Clinicopathological Pattern of Gynecological Malignancies at Tertiary Care Teaching Hospital

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Abstract

Objective: To view current clinicopathological pattern of gynecological malignancies at a tertiary care hospital in Karachi.

Methods: This is a retrospective research performed in the department of obstetrics and gynecology unit 1 from January 2020 to December 2021**.** All cases of gynecological malignancies irrespective of age, race and cast were included for study. Around 164 cases with clinical or radiological diagnosis of malignancy were admitted for gynecological malignancy work up. Out of them 42 were confirmed on histopathology of biopsy or resected specimen. Patients with gestational trophoblastic disease and metastatic malignancies from another primary site were excluded. Data of these confirmed 42 cases fulfilling exclusion and inclusion criteria was included for study. Relevant data on pre-designed Performa was tabulated and histopathology according to WHO histological classification system.

Results: Out of 164 cases of suspected gynecological malignancy 42 histopathological confirmed cases were selected for study. Frequency of gynecological malignancies out of 885 gynecological admission is 4.7%. Ovarian cancers were commonest gynecological malignancy (54.7%), followed by cervical cancer (19.04%), uterine cancer (16.66%), and vulvar /vaginal cancers (9.5%). In ovarian cancers epithelial cancers were (86.9%) and (13.04%) were non-epithelial. In epithelial (65%) serous, (15%) mucinous and (20%) were other less common types. In non-epithelial were dysgerminoma (66.66%) and (33.33) sex cord stromal cancers. In cervical (100%) were squamous cell carcinoma. In uterine (85.7%) were adenocarcinoma and (14.28%) were leiomyosarcoma. In vaginal cancers (50%) squamous cell carcinoma and (50%) was melanoma. In vulvar cancers all (100%) were squamous cell carcinoma.

Conclusion: Ovarian cancer is commonest gynecological malignancy in our study. Common age group, parity, clinical presentation and histopathology is comparable with studies. Majority of cases came late in advanced stage of disease.

Key words: Gynecologic neoplasms,ovarian cancers, human papilloma virus, cancer Screening, BRCA1

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Introduction

Worldwide Gynecological malignancies (ovarian, cervical, uterine, vulvar and vaginal) are very important reason of cancer related deaths in women. It varies in distribution and frequency from one region to the other[1]. In Pakistan gynecology malignancy accounts for about 11.7% and 12.5% of all cancers diagnosed in women[2,3].

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Ovarian cancer is the 6th most common cause of cancer in women, with approximately 7400 new cases diagnosed in the UK per year. It has a life time risk of 1 in 50; however, incidence is projected to rise 15% by 2035 due to population ageing. Of all the gynecological malignancies it has the highest mortality rate as most cases present with advanced disease. The 10-year survival rate is poor at 35%, with around 4100 deaths per year in the UK. Mortality rates are expected to fall due to advances in chemotherapy regimens and discovery of targeted therapies[4].Cervical cancer is the fourth most common cancer in women worldwide.

Furthermore, it is the most common cancer in women aged 15-44 year, accounting for 9% of new cases diagnosed[5].

cases diagnosed[5]. Approximately 85% of cervical cancer cases occur in developing countries, and they comprise 12% of all female cancers[5]. In the UK endometrial cancer is the fourth most common cancer and the most common gynecological malignancy. In the UK, there are over 9000 new cases each year and the incidence has risen by 57% since the early 1990s. This is attributed to the ageing population, a growing prevalence of obesity and declining rates of hysterectomy for benign disease. Survival rates are dependent on stage at diagnosis, ranging from 95% for stage 1 cancers to 15% for stage 1V, therefore early diagnosis is essential for good outcome[6]. Pakistan is a lower middle-income country, with poorly available facilities for cancer care amidst an increasing burden on country finances. Pakistan faces multiple challenges in the field of oncology, due to high disease prevalence in the country and need of advanced diagnostic, curative and palliative facilities for the treatment of advanced disease[7]. In Pakistan Palliative care is hitherto unknown modality, and has been recognized as a component of most health care systems. Lack of supportive facilities, lack of health care providers training and lack of palliative medications and procedures are all contributing factors to this dilemma[8].

