Research Paper

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# CLINICOPATHOLOGICAL SURVEY OF CARCINOMA UTERINE CERVIX IN PATIENTS ATTENDING TERTIARY CARE HOSPITAL OF CENTRAL UTTAR PRADESH

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**ABSTRACT** Carcinoma cervix is the third most common cancer in women worldwide and the commonest cause of mortality in developing countries. The present survey was conducted with the aim to study the different histopathological subtypes and their clinical outcome in a small subset of population from central Uttar Pradesh. Forty six cases of carcinoma cervix were studied, out of which, 91 % were squamous cell carcinoma while remaining 9 % were adenocarcinoma. The mean age of presentation was 56 years and the commonest symptoms were white discharge and postmenopausal bleeding. While most cases of adenocarcinoma showed poor survival rate, a rare case of clear cell adenocarcinoma with good prognosis was also observed in our study. Mortality with carcinoma cervix was highest in stage III patients with perineural invasion and nodal metastasis. Thus, early detection and appropriate management can help prolong disease free survival in patients with carcinoma cervix.

**KEYWORDS**

*Carcinoma Uterine Cervix, Histopathology, Follow-up*

**ARTICLE HISTORY**

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## INTRODUCTION

Cervical cancer is the third most common cancer in women worldwide after breast and lung cancer and the most common cause of cancer deaths in developing countries. It is the major cause of mortality in Indian women accounting for 17 % of all cancer deaths in patients belonging to the age group of 30 to 69 years.[1] It has been well known that human papillomavirus (HPV) is responsible for causing cervical cancer in most cases and 70 % of these lesions occur as a result of infection by high risk HPV 16 and 18. [2] Once the infection by HPV is established in the cervical epithelial cells of transformation zone, a stepwise progression of the events from preinvasive lesions to invasive malignancy takes its course gradually. Mass screening at reproductive age group helps in detecting early lesions that could be cured by complete excision. However, lack of awareness, poor hygiene, early marriages, low socioeconomic status, parity, race, tobacco smoking, and failure to attend regular health campaigns are some of the major factors responsible for the rising trends of carcinoma cervix in India.

This is a retrospective single centre study from northern India conducted over a period of two years with the aim to explore the clinical profile and histomorphological subtypes of carcinoma cervix and their survival impact in a small subset of population from central part of Uttar Pradesh.

## MATERIAL AND METHODS

A retrospective study was conducted on all hysterectomy specimens that were received in the histopathology unit of Pathology department from May 2013 to May 2015. Inadequate biopsies were excluded. Data were collected from patient's medical records and analysed for various clinical parameters including age, presenting signs and symptoms, laboratory and radiological investigations.

All haematoxylin and eosin stained slides were revaluated by two individual pathologists and staging was done according to 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system for cervical cancers. Histomorphological evaluation and Clinical follow up of the patients was conducted in each case. The study was ethically approved by the Institutional Ethical Committee of HIMS.

## STATISTICAL TOOLS EMPLOYED

The data so collected was subjected to statistical analysis using Statistical Package for Social Sciences version 15.0. The data has been presented in numbers and percentages.

## RESULTS

A total of 388 hysterectomy specimens were received in the department of Pathology during the study period of two years. Out of these, 46 were proven cases of carcinoma cervix on histopathology. Amongst these 46 cases, 42 cases (91 %) of squamous cell carcinoma and 4 cases (9 %) of adenocarcinoma were observed. Twenty nine cases (69 %) of SCC were well differentiated, twelve (29 %) were moderately differentiated and one (02 %) was poorly differentiated.

The age of presentation ranged from 40 to 70 years (mean age 56.17 years) with majority of them in their fifth and sixth decade, accounting for eight and seven cases respectively, followed by seventh decade in which there were five cases. The most common clinical complaints were white discharge (n= 33), post menopausal bleeding (n=30), and dysuria (n=16). Fifty two percent of the patients had five or more children indicating multiparity as one of the major cause of carcinoma

