ORIGINAL ARTICLE

FREQUENCY AND HISTOLOGICAL SPECTRUM OF MALIGNANT OVARIAN TUMOURS AT KING EDWARD MEDICAL UNIVERSITY, LAHORE

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ABSTRACT

Background and Objectives: Ovarian cancer is a lethal gynaecological malignancy accounting for a large number of deaths of the female. Ovarian tumours constitute a major bulk of the gynaecologic surgical specimens received for histopathological analysis. The aim of this study was to determine the frequency and the histological patterns of ovarian malignancies.

Methods: This was a 6 – month cross sectional study from May 2014 – November 2014. A total of 180 ovarian tumours were received and reported at the department in collaboration with Lady Willington Hospital and Lady Aitchison Hospital, Lahore, Pakistan.

Results: Out of total of 180 cases of ovarian tumours, malignant tumours were found to be 61 (33.9%) while 119 cases (66.1%) were classified as benign ovarian tumours. Mean age of females with benign tumours was 31.60 ± 9.63 years and in ovarian cancers the mean age was 44.57 ± 12.78 years. Ovarian cancers were classified into 4 major categories and included 38 tumours (62.30%) in the surface epithelial group, 12 tumours (19.67%) in the germ cell group, 7 tumours (11.48%) in the sex cord stromal group and 4 tumours (6.56%) in the metastatic group. Serous Cystadenocarcinoma was the commonest malignant ovarian tumour in the surface epithelial group comprising of 18 cases (29.51%), followed by 14 cases (22.95%) of mucinous cystadenocarcinoma. Dysgerminoma constituted 6 cases (9.84%) and was the commonest ovarian cancer in the malignant germ cell category followed by yolk sac tumour of which there were 3 cases (4.92). In the malignant sex cord stromal group all tumours were granulosa cell tumours (7 cases; 11.48%). Metastatic tumours comprised of 2 cases (3.28%) from colorectal cancer and 2 cases (3.28%) from gastric cancer.

Conclusion: Tumours of surface epithelial category are the commonest malignant ovarian tumours of which serous cystadenocarcinoma is the commonest subtype. The 2nd major category was of germ Cell origin of which dysgerminoma was the commonest subtype.

Key Words: Ovarian cancer, Serous cystadenocarcinoma, Mucinous cystadenocarcinoma, Metastatic tumour, Krukenberg Tumour.

INTRODUCTION

Ovarian neoplasms constitute 25% of all gynecologic tumours in most developed countries and is the 2nd commonest malignancy of the female genital tract following endometrial cancer.[1,2] In developing countries, it is the 3rd most common gynaecologic malignancy (cervical cancer being the most common), with an annual incidence of 5/100,000 and a mortality rate of 3.1 per 100,000.[3] Worldwide, more than 200,000 woman are estimated to develop ovarian cancer every year and about 100,000 die from the disease.[4] Ovarian cancer is the most common cause of death from gynecologic cancer in females in the United States and in the year 2012 it was reported that 22,280 new cases of this malignancy were diagnosed with 15,500 associated deaths.[5,6]

The incidence of ovarian cancer in Pakistan is difficult to assess due to the non-availability of population based data, however, its relative frequency has increased over the past few decades. It ranks among the ten commonest cancers in Pakistani females. Its ranking has varied from 2nd to 5th position in various studies.[7-9] It has been rated as the number three cancer of females in Karachi South.[7] However, according to a recent study it is now ranked as the 4th commonest malignancy of females in Pakistan.[8] Among Asian and South Asian countries, Pakistan has the highest rates of ovarian cancer.[9]

The high case fatality rate and poor prognosis of ovarian cancer most of which are high grade serous carcinomas can be attributed to the advanced stage (Stage III & IV) at presentation, with wide metastatic disease within the peritoneal cavity.[1,10] Predisposing factors for ovarian cancers include early menarche,