Rationale of study is to find out burden of disease in teaching hospital, common vulnerable age group and stage of disease at time of presentation. The current situation of infrastructure, screening, diagnostic and treatment facilities are inadequate in our country**.** We found 42 cases in two year study period means burden is not less and other government and private sector teaching hospitals must also be getting enough number of this high morbidity and mortality disease.

By providing such information we will try to establish need to develop required infrastructure, well equipped teaching hospitals and research centers, college of physicians and surgeons Pakistan accredited institutes for fellowship in surgical oncology and facilities for better early stage diagnosis and treatment of disease. We will try to develop recommendation for improvement of outcomes and early detection of malignancies. In lower middle-income countries like Pakistan (LMIC) due to discrepant low resources setting, awareness of screening test among the population, health care providers and policy makers are mandatory.

Patients and Methods

Retrospective cross- sectional study of gynecological malignancies carried out in the department of obstetrics and gynecology unit 1 at Dow University of health sciences / Dr Ruth K M Pfau Civil hospital Karachi from January 2020 to December 2021.Around 164 suspected gynecological malignancies cases clinically or radiologically during two year study period were admitted for work up. Patients with gestational trophoblastic disease, metastasis to genital tract from other primary site and cervical abnormal Pap smear cases were excluded. Relevant data on predesigned Performa regarding ages, clinical presentation, physical examination, investigations, and necessary surgical procedures was collected. Staging according to FIGO and histologic classification according to WHO histological classification system was done. Forty two cases included for the study had a definite diagnosis made either on biopsy or resected specimen which were collected from the department of pathology. Results were presented as frequencies and percentages. Sample size calculated by taking prevalence of of vulval cancer 4.6% approximate 5% and margin of error 4% with 95% confidence interval[9] sampling technique non probability consecutive .Data was analyzed by statistical package for social sciences (SPSS) version 17.

Results:

A total gynecological admission during study period was 885. Total gynae admission in year 2020 was 390 and in year 2021 was 495. Out of 885 cases 164 were admitted with high suspicion of malignancy. We found a total of 42 new cases of gynecological malignancies during study period. Proportion of gynecological malignancies were 42 (4.7%).Proportion of ovarian cancers 23 (54.7%) cervical cancer, 8 (19.04 %) uterine cancer 7 (16.6 %), vaginal cancer 2 (4.7 %) and vulvar cancer was 2 (4.7 %).

Table 1. Relative frequency of gynecological malignancies: n=42

Malignancy	No	%
Ovarian cancer	23	54.7
Cervical cancer	8	19.04
Uterine cancer	7	16.6
Vaginal cancer	2	4.7
Vulvar cancer	2	4.7

Distribution of gynecological malignancies according to age, parity and clinical presentation is presented in Table 2.

Table 2. Distribution of gynecological malignancy with age, parity and presentation. n=42

parameters	Range	Ovarian cancer n=23	Cervical cancern=8	Uterine cancern=7	Vaginal cancern=2	Vulvar cancern=2
Age	Minimum	20	42	24	47	48
	Maximum	72	54	71	72	70
Parity	Nulliparous	3	0	3	1	-
	Multiparous	20	8	4	1	2
presentation						
	Abdominal pain and mass	22	-	-	-	-
	Irregular bleeding	-	-	4	-	-
	PMB	1	5	3	-	-
	Contact bleeding	-	3	-	-	-
	Enlarged inguinal LN	-	-	-	2	-
	Vulvar growth	-	-	-	-	2

LN= lymph nodes, PMB= post- menopausal bleeding

Table 3. Shows histology and staging of all malignancies. The ovarian cancer 23 (54.7%) was main histological type of gynecological malignancies, with epithelial type observed in 20 (86.95%) cases and non- epithelial in 3 (13.04%) cases. Out of 20 epithelial type 13 (65%) were serous and 3 (15%) were mucinous, remaining Brenner, struma overi, endometroid and clear cell were 1 each (5%). Out of 3 non- epithelial type 2 cases (66.66%) were dysgerminoma and 1 case (33.33%) was sex cord stromal cancer. In Cervical cancer in all 8 (100%) cases histology was squa-mous cell carcinoma. In uterus main histological type was adeno carcinoma 6 (85.71%) and 1 (14.28%) was leiomyosarcoma. Out of 2 vaginal cancer 1 (50%) squamous cell carcinoma and 1 (50%) was melanoma. Out of 2 vulvar cancer 2 (100%) were squamous cell carcinoma.Majority of cases diagnosed in advanced stage.

