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SPECTRUM OF SUSPICIOUS OVARIAN NEOPLASMS AND THEIR ONCOLOGICAL OUTCOMES: A SINGLE CENTER EXPERIENCE

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ABSTRACT

Objectives The objective of our study was to analyse the presentation of various adnexal masses suspicious of malignancy (borderline and malignant) in terms of type of malignancy, associated tumor markers, stage-based management, need for adjuvant therapy and follow up in the form of RIOT (Return To Intended Oncologic Therapy) and disease specific survival (DSS) for malignant masses. **Methods & Materials** A five-year study was conducted at All India Institute of Medical Sciences, Jodhpur on 163 patients who underwent surgery for suspicious or indeterminate ovarian neoplasms on pre-operative work up. The oncological outcomes of patients were analysed after histopathological confirmation of malignancy. Survival analysis was done using Kaplan-Meier method. **Results** Out of 163 cases of suspicious ovarian tumors, 56 (34.3%) were malignant, 13 (8.33%) were borderline and 94 (57.6%) were benign. Among malignant masses high grade serous cystadenocarcinoma formed the majority, while mucinous cystadenoma was the most common benign mass found. Cytoreductive surgery (CRS) was done in all cases of malignancy and chemotherapy offered as per the stage of disease likely neoadjuvant (NACT) and adjuvant. **Conclusion** The study presents oncological presentation and outcome of ovarian neoplasms in a budding cancer unit of a tertiary care hospital. We found that DSS was better for Epithelial ovarian cancers (EOC) as compared to Germ Cell Tumors (GCT), and early-stage disease as compared with advanced stage disease but statistical significance was not reached. There was no evidence that NACT followed by interval debulking surgery (IDS) for advanced ovarian malignancy was superior to cytoreductive surgery followed by adjuvant chemotherapy.

KEYWORDS

Adnexal masses, Cytoreductive surgery, disease specific survival, Kaplan-Meier, Ovarian cancer, tumor markers

INTRODUCTION

Ovarian carcinoma (OC) comprises 3% of all cancers. Among female genital tract related malignancies, the incidence is 25% (1). OC is the 3rd most common cancer among Indian women falling behind cervical cancer and breast cancer. It is considered one of the deadliest malignancies. It is believed to account for a greater number of cancer related deaths than any other gynaecologic malignancy. The most frequent reasons sought behind this are firstly the presenting complains of patients, which are mostly vague or constitutional symptoms; hence by the time diagnosis is made, patient is already in advanced stage of disease. Secondly, lack of any screening protocols, despite so many advancements in treatment and diagnostic workup. This results in late detection, thereby advanced stage by the time of diagnosis and hence poor prognosis. OC is a leading cause of death from cancer in Indian women, with 3.34% (24,015) of all cancer deaths in India. 5-year survival from ovarian cancer when diagnosed in Stage I is 94%, only 15% of cases are diagnosed at this stage. Most (62%) of cases are diagnosed in Stages III and IV, when 5-year survival is only 28% (2). According to the Global Cancer Observatory (GLOBOCAN) 2020, the age-standardized incidence rate of ovarian carcinoma for India was 6.3-7.3 per 100,000 females per year and age-standardized mortality rate was 4.2-4.6 per 100,000 females per year ; whereas age-standardized incidence rate of ovarian carcinoma in 2013 was 10.2/100,000 females (3).

According to cancer stats for ovarian cancer by National cancer Institute, 5-year relative survival 2013-19 was 50.8%. Estimated number of new cases in 2023 was 19,710 and estimated deaths same year were 13,270 (4).

Our study was planned to analyse the distribution and clinical outcomes of ovarian neoplasm in western Rajasthan as a single centre study. It is an amalgamation of presentation (both clinical and imaging) of various adnexal masses suspicious of malignancy, staging, surgical outcomes, extent of resection, corresponding histopathological correlation along with concerned tumor markers, chemotherapy, return to intended oncologic treatment (RIOT) and prognosis/follow-up. We intend to address the scarcity of data on Ovarian malignancy despite being such a common cancer.

