Retrospective Histopathological Analysis of Cervical Cancer in a Tertiary Care Center

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ABSTRACT

BACKGROUND

Cervical cancer is the third most common cancer among females worldwide. Abnormal vaginal bleeding is the most common presenting complaint in these patients. Some patients remain asymptomatic even in the advanced stages of the disease. Surgery is the treatment of choice in early stages of the disease. Radiotherapy alone or combined with chemotherapy is the treatment in advanced stages of diseases.

METHODS

This is a retrospective study of various histopathological patterns of cervical neoplasms over a period of 3 years (January 2017 - December 2019). Various histopathological patterns were correlated with clinical presentations and demographic patterns.

RESULTS

A total of 344 gynaecological malignancies were reported in our study period. Cancer cervix was the most common (238 cases, 69.18 %). There was a progressive increase in the number of cancer cervix cases from 55 in 2017 to 84 in 2019. In our study, age group of patients ranged from 25 to 82 years and the mean age of presentation was 57.4 years. A high standard deviation of 15.3 was observed. 71.1 % (170 cases) of the patients presented with history of bleeding irregularities followed by growth (17.3 %, 41 cases). Squamous cell carcinoma (97.2 %) was the most common neoplasm with varying subtypes. 6 cases of adenocarcinoma were also reported in our study.

CONCLUSIONS

Histomorphology remains the mainstay of diagnosis of cervical cancer. Colposcopy guided biopsy is the preferred course of management to definitely rule out or diagnose neoplasia. Histopathological patterns need to be subtyped along with ancillary techniques such as special stains, immunohistochemistry and molecular studies. The main reason behind this is, the treatment modalities and prognosis varies with each subtype. Also, national level cancer program is the need of the hour and should include human papilloma virus vaccine in the immunization schedule for young girls.

KEY WORDS

Squamous Cell Carcinoma, Cervical Cancer, Post-Menopausal Bleeding, HPV Vaccine, Histomorphological Patterns

BACKGROUND

Cancer cervix is the third most common cancer among women worldwide after breast and lung cancer.[1] The introduction of HPV virus vaccination programs in the adolescent females in the developed countries have widened the incidence gap between the developed and developing countries.[2] The mortality rate of cervical cancer is higher in developing countries and they constitute almost 80 % of the total. India constitutes 15.2 % of total cervical cancer deaths in the world.[3] The natural history of progression from mild dysplasia to cancer cervix is around 10 to 20 years and this provides the rationale for screening.[4] Thus cancer cervix is an early preventable disease. In India 96,922 new cases of cervical cancer are detected every year.[5] In South India carcinoma cervix is the commonest malignant neoplasm in females. The prevalence of the disease is more in low socioeconomic status. The reason being lack of hygiene and periodical health check-ups due to budgetary reasons. Due to expensive HPV vaccine and limitations of cytology based screening programs, disability and death from cancer cervix are high in developing countries which includes India.[6]

Persistent HPV infection is the predominant risk factor of cancer cervix. Risk factors include multiple sex partners, sexual promiscuity, early sexual intercourse, cigarette smoking, multiple pregnancies, OCP (Oral Contraceptive Pills) use and most importantly HPV. Human papilloma virus serves as the etiological factor for many benign and malignant neoplasms of cervix ranging from condyloma acuminata to invasive carcinoma. The infection is transmitted by venereal route and has the propensity for the metaplastic squamous epithelium. Majority of females have self-resolving HPV infection which does not evolve into cancer cervix. Around 10 % develop persistent infections. This subset have a higher risk of developing cervical cancer. Research analysis have proved that HPV infection is associated with 80 % of cancer cervix.[7]