Table 3. Distribution of gynecological malignancies according to Histology and staging:

Ovarian cancer n=23	Histology	No.	%	Staging	No.	%
EOC n=20	Serous	13	65	High grade	12	92.3
				Low grade	1	7.6
	Mucinous	13	15	1A	2	66.66
				111A	1	33.33
	Brenner	1	5	111A	1	100
	Struma overii	1	5	111A	1	100
	Endometroid					
	Clear cell	1	5	1V	1	100
		1	5	111A	1	100
.						
NEOC Sn=3	Dysgerminoma	2	66.66	1A	2	100
	Sexcord stromal	1	66.66	111A	1	100
Cervical cance m=8	Squamous cell	8	100	111A	7	87.5
				11B	1	12.5
Uterine cancern=7	Adenocarcinoma	6	87.5	1A	5	83.3
				111A	1	16.66
	leiomyosarcoma	1	14.2	111A	1	100
Vaginal	Squamous cell	1	50	111B	1	100
	Melanoma	1	50	111B	1	100
Vulvar m=2	Squamous cell	2	100	111	2	100

Discussion

Gynecological malignancies pose a significant problem to women health. In Pakistan number of facilities required both for investigations and treatment of cancer are very insufficient, let alone palliative and hospice care. Nationwide surveys in 2005 and 2010 showed that while there was an increase in resources over time, the number is still insufficient to deal with the ever-increasing number of cancer[10].

Out of 42 gynecological malignancies 23 (54.7%) were cases of ovarian malignancy. In this study ovarian cancer is the commonest malignancy. This is comparable with other studies (47%, 54.4%, 49.18%) [11,12]. In karachi, frequency of new cases of ovarian cancer is 10/100,000 per year wh-

ile in Lahore this cancer type is ranked 4th [13]. In study from Dhaka, Bangladesh ovarian cancer (29%) comes after cervical cancer[2]. Majority of cases 82.6% were between 4th-6th decades. One study observed similar age group with peak incidence in 5th decade [14]. Youngest patient was an unmarried 20 years old girl. Histopathology of her ovarian malignancy was dysgerminoma, similarly in one study youngest 14 years old unmarried girl also diagnosed to had dysgerminoma[14]. Dysgerminoma a non-epithelial ovarian cancer is rare heterogenous subtype of ovarian cancer which originate from the egg producing cells of the ovary. Unlike epithelial ovarian cancers non-epithelial ovarian cancers are usually observed from 10- 20 years of life[4]. Main presenting complaint was abdominal pain and abdominal distention similar to literature and studies **54.55%**[14]. Majority of them (86.95%) were multiparous. In study from Lahore 70% cases with ovarian cancer were multipara[12]. Regarding histopathology of ovarian cancers 20 cases (86.95%) were epithelial and 3 (13.04 %) was non epithelial type. Epithelial ovarian cancer is main histopathology in other studies also, its 72.5% and 90.9% in these studies[14]. We observed serous cystadenocarcinoma was commonest histopathological type of epithelial ovarian cancers also seen in other study[14]. In study by Hina et al mucinous cyst adenocarcinoma is main type of epithelial cancers. Non- epithelial cancers were 3 out of it 2 cases (66.66%) was dysgerminoma 1 case (33.33%) was sex cord stromal tumor. Dysgerminoma is main non-epithelial type of ovarian cancer in study by Hina et al. Sex cord stromal tumor was adult granulosa cell type ovarian non-epithelial tumor found in 72 years old woman presented with post- menopausal bleeding. Granulosa cell tumor is main histopathology type of sex cord stromal tumor in other studies[3]. Majority of epithelial ovarian cancer cases 17 out of 20 (85%) was diagnosed in late stage (stage111, stage1V) and 1 out of 3 non- epithelial cases diagnosed in late stage(stage111) also observed in other studies [2,12,14].In developing countries management of ovarian cancers poses great challenge,diagnosis of ovarian cancers at late stage requires difficult, very costly and immediate treatment. Early detection can improve life expectancy and burden on resources. Ovarian cancer screening is not even well established in western countries. Few strategies are under research which is possible to adopt and to give benefit of simple management and improvement in progression free survival. Hereditary ovarian cancers screening in families is good option. It includes BRCA mutant gene, Lynch syndrome also called hereditary non- polyposis colon cancer and Li-Fraumeni syndrome (LFS) with mutant tumor suppressor gene TP53. Familial screening of high risk cases with ovarian cancers in 1st and 2nd degree relatives is in practice in UK. BRCA 1 affected women carries 35-42% **by the age of 80** and BRCA2 affected carries 17-20% risk of ovarian cancer. The identification of individuals with pathogenic BRCA variants is therefore very important to be able to decide treatment and find out at-risk individuals for appropriate clinical management strategies which may involve increased surveillance and/ or risk reducing procedures[15]. Risk reducing bilateral salpingo-oopherectomy, by the age of 40 and 45 is recommended respectively in BRCA1 and BRCA2 mutation gene positive candidates. Lynch syndrome represent 10-15% of hereditary ovarian cancers and LFS is associated with significantly earlier ovarian cancer. To improve progression free survival in individual with no germ line BRCA mutation, determination of BRCA in resected specimen called BRCA somatic mutation is under research. In one study carried out in 169 population with high grade serous ovarian/ fallopian tubes/ peritoneal cancers germ line or tumor testing BRCA genes by next generation system (NGS). Pathogenic variant was detected at a frequency of 14.8% with 6.5% of patients shown to have an acquired pathogenic variant that would not be detected through germline testing alone. The identification of a pathogenic variant in either the BRCA1 or BRCA2 can have prognostic and predictive implications for patients with ovarian cancer and their families. Targeted therapy by Poly (ADP-ribose) polymerase inhibitor (PARPi) treatment significantly improves progressi-

