Original Article

Received: 2024-03-06
Accepted: 2024-06-25

BCCR
2024, No 3, Vol 16 :151-159
www.bccrjournal.com

http://doi.org/10.18502/bccr.v16i3.19695

Clinicopathological Spectrum of Indian Adolescent and Young Adults (AYA) Gynecological Tumors: A Retrospective Analysis

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ABSTRACT

Background: Cancers in adolescents and young adults (AYA) represent a bridge between childhood and elderly incidence curves of cancers, demanding tailored approaches and management of their distinct presentations. The literature on Indian gynaecological cancer patients aged 15 to 39 years is limited. Thus, our study aims to determine the distribution of gynaecological tumours, modalities of diagnosis, and treatment employed in managing these patients.

Methods: A retrospective cross-sectional analysis of patients from 15 to 39 years of age who presented with gynaecological tumours was done. The data of all the patients during the study period were recorded and statistically analysed.

Results: The study included 50 patients. The tumours observed were ovarian (78%), cervical (16%), and uterine (6%) in origin. Histopathological diagnosis was benign (46%), malignant (50%), and borderline tumour (4%). CA125 was the most frequently done tumour marker and was raised in 17 cases (34%), of which 13 were malignant. The size of the tumour was greater than 10 cm in 56% of cases. Definitive management strategies included cystectomy/ salpingo-oopherectomy (44%), total hysterectomy and salpingo-oopherectomy (38%), chemoradiation (14%), and conization (2%) in different cancers. The most common benign and malignant ovarian tumours were serous cystadenoma and serous cystadenocarcinoma, respectively. All uterine malignancies were sarcomas.

Conclusion: The burden of gynecological cancers among the AYA population is a matter of emerging concern in India. Timely diagnosis and comprehensive and multidisciplinary management can improve survival and preserve future fertility in young patients with cancer.

Keywords: Adolescent and Young Adults (AYAs); Gynecological Cancers; Sarcoma; Epithelial Tumors

INTRODUCTION:

AYA represents an important segment of any country's active population and has a substantial impact on health-care strategy. The National Cancer Institute (NCI) defines AYAs as those aged 15 through 39 years [1]. A study analyzing data from the National Cancer Registry Programme (NCRP) in India, covering 28 population-based cancer registries (PBCRs) from 2012 to 2016, reported that cancers in the AYA age group accounted for 11.57% of all cancers, with a higher age-adjusted incidence rate (AAR) in females (29.2 per 100,000) compared to males (22.2 per 100,000). The majority of AYA cancer patients had locoregional disease at the time of diagnosis, and the projected number of AYA cancer cases is expected to increase to 178,617 by 2025 [2]. A study analyzing 287 AYA cancer patients from two cancer centers in Delhi found that gynaecological, gastrointestinal, and breast cancer were amongst the leading malignancies in females aged 15–39 years [3]. Cancers of these patients have distinct biological, sociodemographic, and behavioral traits, with lower rates of survival than the younger group. The cancer in AYAs is 2.7 times more prevalent than among those under the age of 15, but less prevalent than cancer in older age groups [4]. Also, its incidence is growing faster than that of children or older adults, and has attracted less attention in control and prevention initiatives [5]. Furthermore, AYAs with cancer require personalized approaches and management based on their unique presentations. Genital tract tumors in girls can cause genital bleeding or odorous secretions, abdominal pain, or lumps in the abdomen. These can be uterine, ovarian, cervical, or vulvar in origin. Uterine tumors are rare and more likely to be malignant in this age group. Endometrial cancer usually occurs in 15% of cases in premenopausal women, and just over 1% of patients are diagnosed before 40 years of age. Only a few cases of endometrial cancer have been reported in adolescents. Uterine sarcomas represent about 3–9% of malignant uterine tumors. Neoplasms of the vagina and cervix in the newborns, children, and adolescents are sporadic. Adolescent and young ovarian tumors can appear with a variety of symptoms, including asymptomatic lumps and severe abdominal pain. The most frequent ovarian lesions include benign and functional cysts. Although the majority of lesions are benign, it is critical to detect potentially fatal malignant lesions early for a better prognosis. Gynecologists have a challenging choice between surgical and conservative treatment for young ovarian tumors [6].

