrics (FIGO) Staging	
Stage IA	19 (61.3)
Stage IC	12 (38.7)
Grading (n=27)	
Grade I	21 (77.7)
Grade II	6 (22.2)

Table-III: Treatment-Related Characteristics

Characteristics	Frequency (%)
Adjuvant Chemotherapy	
Yes	22 (71.0)
No	9 (29.0)
Recurrence	
Yes	4 (13.0)
No	27 (87.0)
Post Fertility Sparing Surgery Menstruation	
Regular	16 (51.6)
Irregular	3 (9.7)
Amenorrhea	0
Unknown	12 (38.7)
Post Fertility Sparing Surgery Pregnancy	
Yes	3 (9.7)
No	2 (6.4)
Unknown	26 (83.9)

after cyto-reductive surgery and chemotherapy is a significant concern.

FSS aims to ensure excellent obstetrical outcomes while limiting the recurrence of ovarian cancer. In the current study, after following patients for a median of 52.6 months, the recurrence rate was calculated to be 12.9%. Published literature, to date, also has comparable recurrence rates. Previously a study reported 123 patients, 20 patients underwent FSS, and 103 patients had standard staging procedures. There was no compelling variation in survival rates compared to conventional surgical staging. However, the recurrence rate was 15%, 3 out of 20.[12] A Japanese study in 2010 reported 60 cases of stage I who had FSS, five years OS and DFS were 89.8%, recurrence occurred in 13.3% of cases.[13]

FSS performed for stage I EOC is not associated with increased mortality compared to traditional surgical staging.[14,15] In addition, our data demonstrate a predicted five-year RFS rate of 81% and an OS rate of 82.6%, a finding consonant with published literature.[10,12]

Histological grading is a crucial factor in determining recurrence. Frusico *et al*. reviewed 1,150 patients who had FSS, and 139 relapsed. It was concluded that stage 1A/1C with Grade 1/2 cancers had a much lower recurrence rate (around 11%) than Grade-3 tumours (23-29%).[16] Grade-3 tumours portend distant relapse and lower survival rates.[17,18] Ledermann *et al.* also do not endorse FSS in Grade-3 tumours.[9] In our study, relapse occurred in 12.5% of Grade-1 patients with Grade-1 and 16% with Grade-2, a finding supported by prior studies. There was no patient with Grade-3 tumours in our cohort.

Table-IV: Details of Patients with Recurrence

Case	Age	FIGO Stage	Histopathology	Grade	Adjuvant Chemotherapy	Recurrence Site	RFS	Treatment for Recurrence	Status	OS
1	24	IA	Mucinous	1	Platinum-based	Contralateral ovary	58	Completion surgery and chemotherapy	Dead	59
2	31	IC	Clear Cell	1	Platinum-based	Residual Right Ovary	11	Completion surgery	Alive	48
3	18	IA	Endometroid	2	Platinum-based	Uterus	4	Chemotherapy	Alive	57
4	33	IA	Serous	1	no	Same site adenexal mass	11	Chemotherapy± surgery	Alive	51

FIGO: International Federation of Gynecology and Obstetrics, RFS: Recurrence Free Survival; OS: Overall Survival

DISCUSSION

Despite treatment advances, the life-threatening nature of ovarian cancer makes it the most lethal gynaecological malignancy. In young women with ovarian cancer, loss of fertility and endocrine function

The tumour stage is an added factor which can influence recurrence and affect prognosis.Contrary to previously published data by Bentivegna *et al*. all four recurrences occurred in stage IA, reporting a total of 1115 cases, 16% recurrences in stage IC, compared to 10% in stage IA.[19] The limited number of patients in

our research can be a possible explanation for this finding. In addition, lymphadenectomy was not performed in most patients, which would have upstaged the cases.

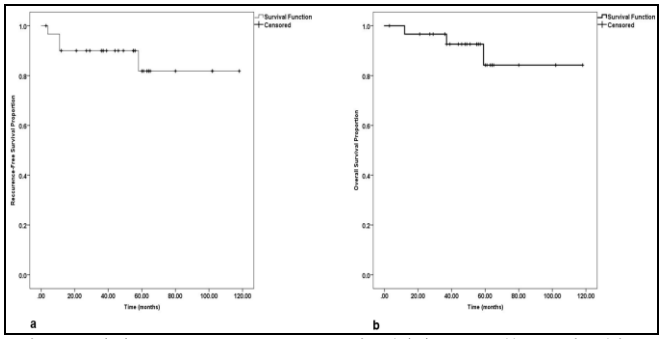

Figure: (A) Recurrence Free Survival (B) Overall Survival in Patients undergoing Fertility Sparing Surgery for Early Stage Epithelial Ovarian Carcinoma

Resumption of menstrual regularity and successful conception were parameters for monitoring reproductive/obstetric outcomes. Thirteen patients resumed regular menstruation median of 3.5 months after surgery, and three patients had a full-term pregnancy median of 32.5 months after FSS, all delivering healthy babies. No congenital anomaly was reported. Due to the teratogenic effects of chemotherapy, international guidelines recommend at least six months gap from chemotherapy.[9] Previous literature advises conception after achieving the estimated recurrence peak, particularly in clear cell histology. The recurrence rate is diminished mostly after two years, but relapsed cases are reported even after several years.[19] Patients who conceive after completing their treatment shall be closely followed up during pregnancy using ultrasound should be considered.[9] Watanabe *et al*. found only 29 patients eligible for the treatment in a decade during a similar study.[20]

LIMITATIONS OF STUDY

For this study, we had a smaller sample size, i.e., 31 patients, despite a high rate of EOCs. Most of the patients do not fulfil the fertility-sparing treatment criteria. The secondary data was extracted from medical files. The research team took extreme caution to keep the demographic parameters constant. Despite the efforts, it was not possible to eliminate the effect of confounding psychosocial factors. Limited data was available on reproductive outcomes following fertility-sparing treatment. The research team will like to investigate it in their future studies.

CONCLUSION

Our study endorses that FSS carries an excellent prognostic outcome. FSS is a valuable treatment measure for early-stage EOC patients of child-bearing age planning pregnancy after completion of surgery and chemotherapy, as it preserves fertility provided their disease is in remission. Our findings are in line with the available literature on FSS. Prospective controlled studies, if organised, could further strengthen these results.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

MA & SAK: Conception, study design, drafting the manuscript, approval of the final version to be published.

SAMH & TY: Data analysis, data interpretation, critical review, approval of the final version to be published.

SY & UKA: Study design, data analysis, critical review, drafting the manuscript, critical review, approval of the final version to be published.

AAS & NS: Data acquisition, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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