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late menopause, nulliparity, small family size, family history of breast and ovarian cancer, gonadal dysgenesis and genetic factors.[11,12] Inherited germ line mutations in BRCA 1 and BRCA 2 carriers increases the susceptibility to ovarian cancers.[13,14] Other well defined risk factors include endometriosis, and pelvic inflammatory disease.[15-17] Protective factors against ovarian cancer include pregnancy, lactation, tubal ligation, bilateral salpingo-oophorectomy, hysterectomy and use of oral contraceptive pills.[18-20]

Ovarian malignancies comprise a complex and heterogenous group of neoplasms with several different morphological types, each having its own underlying molecular genetic events, natural history and prognosis.[1] Ovarian tumours include 3 main histologic types namely surface epithelial category, germ cell category and sex cord stromal category based on the presumed cell of origin.[21-23] In addition, the ovary is a preferred site to receive metastatic deposits from other abdominal cancers and breast cancer.[24,25] It is imperative to classify and categorize ovarian cancers because treatment and prognosis are dependent on the histological patterns, molecular genetics, differentiation and clinical stage at presentation.[26]

The current study aims to classify the ovarian cancers according to their most probable tissue of origin based on the WHO classification,[21,22] and to determine the frequency of the various morphological subtypes of ovarian cancers in our setup.

PATIENTS AND METHODS

This study was a descriptive cross – sectional study carried out at the Department of Pathology, King Edward Medical University, Lahore in collaboration with Lady Willington Hospital, Lady Aitchison Hospital, Lahore and all other affiliated Tertiary Care Hospitals.

A total of 180 females with ovarian tumours diagnosed and reported during a 6 months period commencing from May 2014 to Nov 2014 were included in this study. These cases included both benign and malignant ovarian tumours diagnosed in females between the ages of 20 to 70 years. These females had been diagnosed as having ovarian masses on abdominal and pelvic ultrasound examination. The surgically resected ovarian masses received at the Histopathology Section of the Pathology Department of King Edward Medical University, Lahore were fixed in 10% buffered formalin and gross examination with representative tissue sections were taken according to the guidelines as given by Rosai.[27] Size measurements, presence of solid and cystic areas, cyst contents, papillary structures, areas adjacent to the ovarian surface, bases of the papillary areas, external surface projections and nodules, areas adjacent to the fallopian tube fimbriae if identifiable and ovarian hilar regions were examined and representative tissue sections were taken. These sections were then routinely processed according to the standard procedures for paraffin embedding, microtomy and staining with Haematoxylin and Eosin stains. Prepared slides were examined under the microscope for histopathological evaluation and diagnosis. The inflammatory tubo-ovarian masses and non-neoplastic ovarian cystic lesions like follicular cysts, corpus luteal cysts, endometriotic cysts and other nonspecific pelvic masses were excluded from this study. Ovarian tumours were histologically classified as benign and malignant tumours according to the World Health Organization (WHO) Classification of Ovarian tumours.[21,22]

Results and data were compiled using SPSS Version 20 and presented in the form of tables with calculations, percentages and ratios. Mean and Standard Deviation was calculated for quantitative variable like age. Results and findings so obtained were compared with other similar local and international studies.

RESULTS

A total of 180 cases of ovarian tumours fulfilling the criteria were included in this study during a 6 month period commencing from May 2014 to November 2014.

Out of a total of 180 cases of ovarian tumours, 119 cases (66.1%) were classified as benign and 61 cases (33.9%) were classified as malignant tumours giving a ratio of benign to malignant ovarian tumours as 1.95: 1.00 (Table 1).

Table 1: *Frequency of Ovarian Tumours (n = 180). Ratio of Benign to Malignant Ovarian Tumours.*

Types of Ovarian Tumours	*Frequency (No. of Cases)*	*Percentage (%)*
Benign	119	66.1
Malignant	61	33.9
Total	180	100

Mean age of females in this study was 35.43 ± 12.23 years. Minimum age recorded was 20 years and maximum age was 70 years. Females with benign ovarian tumours (n = 119) presented in the age range of 20 and 70 years with a mean age of 31.60 ± 9.63 years. Females with ovarian cancers (n = 61) presented in the age range of 20 and 67 years having a mean age of 44.57 ± 12.78 years (Table 2).