MATERIALS & METHODS

The study was conducted at All India Institute of Medical Sciences, Jodhpur, Rajasthan over a period of 5 years. The study was initiated in April 2018 after approval from Institute's Ethical committee. A total of 234 patients presenting with an ovarian neoplasm were enrolled and 163 patients were included for analysis as the follow up data for outcome and overall survival was available till 5 years. Patients with ovarian masses, but found out to be degenerated fibroid or broad ligament fibroid intraoperatively were also excluded.

Data was recorded in the form of History, Examination, Pre-op biochemical and radiological workup (USG, CT, MRI), surgical staging (according to FIGO 2014), type of chemotherapy (adjuvant or neo-adjuvant), RIOT (Return To Intended Oncologic Therapy). The oncological outcomes of patients confirmed to have ovarian malignancy on histopathology was analysed. Survival analysis was done using Kaplan-Meier method. DSS (Disease Specific Survival) was evaluated as time from date of diagnosis to disease specific death. DFS (Disease Free Survival) also known as RFS (Relapse Free Survival) was used for the length of time after primary treatment for

the cancer ends, till the time patient survives without any signs and symptoms of the cancer. PFS (Progression Free Survival) was evaluated as the time from date of diagnosis to date of ovarian cancer progression, where progression was established by radiologically confirmed progressive disease (PD), CA – 125 PD or clinical deterioration as determined by treating physician.

Data entry were carried out using MS excel software. Statistical analyses were performed using SPSS version 29. Central tendencies are expressed as mean ± SD. Survival analyses were visualised using the Kaplan–Meier method. Survival statistics are presented as mean survival with corresponding 95% CI. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 163 patients were analysed for the study after confirming their ovarian origin intra-operatively, histopathological diagnosis and availability of follow up, till desirable end points. On histopathological examination benign masses were found in 57.6% patients while 34.3% and 8.33% patients had malignant and borderline masses respectively.

Table 1: Baseline characteristics of ovarian masses suspicious of malignancy:

S. No.	Parameters	Benign (94/163)	Borderline (13/163)	Malignant (56/163)
1.	No. of cases	94 (57.6%)	13 (8.33%)	56 (34.3%)
2.	Mean age at presentation (years)	42.1 (± 16.3)	41.9 (± 23)	50.4 (± 13.4)
3.	Chief primary complain	Pain lower abdomen (66%)	Mass per abdomen (61.5%)	Pain lower abdomen (53.5%)
4.	Median duration of complain (months)	3 (1.5 - 7)	3 (2-12)	3 (2-5)
5.	Parity (most common)	Multiparous (59.5%)	Multiparous (69.2%)	Multiparous (80.3%)
6.	Laterality	Unilateral: R>L (93.6%)	Unilateral: L>R (92.3%)	Bilateral: (56%)
7.	Tumor markers	CA 125 raised in 14.8% mucinous/serous cystadenoma	CA 125 raised in 53.8% borderline mucinous/serous cystadenoma	CA 125 raised in 83.9%, CEA in 5.3%, CA 19.9 17.8% malignant neoplasms
8.	Histopathology report (most common)	Mucinous Cystadenoma (36.1%)	Borderline Mucinous (61.5%)	High-grade Serous carcinoma (51.7%)

Clinicopathological Patterns Of Malignant Tumours:

Maximum patients in our study belonged to the postmenopausal age group 68% (38/56) followed by reproductive age 30% (17/56). We had only one patient who was < 15 years age. The extreme ages in our study were 14 years for youngest patient and 68 years for oldest patient. The most common presenting complain encountered among women with malignant ovarian masses was lower abdominal pain by 53.5% patients (30/56), followed by menstrual irregularities in 21.4% (12/56), 8.9% (5/56) women complained of mass per abdomen and same number had constitutional symptoms viz anorexia, bloating, weight loss etc. The least common primary complain was abdominal distension by 7.1% (4/56) patients.

A total of 25 of 56 (44.6%) with malignant ovarian masses in our study presented within 3 months of onset of symptoms. 16 patients (28.5%) presented within 3 to 6 months of symptom onset. 12.5% patients presented at more than 1 year of symptom onset while 1 patient was incidentally diagnosed with adnexal mass on 1st trimester dating scan. Mean duration of complain for EOC was 7.5 months and for GCT was 2.5 months.