The literature on Indian gynecological cancer patients aged 15 to 39 years is scarce. Thus, this study was conducted to figure out the distribution of gynecological tumors among AYA patients at our institute, which is one of the largest tertiary care institutes in North India. The primary goal was to identify specifications that could enhance the management and the outcomes of cancer patients diagnosed in teens and young adults, with a focus on the clinical signs at diagnosis and the modality of treatment.

Material and methods:

This retrospective cross-sectional analysis was conducted at the Department of Obstetrics and Gynecology at a tertiary teaching hospital in Haryana, India.

Inclusion criteria were chosen from patients between 15 and 39 years old who presented with clinical or preoperative diagnosis of gynecological tumors, with a definite pathological diagnosis for each lesion, and the availability of initial pre-treatment imaging and clinical profile.

Exclusion criteria were emergency surgery, pregnancy, and infectious etiologies.

The study period was from January 2021 to December 2023.

Data collection: Data were retrieved from the medical files of patients after approval from the institute. The following information was obtained: age at diagnosis, medical history, symptoms, location of lesion, serum levels of tumor markers, if available, preoperative biopsy or fine needle aspiration cytology, imaging findings, treatment modality, as well as a pathological diagnosis. Lesions were classified as benign, borderline, or malignant.

Imaging results were all reassessed with regards to size of lesion, cystic, solid or complex lesion, unilocular or multicompartmental lesion, presence of ascites, as well as presence of unilateral or bilateral lesions. The surgical procedure was conducted by the general gynecology or gynecology oncology team as per individualized requirements. The characteristics were compared between benign and malignant lesions.

Descriptive statistics were used to report demographic data. Continuous variables were compared using the Mann–Whitney test. The chi-square test was used to compare categorical data. P value ≤ 0.05 was considered significant.

Results:

The study included 50 adolescent and young women with gynecological tumors who were admitted to the department of Obstetrics and Gynecology, Post Graduate Institute of Health Sciences, Rohtak, Haryana, India, during the study period. The mean age of participants was 29.46 years. Presumptive diagnoses on admission were adnexal masses (54%), carcinoma (42%), and abnormal uterine bleeding (4%). The tumors observed were ovarian (78%), cervical (16%), and uterine (6%) in origin. Table 1 depicts the location of the tumor and the histopathological diagnosis as benign (46%), malignant (50%), and borderline tumor (4%). Baseline characteristics and presenting complaints of patients are shown in Table 2. Biopsy or aspiration cytology done preoperatively was suspicious of malignancy in 23 out of 50 cases (46%). CA125 was the most frequently done tumor marker and was raised in 17 cases (34%), out of which 13 were malignant. The size of the tumor was greater than 10 cm in 56% of cases (Table 3). Table 4 represents the tumor marker and imaging characteristics of patients with ovarian masses. Neoadjuvant chemotherapy was given in 11 cases. Definitive management strategies included cystectomy/ salpingo-oopherectomy (44%), total hysterectomy and salpingo-oopherectomy (38%), chemoradiation (14%), and conization (2%) as per the standard procedure of management in different cancers. Resurgery was required in 4 cases to complete the surgery for malignancy. Histopathological findings of all patients are shown in Figures 1 and 2. The most common benign and malignant ovarian tumors were serous cystadenoma and serous cystadenocarcinoma, respectively. All uterine malignancies were sarcomas. Post-operative chemotherapy was done in 12 ovarian malignancies, and one patient required second-line chemotherapy of etoposide. Vaginal cuff brachytherapy was given to post-Wertheim's surgery in patient with carcinoma cervix. A patient with high-grade endometrial stromal sarcoma received 25 cycles of radiotherapy and seven cycles of vincristine and cyclophosphamide after complete surgery.

Table 1. Location and histopathological diagnosis of patients.