The various benign and malignant ovarian tumours (n = 180) were classified according to the WHO classification [21] into 4 major categories which included surface epithelial tumours, germ cell tumours, sex cord stromal tumours and metastatic tumours to the ovary. Regarding the malignant ovarian tumours (n = 61), their relative frequency and percentages are shown in Table 3. The major category constituted of the surface

Table 2: *Age distribution of patients with Benign and Malignant Ovarian Tumours*

Total No. of Cases n = 180	*Malignant Ovarian Tumours*	*Benign Ovarian Tumours*
	61	119
Minimum age	20 years	20 years
Maximum age	67 years	70 years
Mean ± SD	44.57 ± 12.78 years	31.60 ± 9.63 years

Table 3: *Frequency of the Major Classes/Categories of Malignant Ovarian Tumours (n = 61).*

Category	*Frequency*	*Percentage (%)*
Surface Epithelial Tumours	38	62.30
Germ Cell Tumours	12	19.67
Sex Cord Stromal Tumours	7	11.48
Metastatic Tumours	4	6.56
Total	61	100

epithelial origin ovarian cancers which comprised of 38 cases (62.30%), followed by the germ cell origin category of which there were 12 cases (19.67%). Seven cases (11.48%) were classified into the sex cord stromal group and 4 cases (6.56%) were of metastatic origin (Table 3).

Further subtyping and histopathological analysis of these 4 major ovarian tumour categories is as follows: Out of the 38 surface epithelial origin cancers, 18 (29.51%) cases were serous cyst adenocarcinomas, 14 cases (22.95%) were mucinous cystadenocarcinomas, 4 cases (6.56%) were endometrioid cancers and there was 1 case (1.64%) each of malignant Brenner tumour and mixed mullerian tumour (Table 4). Regarding the malignant germ cell tumours which constituted 12 cases (19.67%), there were 6 dysgerminomas (9.84%), 3 cases (4.92%) of yolk sac tumours, 2 cases (3.28%) of Immature Teratomas and 1 case (1.64%) of mixed germ cell tumour (Table 4).

In the malignant sex cord stromal group, all 7 tumours (11.48%) were granulosa cell tumours. In the metastatic category which comprised of 4 cases (6.56%) out of 61 malignant ovarian tumours, 2 cases (3.28%) were of bilateral metastatic deposits to the ovaries from previously diagnosed and known cases of mucinous adenocarcinoma of the colon and 2 cases (3.28%) were metastatic signet ring carcinomas (Krukenberg Tumous) from the stomach. Figures 1 – 6 show photomicrographs of some of the malignant ovarian tumours diagnosed in this study.

DISCUSSION

Ovarian cancers constitute one of the important forms

Table 4: *Frequency of the Various Morphological Subtypes of Malignant Ovarian Tumours (N = 61).*

Major Category	*No. of Cases (%)*	*Histological Sub-types*	*No. of Cases*	*(%)*
Surface Epithelial Tumours	38 (62.30%)	Serous Cyst Adenocarcinoma	18	29.51
		Mucinous Cyst Adenocarcinoma	14	22.95
		Endometrioid Adenocarcinoma	04	6.56
		Malignant Brenner Tumour	01	1.64
		Malignant Mixed Mullerian Tumour	01	1.64
Malignant Germ Cell Tumours	12 (19.67%)	Dysgerminoma	06	9.84
		Yolk Sac Tumour	03	4.92
		Immature Teratoma	02	3.28
		Mixed Germ Cell Tumour	01	1.64
Malignant Sex Cord Stromal Tumours	07 (11.48%)	Granulosa Cell Tumour	07	11.48
Metastatic Tumours (Krukenberg Tumours)	04 (6.56%)	From Colorectal Cancer	02	3.28
		From Stomach Cancer	02	3.28
Total			61	100