Multiparous females formed the majority 80.3% (45/56) in our study followed by nulliparous constituting 12.5% and least were primiparous females (7.14%).

Bilateral masses were found in 56% of malignant cases. Of unilateral masses, right sided masses were predominant forming 30.3% and left sided masses constituted 14%.

Patients were managed according to staging derived from imaging studies. Those with advanced stage/metastasis beyond pelvis (Stage IIIC/1V) were sent for neo-adjuvant chemotherapy after a tissue diagnosis made on image guided or laparoscopy guided biopsy- 14.3% while those with early stage were planned for primary cytoreductive surgery (CRS) – 76.8%.

Surgical stage:

Surgical staging of patients was done and further categorised into early stage and advanced stage. 44.7% patients fell in early-stage group of which 23.2% (13/56) were stage IA/B and 21.4% (12/56) were stage IC/II. 55.4% patients were advanced disease at the time of diagnosis of which 5.3% were stage IV. Maximum patients (50%) were stage III at the time of diagnosis and six of them required bowel resection and anastomosis.

Histopathology

Most frequent malignant adnexal masses belonged to the group of Epithelial ovarian tumors (76.8%) followed by Germ cell tumors (19.6%) and least Sex cord stromal tumors (3.6%). Table 2 represents the varied histological diagnosis in our series.

Table 2 : Histopathological pattern of malignant ovarian tumors.

S.No.	Type of Tumor	Incidence
1.	Epithelial Ovarian Carcinoma (EOC)	76.8% (43/56)
	a. High grade Serous Ca	67.4% (29/43)
	b. Mucinous Ca	14% (6/43)
	c. Serous Ca	4.6% (2/43)
	d. Endometriod Ca	9.3% (4/43)
	e. Transitional cell Ca	4.6% (2/43)
2.	Germ cell Tumor (GCT)	19.6% (11/56)
	a. Dysgerminoma	36.4% (4/11)
	b. SCC arising from Mature Teratoma	27.3% (3/11)
	c. Immature Teratoma	9.1% (1/11)
	d. Yolk sac tumor	9.1% (1/11)
	e. Mixed malignant GCT	9.1% (1/11)
	f. Carcinosarcoma	9.1% (1/11)
3.	Sex cord stromal tumor (SCST)	3.6% (2/56)
	a. Adult type Granulosa cell tumor	50% (1/2)
	b. Steroid cell tumor	50% (1/2)

Chemotherapy

Of 56 patients with malignant ovarian masses, 14 patients (25%) with early-stage disease did not require chemotherapy. 30 of 56 patients (53.5%) were potential candidates for adjuvant chemotherapy and 8 (14.2%) were for neoadjuvant (NACT) + adjuvant [figure 1].

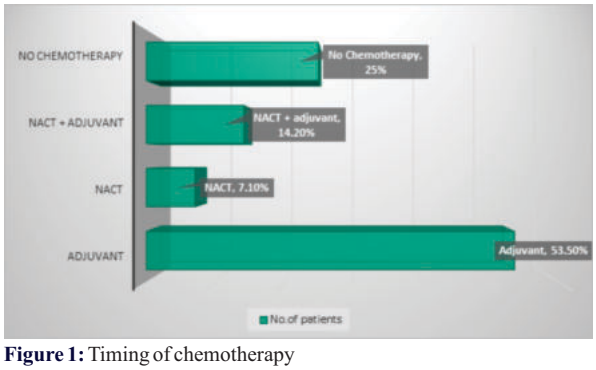

Figure 1: Timing of chemotherapy

Among the surgical complications, wound gap followed by re-suturing was done in 4 patients of which 3 were advanced stage (high grade serous carcinoma -2 and Squamous cell carcinoma arising from mature cystic teratoma -1) and one was early stage (steroid cell tumor). One patient with pulmonary thromboembolism was medically managed and discharged uneventfully. Data as shown in table 3

Table 3 : Incidence of intraoperative and postoperative complications.