Location	Benign and borderline(n)	Malignant (n)	Percentage
Ovarian	23(46%)	16(32%)	78%
Cervical	2(4%)	6(12%)	16%
Uterine	0(0%)	3(6%)	6%
Total	25	25	

Table 2. Baseline characteristics and clinical presentation of enrolled patients.

Variables	Benign and borderline	Malignant	P value
Mean age ± S.D. (years)	25.24±6.5	33.68 ± 5.99	0.0001
Mean parity ± S.D.	1.08±1.25	2.2± 1.47	0.0057
Adolescent(15-19yr), n (%)	5(25%)	1(4%)	0.081723
Young adults(20-39yr), n (%)	20(75%)	24(96%)	
Clinical presentation			
a. Asymptomatic	1(4%)	1(25%)	0.036809
b. Pain	21(84%)	14(56%)	
c. Menstrual disorder	4(16%)	12(48%)	
d. Abdominal distension/ lump	3(12%)	13(52%)	
e. Loss of weight/ appetite	1(4%)	2(8%)	

Table 3. Size of lesion in ovary, uterus, or cervix in patients.

Size of lesion	Benign and borderline(n-25)	Malignant (n-25)	Total	P value
<5cm	2(8%)	7(28%)	9(18%)	0.12616
5-10cm	6(24%)	7(28%)	13(26%)	
>10cm	17(70%)	11(44%)	28(56%)	

Table 4. Preoperative evaluation characteristics of ovarian lesions

	Variables	Benign and borderline (n-23)	Malignant(n-16)	Total(n-39)	P value
1.	*Ca 125 levels(U/ml)*				
	<35	19(83%)	3(19%)	22	0.000076
	>35	4(17%)	13(81%)	17	
2.	*Laterality*				
	Unilateral	21(91.3%)	9(56%)	30(77%)	0.010596
	Bilateral	2(8.7%)	7(44%)	9(23%)	
3.	*Ascites*				
	Yes	3(13%)	9(56%)	12(31%)	0.0040
	No	20(87%)	7(44%)	27(69%)	
4.	*Ultrasound findings*				
	Simple/ Null / N/A	11(48%)	2(12%)	13(33.3%)	0.004552
	Solid-cystic/complex component	3(13%)	11(69%)	14(35.9%)	
	Multi-cyst/Multi-occulated	7(30%)	3(19%)	10(25.6%)	
	Dermoid	2(9%)	0	2(5%)	