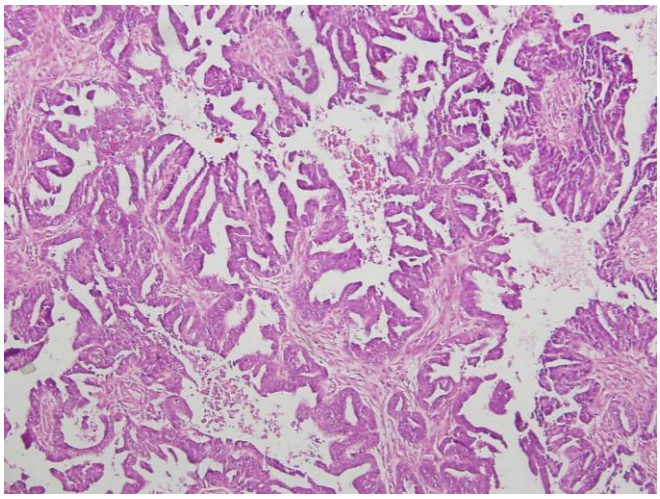

Fig. 1: *Photomicrograph of a high grade papillary serous cystadenocarcinoma (H&E X 100).*

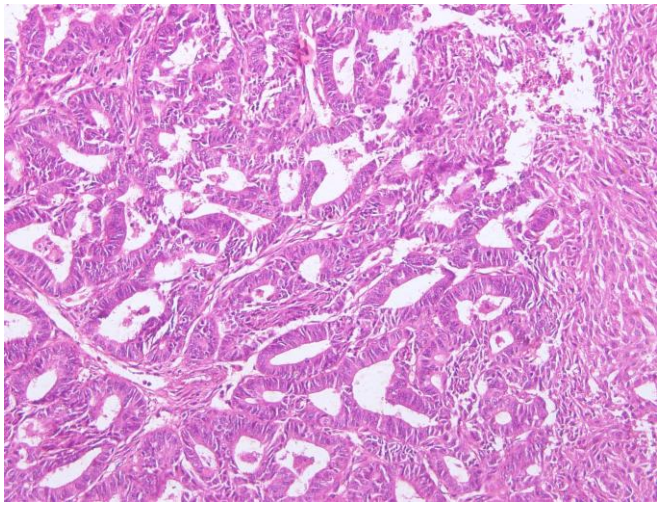

Fig. 2: *Photomicrograph of an endometrioid adenocarcinoma showing well formed glandular structures arranged back to back (H&E, 300 X).*

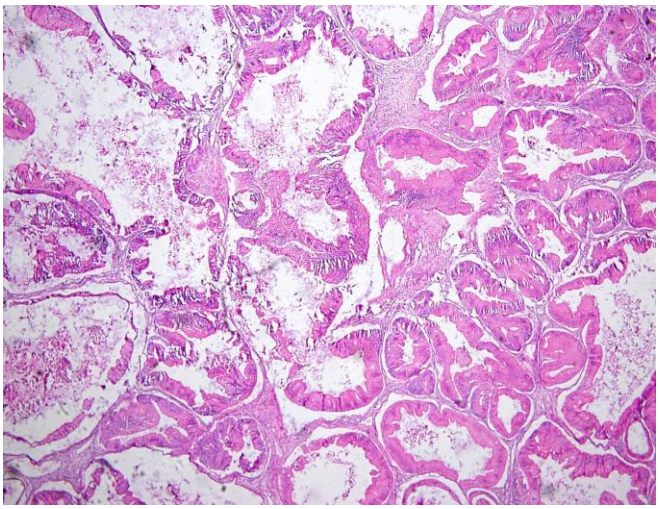

Fig. 3: *Photomicrograph of a mucinous cystadenocarcinoma showing glands filled with mucin pools (H&E, 100X).*