Postmenopausal bleeding is the most common presenting complaint of these patients. This should be evaluated by colposcopy (VIA / VILI tests), Papanicolaou smear and subsequently cervical biopsy. Patients with abnormal Papanicalaou smear findings have better prognostic outcome. The reason being early diagnosis of the lesion. On an average, a women in 4th decade has 2 % chance of developing malignant cervical neoplasm. This pre and postmenopausal age group constitute the major working population. Cervical cancer not only contributes to mortality, but also it has major impact on socioeconomic status of their families.[8] Pap smear is a vital screening tool. But it has limited sensitivity between 47 % and 62 %. It has disadvantage of subjective interpretation of the results.[9] The prognosis mainly depends on the clinical stage of the cancer at the time of evaluation. Five year survival rate for stage I of invasive cancer is 92 %. The 5 year survival rate of stage III and IV are 25 % and 15 % respectively. The single best gold standard method for the diagnosis of cervical cancer is systematic histopathological examination of cervical biopsies.[10] Among the varying subtypes, adenocarcinoma, small cell carcinoma, clear cell carcinoma and sarcoma have poor prognosis.

This retrospective study analysis was undertaken with reference to presenting complaints, demographic patterns, morphological features including gross and microscopic features of the study population.

METHODS

A retrospective study of biopsy specimens of cervix and hysterectomy specimens received in our Pathology Department, KAPV Govt Medical College, Trichy from January 2017 to December 2019 were included in our study. Patient's data comprising of age, presenting complaints, clinical findings, clinical staging, gross and microscopic findings were obtained from the records. All diagnosed cases histologically showing cervical neoplasm in the biopsies and hysterectomy specimens were included in the study. Non neoplastic lesions including inflammation and preneoplastic lesions were excluded. The specimens were examined grossly. Bits taken were fixed in 10 % buffered formalin overnight. The biopsy specimens were processed completely. Multiple sections were taken from hysterectomy specimen. The tissue sections were processed in tissue processor (Leica), paraffin embedded and sections of 3 - 4 micron thickness were cut using rotary microtome (Leica). The sections were stained with hematoxylin and eosin stain. Detailed Histopathological analysis and staging was performed.[6]

Statistical Analysis

Data was analyzed by descriptive analysis. Results were expressed in percentages.

RESULTS

A total of 344 gynaecological malignancies were reported during our study period out of which cervical malignancies constitute (69.1 %) 238 cases. The present study included 224 biopsies and 14 hysterectomy specimens. The age group of malignancies varied from 20 years to 80 years. Among 238 cases studied, maximum number of cases 75 (31.5 %) belonged to the age group of 51 - 60 yrs. 65 (27.3 %) patients were in the age group of 41 - 50 years, 19 patients (7.98 %) cases were reported in the age group of 31 - 40 yrs. age group. 16 (6.72 %) cases in 71 - 80 years, (1.68 %) patients in 21 - 30 years and only 3 patients (1.26 %) in 81 - 90 years age group. (Table 1)

Age (in Years)	No. of Cases	Percentage
21 - 30	4	1.68 %
31 - 40	19	7.98 %
41 - 50	65	27.31 %
51 - 60	75	31.51 %
61 - 70	56	23.52 %
71 - 80	16	6.72 %
81 - 90	3	1.26 %
Table 1. Age Distribution of Malignancy		

The mean age of presentation of neoplastic lesion is 57.4 years and a high standard deviation of 15.3 was observed. Youngest patient was 25 years of age and oldest was 82 year old. The mean age was not significantly different for different histological sub types of squamous cell carcinoma with majority being postmenopausal. (Table 4)

The majority of the patients, 170 cases (71.7 %) presented with history of bleeding irregularities such as post-menopausal bleeding, menorrhagia, post coital bleeding and

intermenstrual spotting. This was followed by complaints of growth in 41 cases (17.3 %). 19 cases (7.9 %) presented with pain abdomen and 8 cases (3.1 %) presented with white discharge and itching. (Table 2)

Sl. No.	Clinical Presentation	No. of Cases	Percentage
1.	Bleeding P / V	170	71.7 %
2.	Growth	41	17.3 %
3.	Pain Abdomen	19	7.9 %
4.	White Discharge	8	3.1 %
Table 2. Clinical Presentation of Malignancy			