on free survival in patients with advanced ovarian cancer disease, its indication is rapidly evolving. Ithas been suggested in this study that both germline and tumor BRCA1 and BRCA2 path-ogenic variant by NGS testing should be requ-ested in parallel would ensure that all eligible pat-ients with non- mucinous ovarian, fallopian tubes, peritoneal cancer are afforded the opp-ort-unity to access the significant benefit of PARPi in timely way. Somatic mutation BRCA cases can be given targeted therapy and results in term of pro-gression free survival are encouraging[16].

Cervical cancers are 2nd commonest malignancy after ovarian cancers. Other studies also found cervical cancer 2nd most common gynecological malignancy in their studies[3,11,12]while its commonest in one study[2] and 3rd in position in other study[14]. Out of 42 gynecology malignancy cases 8werecases of cervical malignancy (19.04%), frequency in other studies is 29%,18.8%, 23.7%[3,11,12]. Range of age is between 42-54 years while its 40 -49 years in other study[11]. All women were multiparous in our study as well as in one study and about 92.4% were multiparous in other study[2,12]. Presentation in majority of cases was post -menopausal bleeding (PMB) and contact bleeding (87.5%) followed by irregular menstruation (13.5%). In one study more than 50% cases had PMB and contact bleeding followed by menstrual irregularities (41.5%)[2]. Histopathology in all cases (100%) was squamous cell carcinoma. In many studies squamous cell carcinoma was histopathology in majority of cases (96.22%, 75.9%, 90.0%, 60%)[2,3,11,14]. Majority 87.5% cases diagnosed in advanced stage on examination under anesthesia therefore instead of surgery, cases were sent for radiotherapy and one case (13.5%) underwent surgery. In Pakistan incidence of cervical cancer is low, nevertheless mortality is higher due to late diagnosis and lack of structural program for cervical screening[17]. There is 60-70% reduction in mortality associated with carcinoma cervix in countries where cervical screening is in practice[18]. For the identification of women at increased risk of cervical pathology cervical scrap is taken in cervical screening. Human papilloma virus (HPV) is responsible for cervical pathology. Among Pakistani women it has been shown in many studies conducted in different parts of Pakistan that HPV is very important cause of cervical cancer[19]. Recommended strategy of cervical screening for low grade or borderline dyskaryosis cases is HPV testing and for high grade or worse cases to referred them directly for colposcopy. Colposcopy is not available in all set ups and thus this policy decreases its unnecessary application. Along with early detection through cervical screening HPV vaccine has been introduced in UK since 2008[20]. HPV vaccine is HPV like particles human papilla virions capable of inducing immune response when given to high school girls[21]. Both cervical screening and vaccination are doable in Pakistan. Lack of awareness is big issue for satisfactory results both in public and health care providers.