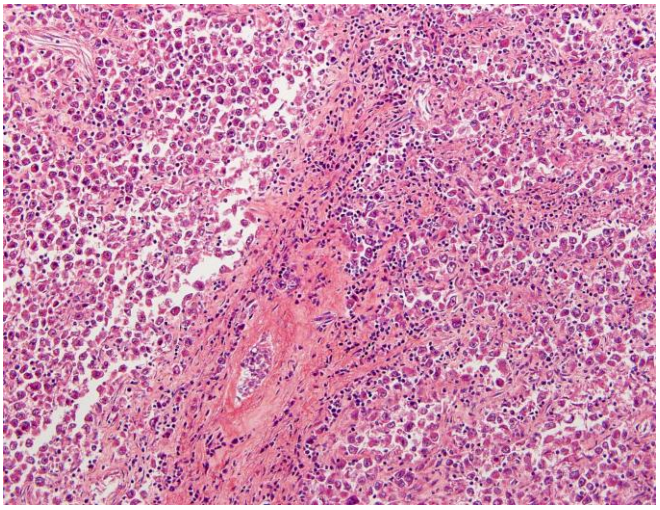

Fig. 4: *Photomicrograph of a dysgerminoma showing germ cells and a fibrous band with lymphocytic infiltrate (H&E, 100X).*

of gynaecologic malignancy. Despite advances in therapeutic approaches and management protocols, it still remains a leading cause of death in females.[5,6]

Attempts at screening and early detection using a combination of transvaginal ultrasound, measurements of serum CA-125 levels and other tumour markers have been unsuccessful because of lack of specificity and sensitivity.[10] The high mortality rate of this tumour is due largely to the fact that the vast majority of females present at advanced stage (Stage III & IV) with wide metastatic disease within the peritoneal cavity.[10,28] The prognosis of ovarian cancer is closely related to the stage at diagnosis, thus the overall prognosis for these patients remains poor.[26] The 5 year survival rate for females with advanced stage ovarian cancer is less than 30%. In contrast patients diagnosed with Stage I Ovarian cancer (which constitute only a small proportion of cases) confined to the ovary have a 5 year survival rate in the range of 90%.[26,28]

Tumours of the ovarian surface epithelium represent approximately 2/3rd of all ovarian neoplasms. These include 3 main histologic types based on the degree of differentiation of neoplastic epithelium: Serous, mucinous and endometrioid. Other types include clear cell tumours, transitional cell tumours, undifferentiated and mixed tumours.[21,22] Serous tumours are the most common malignant ovarian tumours accounting for 35-40%.[1,21,22]

On the basis of clinicopathologic and molecular genetic studies ovarian epithelial cancers have been recently reclassified as Type I and Type II tumours.

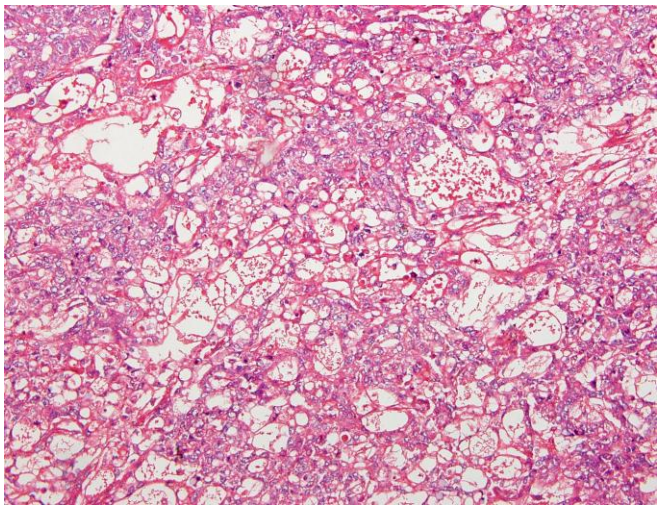

Fig. 5: *Photomicrograph of a yolk sac tumour showing the lace like (sieve - like) pattern (H&E, 200X).*