S. No.	Intra-op/Post-op complications	Incidence
1.	Surgical spill	1.8%
2.	Wound gap f/b resuturing	7.1%
3.	Thromboembolism	1.8%
4.	Re-admission/ Re-laparotomy	0%

Tumor markers

Tumor markers were done for all patients with adnexal masses. CA 125 was found raised in 83.9% of all patients with malignant ovarian masses and 76.1% patients with Epithelial ovarian masses. Alpha feto-protein and bHCG were raised in 27.3% while LDH was found raised in 45.4% of germ cell tumors. Inhibin was raised in 50% of sex cord stromal tumors.

Follow up of patients with malignant ovarian masses

Return to intended Oncologic therapy (RIOT)

Return to intended oncologic therapy rate in our study was 77%. Of all our patients (30/56) with primary CRS planned for adjuvant chemotherapy, 23/30 were able to get back to it at scheduled time (<28 days). 7/30 patients took >28 days due to delayed recovery resulting from intra-op requirement of bowel resection and anastomosis followed by colostomy/ileostomy (in view of tumor deposits) and wound re-suturing; thereby delay in starting adjuvant chemotherapy. Of 7 patients with delayed recovery after surgery, 2 were lost to follow up. 6/30 patients (20%) were lost to follow-up after completion of treatment. The DSS (mean survival) in patients with RIOT (n = 19) <28 days was 43.1 months (CI: 33.2 – 53.8) while those in RIOT (n = 5) >28 days was 17 months (CI: 2.7 – 11.7), the difference in DSS was statistically non-significant (log rank test, p value – 0.966), figure 2.

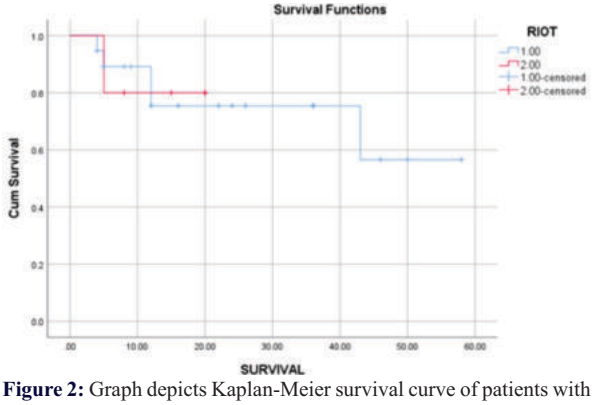

Figure 2: Graph depicts Kaplan-Meier survival curve of patients with RIOT >28 days "1" Vs RIOT <28 days "2".

Disease specific survival (DSS) based on histopathology

8 of 56 patients (14.3%) with malignant ovarian masses who died of disease, DSS in our study (mean duration) was 50.7 months for EOC (CI : 43.4 – 57.9) and 39 months for GCT (CI : 23.3 – 54.7). The difference in survival between EOC and GCT was found to be non-significant (log rank test, p-value : 0.274), figure 3.

We had 2 patients of 56 (3%) who had disease recurrence. Both were stage III high grade serous carcinoma. The PFS of one of the patients was 53 months while of the other was 36 months. Recurrence was diagnosed by raised levels of CA 125 found on routine follow-up of patients post treatment.

12 of 56 patients (21.4%) were lost to follow-up. 34 of 56 patients (60.7%) were disease free till the duration of study (DFS). Thus, we were able to achieve R0 resection in 60.7% patients.

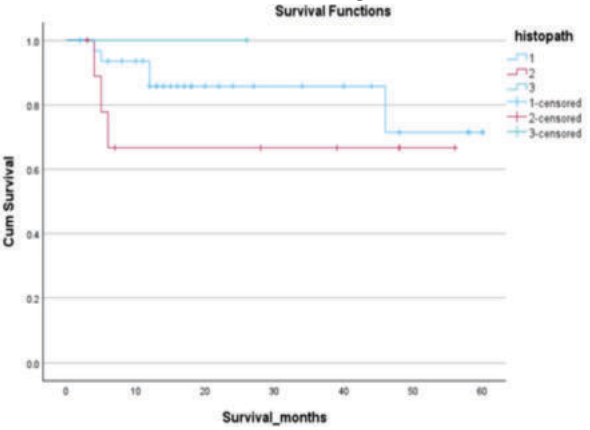

Figure 3: Graph depicts Kaplan-Meier survival curve of patients with EOC "1", GCT "2" and SCST "3".