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cervix. Also, all patients were of low socio-economic status with history of first coitus at an age of less than 20 years in 83 % of the cases. 93 % of the women were illiterate while remaining 7 % had basic primary education. A preoperative Ultrasonography revealed hypoechoic heterogeneous mass in the cervix with bulky uterus in 80 % of the patients. The tumour size varied from 1.2 cms to 6.5 cms. In five (11 %) of the above mentioned cases mesenteric lymph nodes were also involved. [Table 1]

**Table 1 Clinicopathological Features in 46 cases of Carcinoma Uterine Cervix**

| CLINICO-PATHOLOGICAL PROFILE | CASES | PERCENTAGE |
|---|---|---|
| **1. AGE** | | |
| =< 40 years | 40 | 87 % |
| > 40 years | 06 | 13 % |
| **2. PRESENTATION** | | |
| - White discharge | 33 | 72 % |
| - Postmenopausal bleeding | 30 | 65 % |
| - Dysuria | 16 | 35 % |
| - Pain abdomen | 13 | 28 % |
| - Weight loss | 15 | 33 % |
| - backache | 07 | 15 % |
| - Rectocoele/cystocoele | 06 | 13 % |
| **3. PERSONAL HISTORY** | 43 | 93 % |
| - Education status - Illiterate | 03 | 07 % |
| Primary education | 38 | 83 % |
| - First coitus - =<20 yrs | 08 | 17 % |
| >20 years | 24 | 52 % |
| - Parity - >= 5 | 22 | 48 % |
| < 5 | | |
| **4. ULTRASONOGRAPHY** | | |
| - Tumour characteristics | 37 | 80 % |
| – Hypoechoic mass in cervix | 09 | 20 % |
| Pyometra | 26 | 57 % |
| - Tumour size - < = 4 cms | 20 | 43 % |
| >4 cms | 05 | 11 % |
| - Lymph nodes - Positive | 41 | 89 % |
| Negative / Unknown | | |
| **5. GROSS** | | |
| - Ulceroinfiltrative | 33 | 72 % |
| - Exophytic | 01 | 02 % |
| - Hypertrophix cervix | 09 | 19 % |
| - No visible lesion | 03 | 07 % |
| **6. MICROSCOPY** | | |
| - Squamous cell carcinoma | 42 | 91 % |
| Keratinizing | 38 | 91 % |
| Non keratinizing | 03 | 07 % |
| Basaloid | 01 | 02 % |
| - Adenocarcinoma | 04 | 09 % |
| Endometrioid | 03 | 75 % |
| Clear cell variant | 01 | 25 % |
| **7. STAGE** | | |
| - IIA | 18 | 39 % |
| - IIB | 19 | 41 % |
| - IIIA | 06 | 13 % |
| - IIIB | 03 | 07 % |
| **8. TREATMENT** | | |
| - Surgery alone | 46 | 100 % |
| - Surgery and radiotherapy | 21 | 46% |
| **9. MORTALITY** | | |
| - IIA | 01 | 10 % |
| - IIB | 00 | 00 % |
| - IIIA | 02 | 20 % |
| - IIIB | 07 | 70 % |

On gross examination, the growth was ulceroinfiltrative and friable in 33 cases and exophytic in one case [Fig 1], hypertrophic cervix was noted in 9 cases and in 3 cases no visible lesion was detected. In seven of the hysterectomy specimens, the growth was seen infiltrating bilateral adnexa with multiple deposits on paratubal tissue. Endometrial thickness varied from 2 cms to 3.5 cms. Two cases showed intramural fibroids with a mean diameter of 2.5 cms and 1.6 cms respectively as an additional pathology. A focus of adenomyosis was seen in one case.

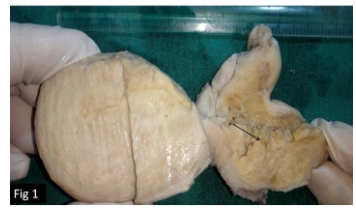


**Fig 1 Gross photograph of a greyish white exophytic growth (marked with arrow) in clear cell adenocarcinoma of cervix**

On Microscopy, all 46 cases were diagnosed as epithelial malignancies with 42 cases of squamous cell carcinoma (SCC) and four cases of adenocarcinoma. Of these forty two cases of squamous cell carcinomas, two cases were reported as microinvasive squamous cell carcinoma where depth of invasion was less than 5 mm and horizontal spread was more than 7 mm. Large cell keratinizing squamous cell carcinoma was the commonest type (90 %). [Fig 2A] Most cases were accompanied by moderate to dense lymphoplasmacytic cell infiltrate. [Fig 2B] In seven cases, metastatic squamous cell carcinoma was observed in bilateral ovaries and paratubal tissue. [Fig 2C] Additional histopathological findings included presence of koilocytic changes in three cases of SCC and cervical intraepithelial neoplasia – Grade III in two cases of SCC. In two of the cases, well circumscribed leiomyomas with interlacing fascicles of smooth muscle bundles were seen in the myometrium.