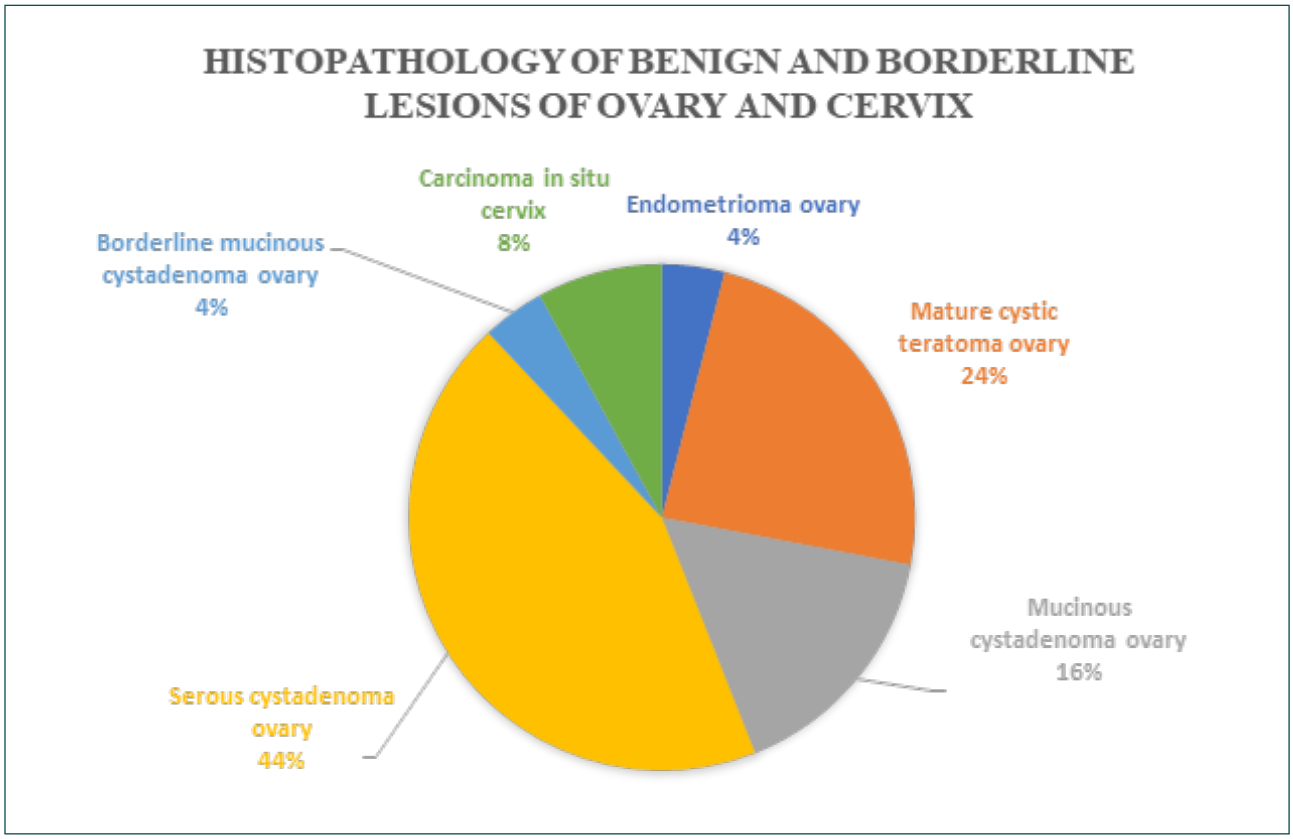

Figure 1: Histopathological findings of benign and borderline lesions of the ovary and cervix

Discussion:

Gynecological malignancies are rare in AYA population, and they tend to develop mostly from the ovary, but also from the uterus, cervix, vagina, and vulva. In a study by Wohlmuth et al, the incidence per 1,000,000 women (95% CI) and relative frequency (%) of gynecological malignancies are as follows: Ovarian malignancies 5.882(5.540–6.241), 87.5%; Uterine malignancies 0.170(0.116–0.240), 2.5%; Cervical malignancies 0.262(0.193–0.346), 3.9%; Vaginal malignancies 0.298(0.225–0.388), 4.5%; and Vulvar malignancies 0.106 (0.065–0.164), 1.6% [7]. Our study demonstrated that the tumors observed were ovarian (78%), cervical (16%), and uterine (6%) in origin.

The mean age was significantly higher for malignant lesions as compared to benign lesions in our study. A cancer diagnosis occurring between the ages of 15 and 30 is 2.7 times more prevalent than one that takes place during the first 15 years of life.[4] Tumors of the ovary, both benign and malignant, are rare in the pediatric age group, and their incidence increases with age. Sharma D and Singh G also reported that the incidence of cancer increases with age in AYAs, as the majority of the patients were in the age group of 25–29 years (n = 213, %42.9), followed by 24–20 years (n = 160, %32.3) [7]. The relatively higher incidence of malignant neoplasms in adult women compared to the pediatric age group is likely related to the influence of environmental factors, including the exposure to sexually transmitted diseases, such as human papillomavirus (HPV), or due to somatic exposures to carcinogens [5,6]. Uterine tumors observed in our study were all malignant. Triarico S, et al also reported that uterine leiomyosarcoma (LMS) may occur in younger women and premenopausal patients and is very rare during childhood and adolescence [6]. Overall, soft tissue sarcomas had higher rates among the young adults, but rates for rhabdomyosarcoma were significantly higher at younger ages [8].