Disease specific survival (DSS) based on stage of disease

The DSS (mean survival) of early-stage ovarian malignancy was 56.5 months (CI: 49.8- 63.1) in our study while that of advanced stage malignancy was 44.1 months (CI: 34.3 – 53.8). The difference between the groups was not significant (log rank test , p-value: 0.09), figure 4.

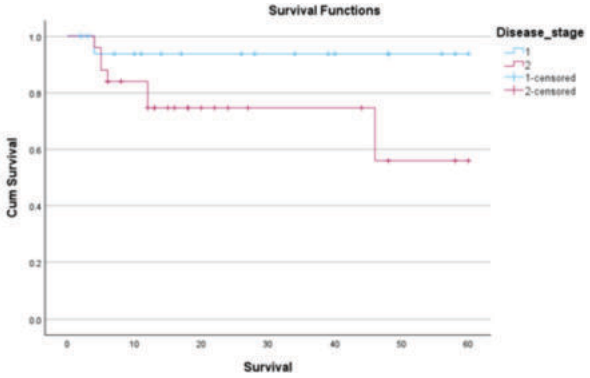

Figure 4: Graph depicts Kaplan-Meier survival curve of patients with early "1"vs advanced stage "2" malignant ovarian masses.

Disease specific survival based on chemotherapy

The DSS (mean survival) of patients who received adjuvant chemotherapy was 45.8 months (CI: 36.1 – 55.6) while in patients who received neoadjuvant with adjuvant chemotherapy, DSS was 52 months (CI : 43.7 - 60.3). The difference between the groups was not significant (log rank test, p-value : 0.425) as depicted in figure 5.

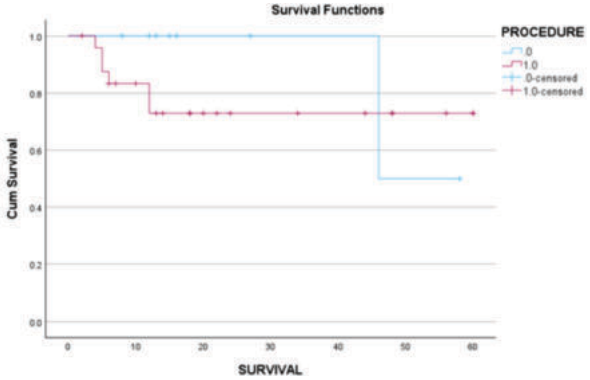

Figure 5: Graph depicts Kaplan-Meier survival curve of patients who received neoadjuvant with adjuvant Chemotherapy '0' Vs patients receiving adjuvant chemotherapy '1'.

DISCUSSION

Most common ovarian masses in our study were benign followed by malignant and least by borderline tumors or tumors of low malignant potential. 63.06% benign, 33.76% malignant and 3.18% borderline neoplasms were found in study done by Mukhiya et al(5). Similar results were found in study by Sudha V et al (6). Of malignant ovarian masses, EOC formed majority followed by GCT and SCST. Similar results were found in study done by Pilli et al and Maheshwari et al (7,8).

Most patients in our study with malignant ovarian masses were postmenopausal; in studies done by Sudha V et al and Mondal SK et al, most common age group was 41-50 years (6,9). Most frequent benign ovarian masses were Mucinous Cystadenoma and malignant masses were High grade serous carcinoma. Similar results were found in study by Pilli et al, Mehra et al and Zarci et al(7,10,11). While Mucinous cystadenocarcinoma was the commonest malignant epithelial tumour in study done by Maheshwari et al (8). This study being conducted in 1994, shows the most common malignant tumor prevalent 30 years back. Study done by Irodi et al on patterns of clinicopathological features of EOC have shown a decreasing trend of Mucinous histotype and increase in High grade serous carcinoma (12).