Amongst the four cases of adenocarcinoma, one case revealed clear cell morphology with tubulocystic and papillary arrangement of tumour cells showing abundant clear to eosinophilic cytoplasm and large irregular nuclei. At places hobnailing of the cells was prominent. [Fig 2D] In one case, endometrial glands and stroma were seen embedded in the myometrium.

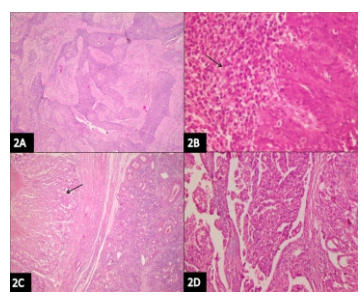


**Fig 2A Photomicrograph shows large cell keratinizing squamous cell carcinoma arranged in nests and islands (H&E,50X) , 2B Photomicrograph shows dense lymphoplasmacytic infiltrate (Marked with arrow) adjacent to tumour cells (H&E,100X) , 2C Photomicrograph shows ovarian metastasis (marked with arrow) by large cell keratinizing squamous cell carcinoma of cervix (H&E,50X), 2D Photomicrograph shows clear cell adenocarcinoma arranged in tubulo-cystic pattern (H&E,100X)**

Of the total 46 cases, 18 (39 %) patients were in stage IIA, 19 (41%) patients in stage IIB, 6 (13%) patients were in stage IIIA and 03 (07%) patients were in stage IIIB. Lympho-vascular and perineural invasion was present in four and five cases respectively with all cases in stage III.

Treatment offered in these patients was either surgery alone or a combination of surgery and radiotherapy both. Twenty one cases received adjuvant radiotherapy. The mean follow up period of these patients was 30 months (Range: 12 months to 48 months). Ten patients expired within the first year of follow up of which seven patients were in stage IIIB , two patients in stage IIIA and one patient in stage IIA. Three of these patients had adenocarcinoma and remaining seven had squamous cell carcinoma. All the three cases of adenocarcinoma were in stage IIIA and two cases of SCC were in stage IIB, one in stage IIIA and four in stage IIIB.

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## DISCUSSION

Carcinoma cervix is a public health problem in developing countries like India where every year 122,844 women are diagnosed with cervical cancer and 67,477 die from the disease. [3] Increased burden of cervical cancer in India and Southeast Asian countries is due to poor living standards, high prevalence of HPV and lack of screening. [4] Moreover, there is a marked diversity in the incidence of carcinoma cervix between the urban and rural population of India alone. Effective screening programs and enthusiastic participation in awareness camps has reduced its prevalence in educated section of the society while the incidence is still high in rural India. In a study by Krishanappa et al, cancer cervix was observed in 10.28 % of the cases over a period of five years. [5] The incidence was 11.85 % in the present study which depicts a fraction of population from northern India. Contrary to this, the incidence was high (17.5 %) in another study from South India. [6] Our institute caters predominantly patients belonging to low socio-economic status who cannot bear the expenses of surgery. The lower incidence in the present study could be attributed to fewer patients visiting the hospital on the day of surgery.

In the present study, mean age at the time of presentation was 56 years with most cases seen in fifth and sixth decade. In a study by Thakur et al and Christe et al, mean age was 48.1 years and 34.5 years respectively. [7,8] Overall the peak incidence of cervical carcinoma has been recorded between 55 to 59 years in India. [9] 93.5 % of the women were illiterate in our study which is in concordance with the findings described by Satyanarayana et al with 63.2% of the women being illiterate and belonging to poor living standards. [10]

Although HPV infection is one of the major causes of carcinoma cervix, the long interval between initial infection and disease indicates involvement of some other factors such as sexual habits like early age at first coitus, co-infection with HIV, multiparity, smoking, nutritional deficiency, genetic susceptibility and use of hormonal contraceptives as was observed in our set up also.