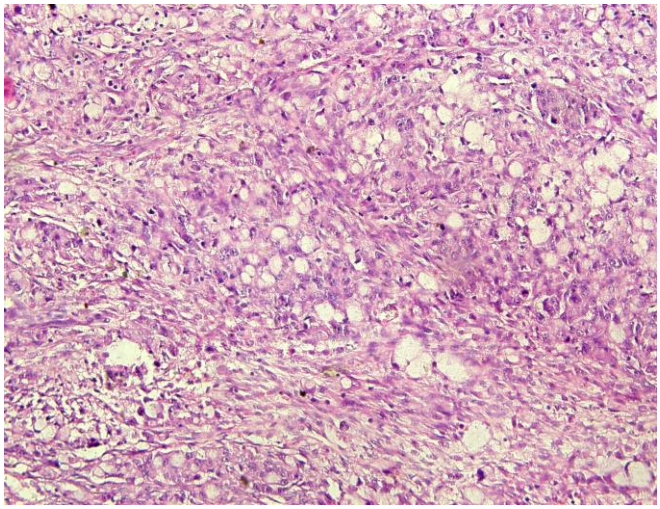

Fig. 6: *Photomicrograph of a Krukenberg tumour of the ovary showing signet ring like cells. (H&E, 100X).*

Type I cancers are low grade, slow growing indolent tumours confined to the ovary at the time of diagnosis and include low grade serous, endometrioid, mucinous, clear cell and malignant brenner tumours. Type II tumours are rapidly growing, highly aggressive neoplasms presenting at an advanced stage and include high grade serous carcinomas, undifferentiated carcinomas and malignant mixed mullerian tumours.[22,27,29] Type II tumours are genetically unstable, the majority having TP53 and BRCA 1,2 mutations.[22,29,30] Several studies indicate that Type II high grade serous carcinoma originate from the epithelium of the fimbriated portion of the fallopian tube called Serous Tubal Intraepithelial Carcinoma (STIC).[1,31,32,33,34]

In Pakistan, the incidence of ovarian cancer is on such a swift rise that there is a need to understand various contributory and predisposing risk factors including both genetic and non-genetic factors. One important such predisposing factor is germ line mutations in the BRCA-1 and BRCA-2 genes.[13,14]

Comparing the age distribution of ovarian cancers with other local studies, a study conducted by Ahmad and Kayani[35] at Aga Khan University Hospital, Karachi showed a mean age of 43.75 years for ovarian cancer which is more or less similar to this study. Another study published by Ahmad and co-workers[36] from Army Medical College, Rawalpindi showed a mean age of malignant ovarian tumours as 49years.

A study published from Brazil in 2011,[37] on 146 ovarian malignancies showed a mean age at diagnosis as 54.67 ± 13.84 years which is obviously quite high compared with our local studies. This could be due to the higher life expectancy in that region because of better living standards and health care facilities like routine screening and other advanced diagnostic modalities as well as health awareness, higher educational and socioeconomic status.

Determination of the various histologic patterns of ovarian cancers is very important for diagnosis as well as prognosis. Prognosis of ovarian cancers can be predicted from the histologic type and clinical stage at presentation.[20] In this study out of a total of 180 females with ovarian tumours, 119 cases (66.1%) were classified as benign tumours and 61 cases (33.9%) were malignant giving an almost 2:1 ratio of benign and malignant tumours.

The morphological breakup of the various ovarian cancers (n = 61) included 38 tumours (62.30%) in the surface epithelial category of which 18 cases (29.51%) were serous cystadenocarcinoma, 14 cases (22.95%) were mucinous cystadenocarcinomas, 4 cases (6.56%) were endometrioid adenocarcinomas and there was 1 case (1.64%) each of malignant brenner tumour and malignant mixed mullerian tumour. Thus the surface epithelial origin ovarian malignancies were the commonest category of ovarian cancers in our study.