The most common malignancy was squamous cell carcinoma (88.1 %) among which moderately differentiated squamous cell carcinoma comprised (73.1 %) followed by well differentiated squamous cell carcinoma (11.3 %) and poorly differentiated (3.7 %). (Table 3). 15 cases of papillary variant, 4 cases of adenosquamous and 3 cases of basaloid variant was reported.

| Sl. No.	Various Histomorphological Variants	No.	%
1.	Well Differentiated Squamous Cell Carcinoma	27	11.3 %
2.	Moderately Differentiated Squamous Cell Carcinoma	174	73.1 %
3.	Poorly Differentiated Squamous Cell Carcinoma	9	3.7 %
4.	Papillary Squamous Cell Carcinoma	15	6.3 %
5.	Adenosquamous Variant of Squamous Cell Carcinoma	4	1.6 %
6.	Basaloid Variant of Squamous Cell Carcinoma	3	1.2 %
7.	Adenocarcinoma	6	2.5 %
Table 3. Different Variants of Carcinoma			

6 cases of adenocarcinoma were reported. The mean age of presentation of adenocarcinoma was 58.7 %. The endocervical variant was more common. 1 case was reported as clear cell variant.

According to the International Federation of Gynaecology and Obstetrics (FIGO) staging of patients included in our study, most common presentation was in stage II B. Only few cases were amenable to early treatment and better prognosis category, while cases presenting with distant metastasis and worst prognosis category belonged to older age.

Studies (Place)	Time Period	Age in Years	Peak Decade	Mean + S.D
Olu-Eddo et al,[19] Benin, Africa	1987 - 2006	15 - 90	5th	50.4 + 13.5
Okoyo[20] Nigeria, Africa)	2000 - 2009	18 - 89	5th	51.5 + 12.8
Pathak et al[11] Nepal	2013	24 - 92	5th	42.5
Present Study	2017 - 2019 (3 years)	25 - 83	5th	57.4 + 15.33
Table 4. Comparison of Age Parameters with Other Studies				
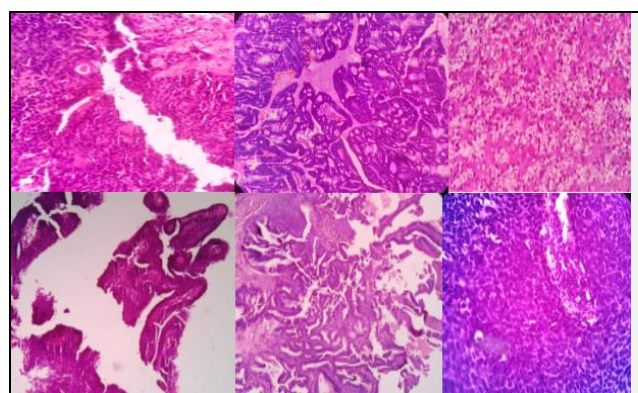
Figure A. Squamous Cell Carcinoma 40x View, Figure B. Adenocarcinoma 10x View, Figure C. Clear Cell Carcinoma 40x View, Figure D. Papillary Carcinoma 10x View, Figure E. Villoglandular Variant 10x View, Figure F. Poorly Differentiated Squamous Cell Carcinoma 40x View

DISCUSSION

Cervical cancer is one of the leading causes of morbidity and mortality in women worldwide. 4,93,000 new cases and 2,74,000 deaths have been reported each year. The patients are asymptomatic in early stages. Symptomatic patients in the due course of the disease present commonly with vaginal growth, contact bleeding, dyspareunia and discharge per vagina. Stage III and IV cervical cancer patient's complaint of loss of weight, appetite, fatigue, pelvic pain, back pain, heavy bleeding P / V and bone fractures in case of metastasis. Our study shows bleeding per vagina as the most common symptom as seen in literature.[11]

Our study revealed that cancer cervix is still the predominant gynaecological malignancy in our institution (69.18 %). This pattern follows known trends in our country.[12]

Western literature reports have claimed that adenocarcinoma cervix occur in younger age group and a rise of proportion as high as (18.5 - 27 %) of cases.[13]

But in our study the mean age of diagnosis of both adenocarcinoma and squamous cell carcinoma was similar that is 58.7 years and 57.4 years respectively.