Many times early malignancy is so inconspicuous that patients are often asymptomatic. However, most common symptoms are white discharge, vaginal bleeding, painful coitus, menorrhagia, and abdominal pain. Advanced malignancies can present with profused bleeding, weight loss, severe backache, prolapse, cystocoele, rectocoele, bone fractures and distant metastasis. In the present study, white discharge and vaginal bleeding were the commonest symptoms as was observed in other studies by Shruthi et al., Das et al and Krishanappa et al. [5,6,11]

Squamous cell carcinoma is the most common type of cervical malignancy all over the world. [5,12,13] In the present study also, squamous cell carcinoma accounted for ninty one percent of all cases. These lesions arise from the squamo-columnar junction and may be keratinizing or non-keratinizing type. The present study demonstrated large cell keratinizing squamous cell carcinomas (90 %) as the most common subtype. This finding was similar to a study done by Bisht et al who also reported large cell keratinizing SCC as the commonest type. [14] However, in a study by Sinha et al and Krishanappa et al, large cell non keratinizing SCC was the most common variant accounting for 55 % of the SCC.[5,15]

Over the last four decades, various studies from developed world have documented a relative increase in the incidence of adenocarcinoma from 12 % to 24 % when compared to SCC. [16] The present study showed only 9 % (n=4) of the adenocarcinoma cases. One rare case of clear cell adenocarcinoma (CCA) was observed in a 48 years old woman who presented with postmenopausal bleeding and pain in the pelvic region. Of all the adenocarcinoma, CCA accounts for 4 % - 9 % being relatively rare in the lower genital tract. [17] It usually presents in younger patients with history of exposure to diethylstilbestrol (DES) in utero. However, it has been described in older women also with a median age of 53 years. According to Thomas et al, clear cell cervical cancer in itself does not have a worse prognosis than SCC. [18] This patient received radiotherapy following surgery and is doing well till today.

Mortality is higher with adenocarcinoma than squamous cell carcinoma of the cervix. [19] In the present study also, death rate (75 %) with adenocarcinoma was much high when compared to SCC (17 %). Thus, survival with squamous cell carcinoma had been far better than adenocarcinoma. Also majority of the deaths occurred in patients with advanced stage of the disease (stage III) due to complications arising out of treatment or disease per se.

Pre-treatment imaging studies are useful to assess the primary tumour size, site, local extent, associated lymphadenopathies, staging and thereby help in providing prognostic information and subsequent treatment planning. In the present study, most cases were in stage II accounting for an incidence of 70 % followed by 20 % in stage III which was comparable to a study by Rani et al with 71.65% of the patients in stage II and 22.83% in stage III. [20] Another study from southern part of India revealed that modal presentation of cervical cancer was in stage IIIB. [21] This is because most of the times patients neglect the initial symptoms, there is lack of a competent oncologist and referral centres.

Involvement of lymph nodes and distant metastasis relates directly to the advanced stage of the disease and has a negative impact on the overall survival of the patients. In the present study, 11 % of the cases showed nodal involvement and all patients were in stage III while in a study by Chauhan et al, 34 % of the cases had lymph node metastasis. [22]

To conclude, carcinogenesis in cancer cervix is a multistep process which begins with dysplasia, progresses to carcinoma-in situ and ends up in frank invasive malignancy. Most early lesions are asymptomatic and diagnosis can be missed at this stage if left neglected. Moreover, invasive malignancy once diagnosed affects the physical and emotional wellbeing of a woman. Therefore, the objective must be to prevent development of invasive lesions by early detection of preinvasive processes by more reliable and cost-effective screening methods. This can be achieved by spreading awareness amongst the lower section of society through measures that would help them understand the burden of disease. However, when diagnosed with invasive malignancy, histological sub typing becomes essential as prognosis and further management depends largely on the morphological type of carcinoma.

There are few limitations of the study that include the retrospective nature and small sample size of the study.

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