Malignant germ cell tumours constituted the 2nd major category of ovarian cancers and included 12 cases (19.67%) out of the total 61 malignant tumours. These constituted 6 cases (9.84%) of dysgerminomas, 3 cases (4.92%) of yolk sac tumours, 2 cases (3.28%) of immature teratomas and 1 case (1.64%) of mixed germ cell tumour. The 3rd category was the malignant sex cord stromal group comprising all 7 cases (11.48%) of granulosa cell tumours, followed by the 4th category of metastatic tumours which comprised of 4 cases (6.5%).

Comparing the frequency of ovarian malignancies with a study conducted by Ashraf et al[38] at Fatima Jinnah Medical College, Lahore on 127 ovarian tumours, classified 82 cases (64.57%) as benign and 45 cases (35.43%) as malignant which is very similar to the present study. Morphological breakup of their malignant tumours was as follows: There were 34 ovarian cancers (75.56%) in the surface epithelial category which con-

stituted the commonest ovarian malignant group. Further breakup of this group showed that there were 11 cases of serous cystadenocarcinoma, 9 cases of mucinous cystadenocarcinoma and 7 cases of endometrioid adenocarcinoma. Other less common ovarian cancers included papillary cyst adenocarcinoma (3 cases), clear cell carcinoma (2 cases) and malignant Brenner tumour (2 cases). Serous cystadenocarcinomas, mucinous cystadenocarcinomas and endometrioid adenocarcinoma constituted the commonest malignant subtype in the surface epithelial group which is similar to the present study. Likewise malignant germ cell tumours constituted the 2nd major category of ovarian cancers in Ashraf's study [38] comprising of 7 cases (15.56%), which included 3 cases of yolk sac tumours, 2 cases of dysgerminomas and 1 case each of mixed germ cell tumour and teratocarcinoma. Sex cord stromal group constituted the 3rd category of which of all 3 cases (6.67%) were granulosa cell tumours. In their study metastatic (Krukenberg) tumour comprised of only 1 case. Thus most of the findings of Ashraf's study [38] are in accordance with the present study.

The study by Ahmad [36] on 762 ovarian tumours during a 9 year period at Army Medical College, Rawalpindi, classified 498 tumours (65.35%) as benign, 33 tumours (4.33%) as borderline and 231 tumours (30.31%) as malignant. These figures are very similar to the frequency of benign and malignant tumours as seen in the present study and Ashraf's study.[38] However, no borderline tumours were reported in the present study. Further categorization showed 181 ovarian tumours (78.35%) as belonging to the surface epithelial group in which serous cystadenocarcinomas, mucinous cystadenocarcinomas and endometrioid carcinomas each constituted of 108 cases (46.75%), 53 cases (22.94%) and 11 cases (4.76%) respectively similar to the present study. Other less common entities in their epithelial category included undifferentiated carcinomas (4 cases), malignant mixed mullerian tumours (3 cases) and clear cell carcinomas (2 cases). Malignant germ cell tumours constituted the 2nd major category comprising of 37 cases (16.01%) of which dysgerminoma was the commonest malignant subtype constituting 14 cases (6.06%) followed by yolk sac tumour comprising of 6 cases (2.60%). Other germ cell tumours included embryonal carcinoma and immature teratomas which constituted of 5 cases (2.16%) each, mixed germ cell tumours and choriocarcinomas which constituted of 4 cases (1.73%) and 3 cases (1.30%) respectively out of the total 231 malignant tumours. The relative frequency of the 2 common malignant germ cell tumours is quite similar to the present study. However no embryonal carcinoma and choriocarcinoma was seen in the present study as the number of cases and the duration of study was small as compared to the 9 year study duration and the relatively large sample size of Ahmad's study.[36] In the sex cord stromal category, granulosa cell tumour was the only subtype constituting of all 13 cases (5.62%). This observation is also similar to the present study and Ashrafs' study.[38]