Uterine/endometrial cancer is 3rd most common gynecological malignancy in our study also comparable with other studies[2,11,12] while its 2nd in number of gynecological malignancies in another study[14]. In our study it constitutes 16.6% of all gynecological malignancies while 15.2% in another study[11]. Age range is between 24-71 years. Majority (57.1%) were less than 45 years and presented with menstrual irregularities while (42.85%) were more than 45 years and presented with PMB. While PMB is presentation in 75% cases of study by Sayma Afroz et al [2]. Histopathology in 85.7% was adenocarcinoma and in 14.2% it was leiomyosarcoma. Histopathology observed in one study is endometrial cancer 75.9% and 21.87% is sarcoma[3]. Majority of them (71.4%) diagnosed in stage 1, while 28.7% came with advanced stage disease. In study by Tayyaba Wasim in Lahore 59.25% presented in stage 1 and 25.9% in stage111 and 1V[12].Uterine malignancy reputation is of good prognosis due to early detection by evaluation of cases presenting with menorrhagia, irregular vaginal bleeding and post meno-pausal bleeding (PMB). Despite this, rapidly rising incidence of poor outcome from late diagnosed disease is very disappointing as increasing number of women are dying [22]. Screeni-

ing of women with risk factors like PMB, BMIe"30kg/m^2, polycystic ovaries (PCO), Lynch syndrome, women on hormone replacement therapy (HRT) or tamoxifen therapy is recommended. Every additional 5 kg/m^2 of BMI is associated with 50% (40-60%) increased risk of endometrial cancer[23], women with Lynch syndrome have a 25-60% life time risk of endometrial cancer and they present at younger age than women with sporadic endometrial cancer[24]. TVS is very cost-effective non-invasive tool for screening of these high-risk cases through endometrial thickness[22].

We found 4 cases of vulva/ vagina cancers. It accounts for 9.5% of all gynecological malignancies. In other studies, its frequency among gynecological malignancy is 6% and 13.7%[3,9]. Vulvar and vaginal cancers are rare cancers of female genital tract malignancies. Histopathology of all cases was squamous cell carcinoma except one case of vaginal cancer came out undifferentiated melanoma. Melanoma in 72 years old unmarried woman. She presented with 3rd degree cervical descent and vaginal growth. Melanoma is very rare cancer of vagina. In literature only 500 cases are reported constituting 0.3% of melanoma[25]. Regarding histopathology of vulvar and vaginal cancers results are comparable with other studies. In one study squamous cell carcinoma was observed in 100% of vulvar and 60% cases of vaginal cancers[9]. One case of both vulvar and vaginal cancers was observed in women before 50 years of age. HPV infection is also responsible for vulvar and vaginal pathology and importance of screening awareness is evident here also.

Limitations of this study is hospital-based study therefore a smaller number of cases reported. Study should be multi-center as well as community based to see correct situation of burden. Outcome of treatment is not included.

This information we have gathered will help to develop adequate facilities for screening, diagnosis and treatment of gynecological malignancies. Development of equipped research, teaching and surgical oncology centers is required. There is need to develop changes in whole health care system according to resources.

There is established role of cervical and various cancer screening programs. HPV vaccination in young girls is very important. Familial screening in high risk cases for hereditary ovarian and endometrial malignancy. Through workshops, posters and public awareness campaigns we can give health and sexual education. Through well-equipped oncology research centers, we can develop better cancer therapeutics. One step clinic, under one roof where vulnerable cases are examined, scanned and offered minor diagnostic procedures to avoid delay is required.

Conclusion

Ovarian cancer is the leading gynecological malignancy followed by cervical and uterine. The most common age groups, parity, presentation and histopathology are comparable. Majority of cases presented in advanced stage of disease.

Conflict of Interests

The authors have no conflict of interests and received no grant/funding from any organization

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