Gynecologists' opinions may be sought for the following issues in this age group: pubertal concerns, menstrual irregularities including heavy menstrual bleeding and anemia, contraception, carcinoma screening, or

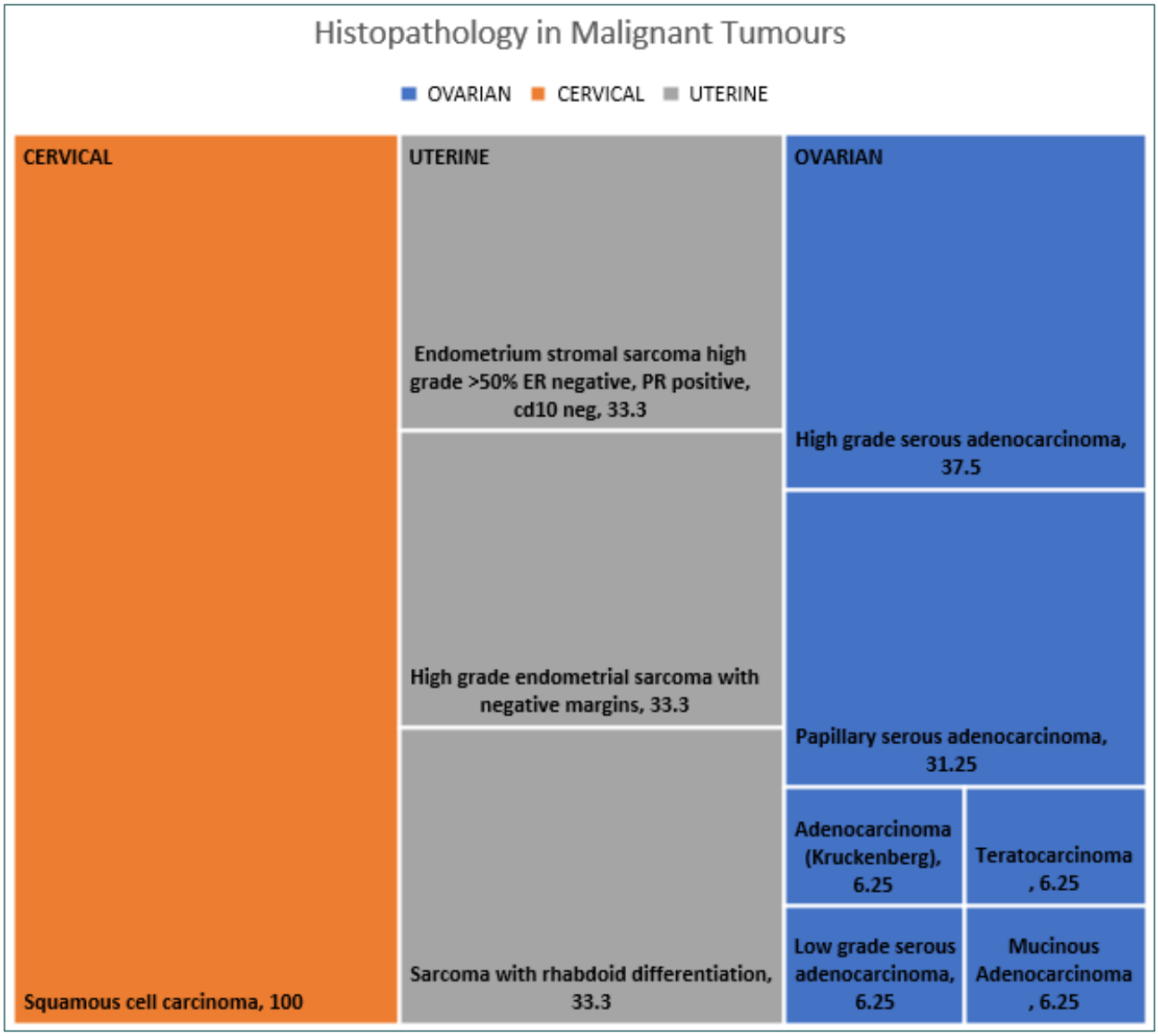

Figure 2: Histopathology in malignant tumors.
Footnote: Values written are percentage of patients with that histological finding, ER: estrogen receptor, PR: progesterone receptor, CD10: Immunohistochemical marker.

fertility preservation in various conditions. Patients were admitted with a presumptive diagnosis of adnexal masses (54%), carcinoma (42%), and abnormal uterine bleeding (4%) in the present study. AYA patients may develop benign ovarian lesions such as functional cysts, endometrioma, torsion, abscess, and lymphangioma, as well as malignant neoplasms classified as germ cell, epithelial, sex-cord stromal, and miscellaneous tumors.