A study by Khan and Luqman[39] at AFIP, Rawalpindi on 194 ovarian tumours classified 148 cases (76%) as benign and 46 cases (24%) as malignant. In their study out of 36 epithelial (76.09%) ovarian cancers, serous carcinoma was the commonest constituting 15 cases (34.78%) followed by endometrioid carcinoma comprising of 10 cases (21.73%). In their study mucinous carcinoma occupied 3rd position constituting of 7 cases (15.21%). This contrasts with the present study and the 2 previously quoted studies.[36,38]

Comparing our local studies with a study by Abdullah[40] from Saudi Arabia which included 382 ovarian tumours, 278 tumours (72.8%) were classified as benign, 20 cases (5.2%) as borderline and 84 cases (22%) as malignant. Breakup of the malignant cases showed 51 tumours (60.7%) to be of surface epithelial origin, 13 cases (15.5%) of germ cell origin, another 13 cases (15.5%) of metastatic origin and 7 cases (8.3%) were sex cord stromal tumours. In their study serous cyst adenocarcinoma constituted the major bulk of ovarian cancers comprising of 28 cases (33.33%) followed by mucinous cystadenocarcinoma constituting of 13 cases (15.4%), similar to the present data and other local studies.[35,36,38]

Metastatic group of ovarian tumours is being recognized with increasing frequency in most recent studies based on better diagnostic and screening facilities and the availability of immunohistochemistry.[24,25] These modalities have helped to re-classify many mucinous carcinomas in the ovary as being of metastatic nature. It is now widely accepted that bonafide primary ovarian mucinous carcinomas are rare and are typically low stage at presentation (Figo Stage I/II). With an advanced stage ovarian mucinous carcinoma, a metastasis should always be suspected.[34] Recent studies have shown that mucinous carcinomas account for only 3% of primary ovarian epithelial cancers.[22,23] This is in contrast to older literature where mucinous carcinoma was the 2nd most common subtype and accounted for approximately 12% of primary ovarian carcinomas.[1] Similarly in most of our local studies [35,36,38] and the present study mucinous carcinoma is still being reported to be much more prevalent. This discrepancy is due to the nonavailability of advanced diagnostic modalities, lack of screening and health care facilities, poverty and expensive cost of immunohistochemistry. Most ovarian metastatic tumours are now known to be of gastrointestinal and breast origin.[24,25] The present study included 4 cases (6.56%) of metastatic tumours; 2 being bilateral ovarian tumours from known cases of Colorectal cancers and 2 cases were metastatic signet ring carcinomas (Krukenberg tumours) of gastric origin. Ahmad and Kayani[35] reported 21 cases (6.54%) of metastatic tumours to the ovary out of 321

malignant ovarian tumours in their study. This percentage of metastatic tumours is exactly similar to the present study's figure of 6.56%. They also reported an additional 5th category of tumours not specific to the ovary comprising of 8 cases which included 7 cases of lymphoma and 1 case of leukemia out of 321 malignant tumours cases in their study. This category however has not been reported in the various studies discussed in the present study.

It is ***concluded*** that ovarian cancers of surface epithelial origin are the commonest group followed by the germ cell variety. Serous cyst adenocarcinoma is the commonest subtype observed in the present study was well as other studies quoted in this article.

Patients with ovarian malignancies usually present at advanced and complicated stages consequently having a dismal prognosis. In Pakistan, the incidence of ovarian cancers is on such a steep rise that there is a need to explore and evaluate the various genetic and other contributory risk factors. Periodic serum CA-125 levels, transvaginal ultrasounds, annual pelvic examinations and genetic testing of females (for BRCA 1,2 mutations) at high risk and having genetic predisposition can be used as regular screening tools for early diagnosis and management of these lethal cancers. In addition bilateral salpingo-oophrectomy may be considered a risk reducing strategy in females with a strong family history of breast / ovarian cancer and those who have computed their families.

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