The reason for this discrepancy may be, in western countries effective screening programs are in place and invasive squamous cell carcinoma is in its decreasing trend as the pre invasive lesions are easily detected and treated, whereas adenocarcinoma, being endocervical is less amenable to screening, hence the incidence is on rise.

In our study patients' age ranged from 25 years to 83 years. The mean age of presentation is 58.7 years. Bleeding irregularities was the most frequently reported presenting complaint which is similar to the studies done by Mostafa MG et al,[10] Shruthi et al,[14] Dasetal.[15]

Radical Hysterectomy specimens constituted 5.9 % and cervical biopsies accounted for 94.1 % in this study. The reason for less number of hysterectomy specimens is due to referral of patients diagnosed as carcinoma for radiotherapy in higher centres.

The total number of cases were in increasing trend which reflects the general population. The need of the hour is frequent and effective PAP smear screening program in our country. HPV vaccination programs should be included in the universal immunization program of India. Due to expensive HPV vaccine and limitations of cytology screening program the death and disability are high in developing countries including India.[16] WHO recommends that every women should be screened at least once in her lifetime at 40 years. The frequency of screening should be increased to "once every 10 years" and then once every 5 years for women 35 - 55 years of age.[17] Community programs are essential to educate parents, teachers, adolescents about human papilloma virus infection, cervical cancer and preventable measures such as vaccine.[18]

Histopathological study of specimens showed squamous cell carcinoma to be the predominant cancer (97.2 %). Our study showed varying subtypes of squamous cell carcinoma. The well differentiated verrucous carcinoma, warty type being the exception. This is in concordance with studies of Olu-Eddoet al.[19] Okoyo[20] Abudu et al.[21]

In our study 15 cases (6.3 %) of papillary squamous cell carcinoma was reported (2.5 %). The papillary squamo transitional cell carcinoma of cervix is an aggressive tumour

and it has to be distinguished from the common benign papillary lessons of the cervix. These tumours are distinct homogenous group that display a morphological spectrum.

6 cases of adenocarcinoma was reported. Adenocarcinoma should be delineated clearly from squamous cell carcinoma and adeno squamous variants. This is because adenocarcinoma has a high recurrence rate and mostly present in stage III and IV and has a poor prognosis.[22]

1 case of clear cell adenocarcinoma was reported in our study. Clear cell adenocarcinoma is a rare subtype associated with cervical endometriosis and exposure to diethylstilbesterol. Studies have shown a lower 5 year survival rate. This subtype classically presents as endophytic growth and infiltrates deep into the cervix. Hence early diagnosis helps in better treatment of these patients.[23]

4 cases (1.6 %) of adenosquamous cell carcinoma was reported with age distribution being (40 - 60 years). This is similar to study done by Alfsenetal.[24]

The mitotic index is a key prognostic factor for behaviour and treatment of cervical cancer. Significantly higher mitotic count is seen in moderately and poorly differentiated squamous cell carcinoma.[25] In our study, well differentiated squamous cell carcinoma had mitotic count of 4 / 10 HPF whereas poorly differentiated squamous cell carcinoma showed mitotic count of 11 / 10 HPF.

In conclusion, clinical presentation and the peak age presentation (51 - 61 years) was similar to most of the studies. Majority of the cases were in stage IIB followed closely by advanced stage (III and IV). This is in concordance with other studies from India.[26]

CONCLUSIONS

In our study, a wide spectrum of morphological (gross and microscopic) subtypes of carcinoma cervix was diagnosed. Histopathological examination and subtyping remain the basis for clinical management, treatment, prognosis and subsequent follow up of a patient. Our study demonstrates that carcinoma cervix is still the predominant malignancy among gynaec patients in our institution. Above findings stress that the cervical screening procedure should be initiated in an earlier age group who are sexually active. This will reduce the long term morbidity, mortality and socioeconomic burden related with carcinoma cervix.

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