Abdominal pain was the most common presenting complaint (70%), followed by menstrual abnormality or palpable lump in our study. Similar results were obtained by Triarico S et al [6]. Clinically predictive criteria described for malignancy were abdominal distension and the presence of a palpable mass. The most common finding was abdominal pain or mass in about half of the adolescent patients, as the ovaries have their embryonic origin at the level of the tenth thoracic vertebra and are positioned inside the abdomen during childhood [9].

Tumor markers are essential for diagnosis, emphasizing the importance of testing before any ablation is performed. CA125 was significantly higher in malignant ovarian neoplasms in our study as compared to benign

lesions. CA125 is an antigenic tumor marker expressed by epithelial ovarian neoplasms and cells lining various organs such as the endometrium, fallopian tubes, pleura, peritoneum, and pericardium. This correlates well with our study, as the most common histopathology observed was serous adenocarcinoma (epithelial ovarian tumor) [10].

The primary goal of evaluating an ovarian mass is determining the likelihood of malignancy, as the management of benign and malignant lesions differs significantly. As a result, accurate identification of ovarian masses in children and adolescents is essential for optimal treatment [5]. Several biomarkers, such as imaging characteristics and serum tumor markers, can help in the process of diagnosis and have been proposed as indicative of a high or low risk of malignancy. Ultrasonography (US), magnetic resonance imaging (MRI), and computed tomography (CT) are the standard imaging modalities used to evaluate an ovarian mass. The US is often the first modality of choice for assessment. The presence of ascites and complex solid lesions was significantly associated with malignancy in the present study. Literature also suggests that the predictive diagnostic imaging criteria for malignant ovarian tumors in adolescence are tumors larger than 12 cm ($P < 0.05$), tumoral hypervascularity ($P < 0.01$), and voluminous ascites ($P < 0.01$) [11].

The mass arising from the ovary may range over a wide spectrum of pathology, from benign to highly aggressive malignant tumors. Patients in the early stages are usually asymptomatic. Cystadenomas, or benign neoplasms, are cystic lesions with thin walls, septa less than 3 mm thick when present, and no solid components. Serous cystadenomas normally present as unilocular cystic masses that lack septa and may be radiologically identical to follicular cysts, but they may contain one or two septa and a few locules. Imaging findings suggestive of borderline or malignant neoplasms include larger size, complex morphology, thick and irregular walls, septa thicker than 5 mm, and solid components with necrosis or papillary projections [11].

The most common benign and malignant lesions observed were serous cystadenoma and serous cystadenocarcinoma in the present study. Epithelial carcinoma constitutes the majority of ovarian cancers in our study. This can be attributed to a significantly higher number of malignant cases in young adults as compared to adolescents. Epithelial cancers in young adults are diagnosed in advanced stages and require neoadjuvant chemotherapy and adjuvant chemotherapy. One patient was diagnosed with a malignant germ cell tumor. Germ cell tumors, which originate from pluripotent germ cells, are the most frequently encountered ovarian neoplasms in the pediatric population, accounting for approximately 60-80% of cases, with mature teratoma representing the predominant histological type, in contrast to adults, who most frequently present with epithelial tumors [12]. Conservative treatment is indicated in benign tumors, especially in mature teratomas. Treatment of a suspicious lesion is surgical (or after chemotherapy in an inoperable lesion), and preserving fertility is a major consideration at an early age. The prognosis for malignant ovarian germ cell tumors is dismal. When treated with surgery or radiotherapy, the fatality rate ranges between 85-90% [6]. The prognosis for malignant teratoma varies based on the histological grade, nature of the immature component, and stage at diagnosis. Re-surgery was required for the patient of germ cell carcinoma in our study to complete surgery, which included hysterectomy, contralateral salpingo-oopherectomy, omentectomy, hemicolectomy, and lymphadenectomy as the tumor spread in the abdomen even when the patient was on chemotherapy of bleomycin, etoposide, and platinum (BEP). The management of AYAs with gynecological malignancies requires a multidisciplinary tumor board of gynecologic oncologists, pediatric oncologists, psychologists, teachers, social workers, and onco-fertility experts who should work in an informal way that has been demonstrated beneficial to AYAs.