Most common complain encountered in our study was lower abdominal pain. Similar results were found in study by Sudha V et al (6). While in study done by Pilli et al and Mehra et al, most common complaint was lump per abdomen (7,10). Mean age at presentation for malignant ovarian masses in our study was 50.4 (± 13.6) years. The

mean age of patients in study done by Zarchi et al was 53.87 ± 14.11 years, by Mukhiya et al was 47.79 ± 14.53 years (5,11). 44.7% patients were early stage at the time of diagnosis. 50% i.e bulk of patients were stage III and 5.5% were stage IV in our study. In study by Mondal SK et al, most of the malignant tumors presented as stage III (60%)(9). In contrast to our study, Zarchi et al had most participants in stage I (36.7%) or stage II (35%) disease in their study (11). This might be accounted for the fact that their study was conducted at oncology clinic which was a referral centre as well; patients being referred at the earliest even with suspicion of pelvic mass, thereby accounting for early stage at diagnosis and improved survival in their study.

RIOT (Return to intended oncologic therapy) was first coined in 2014. It was discerned through an observational study that the implementation of enhanced recovery after cancer surgery reduces the time interval to starting chemotherapy. This results in improved overall survival of patients with malignancy (13). In our study, RIOT rate was 77%. There are studies supporting the association of early chemotherapy and late chemotherapy following cytoreductive surgery with survival benefit (14). Contradictory to this, there are a number of studies which have contemplated no link between RIOT and overall survival in ovarian cancer patients (15,16).

DSS in our study was 50.7 months and 39 months for EOC and GCT respectively. The difference was not found to be statistically significant. Mean survival of early-stage ovarian malignancy/ DSS was 56.5 months while that of advanced stage malignancy was 44.1 months. In study done by Zarchi et al on 120 patients with EOC, the mean overall survival for early stage disease was 84.18 months; 48.73 months and 10 months for stage III and IV disease respectively (11). In our study, we compared disease specific survival of patients who underwent primary debulking surgery (PDS) followed by adjuvant chemotherapy vs those who received neoadjuvant chemotherapy prior to surgery. DSS in patients who underwent PDS followed by adjuvant chemotherapy was 45.8 months while those who received neoadjuvant followed by interval debulking was 52 months, the difference was not statistically significant. Various studies done by Zarchi et al, Glasgow et al, Morrison et al, on same have compared overall survival of patients who received chemotherapy and those who did not; the results in none were found to be statistically significant (11,17,18).

Several studies have shown that patient survival depends on multiple factors as stage of disease, histology of tumor and treatment (19). 5 year survival rate when the disease is diagnosed and treated at that stage when cancer is confined to ovary is 95%; however only 29% cancers are detected at this stage (20). Cytoreductive surgery or interval debulking surgery with chemotherapy is the centrepiece of treatment for advanced EOC (21).

The strength of our study is that it was prospective in nature and all the participants were followed up for a duration of 3 years without any recall bias. At the same time, some limitations of the study include it being a single-center study at a tertiary hospital so generalizability cannot be ensured. We did not have resources for genetic testing for BRCA gene mutations in patients diagnosed with high grade serous carcinoma. To the best of our knowledge, we could not find a single study giving so broad a dissertation of ovarian masses as this. Also, most literature sited has been from the Department of Pathology through retrograde study of specimens

CONCLUSION

Ovarian neoplasms have varied presentations. Despite all advances, we cannot differentiate between malignant and benign ovarian masses just by clinical, radiological and biochemical workup. The gold standard for diagnosis remains histopathological examination of the gross specimen. From our study we conclude that stage of disease, histological type of carcinoma or timing of chemotherapy, neither have any effect on DSS. This might be explained by the paucity of long term data (mean follow-up 5 years); right censoring. RIOT following early recovery or delayed recovery after surgery, neither had any effect on DSS. Similarly, NACT followed by interval debulking was not found to be superior or improve survival when compared to primary debulking surgery followed by adjuvant chemotherapy.

Conflict Of Interest: The authors have no conflicts of interest.

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