Cervical cancer is the second most prevalent cancer among women aged 15-44 years [13]. It is the only cancer with a well-known cause, making it manageable and preventable. Younger people are more infected with the Human Papillomavirus Virus which is the main cause of cervical cancer, because of their connection with numerous risk factors, including multiple sexual partners, early sexual debut, and high HIV incidences, which increase the probabilities of developing cervical cancer. We had eight cases of cervical lesions. Conization was done in benign lesions, and radical Wertheim's hysterectomy with lymph node dissection was done in two cases. Chemoradiation was the standard of care in advanced-stage carcinomas. Radical hysterectomy and pelvic lymphadenectomy are the standard surgical options to treat early-stage cervical cancer, but are linked with impaired fertility in patients [14]. Examination under anesthesia, colposcopy, and biopsy should be carried out to diagnose cervical carcinomas. All patients

had squamous cell carcinoma in our study. Squamous cell cancer was indeed the most frequent type of histology in cervical cancer, both in patients aged ≤25 and 26–35 years in a study by Pan S et al [15]. Cervical cancer screening and HPV vaccination are two emerging weapons to fight against this cancer, and hence, their routine implementation is strongly recommended.

All the uterine malignancies observed were uterine sarcomas. They presented with abnormal uterine bleeding and were presumptively diagnosed as leiomyoma intraoperatively. However, the histopathological diagnosis turned out to be sarcoma. Two patients underwent re-laparotomy for completion of bilateral salpingo-oophorectomy and lymph node dissection, followed by radiotherapy and chemotherapy. Sarcomas have four categories: endometrial stromal nodule, low-grade endometrial stromal sarcoma (ESS), high-grade ESS, and undifferentiated uterine sarcoma as per the WHO 2014 classification. ESS closely resembles normal endometrium, making diagnosis challenging. No imaging approach offers a high level of diagnostic accuracy. The ultimate diagnosis method is histology combined with immunohistochemistry of the hysterectomy specimen. Ultrasound findings may lead to adenomyosis and uterine leiomyoma. The management depends on the stage of the disease. Ovarian conservation can be considered in young women with stage I disease. Extrauterine extension, older age, black race, lymph node involvement, and immunohistochemical indicators like negative CD10 and lack of estrogen and progesterone receptors are poor prognostic markers [16, 17]. One patient in our study had high-grade ESS with negative CD10, and a lack of estrogen and progesterone receptors. She underwent complete surgery followed by 25 radiotherapy cycles and 7 cycles of chemotherapy with vincristine and cyclophosphamide. She is still on follow-up.

Limitations:

This was a retrospective cross-sectional study for a 3-year duration; hence, the chances of missing data may be there. A prospective study will always yield better results for the prevalence and management of adolescent and young gynecological cancers.

Conclusion:

AYAs with cancer require multidisciplinary management at specialized medical centers that can provide top-notch physical and psychological care and ensure the best potential therapeutic outcome. Imaging and tumor markers aid with the diagnostic procedure by distinguishing between benign and malignant lesions and, as a result, selecting the optimal management options. Preserving gonadal tissue in children and adolescents is critical not just for fertility maintenance but also for the normal progression of puberty, especially in benign cases. High-grade malignancies require aggressive management to improve survival and quality of life.

Acknowledgement: We wish to acknowledge the Department of Obstetrics and Gynecology, Pt BD Sharma University of Health Sciences, Rohtak.

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