

Radiotherapy Induced Changes in the Cervical Pap Smears- A Study of 50 Cases.

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Received: April 2019

Accepted: May 2019

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ABSTRACT

Background: Pap smear is an important tool to assess, follow up and monitor the diagnosed cases of carcinoma cervix. In the present study we have taken cases which were already diagnosed of cervical carcinoma, took radiotherapy and chemotherapy and surgical intervention as whole or one entity. These cases were assessed for cytological features of therapy induced changes, recurrence of carcinoma or no intraepithelial lesion or malignancy (NILM). Aim: The aim of the present study is to study the effects of radiotherapy and chemotherapy on squamous epithelial cells and to study the rate of recurrence of Squamous cell carcinoma after completion of chemotherapy and radiotherapy. **Methods:** Total No. of 50 cases were taken ranging from 27 yrs. to 70 yrs. age group who presented at tertiary care hospitals in northern part of India for about 1.5 year duration where facilities of radio and chemotherapy and surgical oncology was present. **Results:** In the present study, nucleomegaly was found to be most common finding in 46 (92%) of cases, next came vacuolisation both cytoplasmic and nuclear however nuclear vacuolisation outnumbered cytoplasmic. **Conclusion:** The total no. of cases having malignant or dysplastic cells varied with age and found to be higher in advancing age groups although in younger age group (20-29) having only one case was found to be positive for malignant/dysplastic cells.

Keywords: Cervix, Pap smear, Radiotherapy.

INTRODUCTION

Cervical cancer is a major public health problem. Globally, cervical cancer is next only to breast cancer in incidence and is the third leading cause of cancer mortality.^[1] The World Health Organization (WHO) made out three different categories of invasive carcinoma of the cervix: squamous cell carcinoma, adenocarcinoma and other epithelial tumours.^[2] Out of these tumours squamous cell carcinoma is the most common histo-pathological subtype which accounts for 70–80% of invasive carcinomas while adenocarcinoma and adeno-squamous carcinoma comprise about 10–15% of all cases, and all others 10–15%.^[3,4] Various clinical, molecular and epidemiological studies have found the association of HPV infection in the pathogenesis of cervical carcinoma. About more than 90% of cervical carcinoma contains DNA sequences of specific HPV types especially HPV 16 and HPV 18.^[5] The majority of women with invasive Squamous cell carcinoma are diagnosed in their mid

40s or 50s however, it can occur at almost any age between 17 and 90 years.^[6] Cytological examination of the exfoliated cells from uterine cervix (pap smear) plays a significant role in the prevention and diagnosis of cervical cancer. Cytological screening if performed only twice in a woman's lifetime can reduce her risk for invasive cervical cancer by up to 43% and regular yearly screening is estimated to reduce a woman's risk by over 90%.^[7,8] However some patients develop squamous cell carcinoma of cervix even after regular pap smear examination signify drawbacks of screening test. The most widely accepted staging system for tumors of the cervix is the four-stage system of the International Federation of Gynecologists and Obstetricians (FIGO).^[9]

Radiotherapy and chemotherapy are some of the different treatment modalities of squamous cell carcinomas at Stages IB and IIA and afterwards.^[10] Radiotherapy may cause morphological and molecular changes in neoplastic and non-neoplastic epithelial cells due to interference in messenger ribonucleic acid (mRNA) synthesis, decline in protein production, inhibition of deoxyribonucleic acid (DNA) synthesis and mitotic activity, as well as cyto-chemical alterations, with protein denaturation and enzyme release, with the resultant destruction of cytoplasmic organelles.^[11,12] The effects of ionizing radiation on cells can lead to cytological features

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which may be mistaken for neoplastic or pre-neoplastic conditions.^[13]

Pap smear is again an important tool to assess, follow up and monitor the diagnosed cases of carcinoma cervix. In the present study we have taken cases which were already diagnosed of cervical carcinoma, took radio and chemotherapy, and surgical intervention as whole or one entity. These cases were assessed for cytological features of therapy induced changes, recurrence of carcinoma or no intraepithelial lesion or malignancy (NILM)

Aims and Objectives

1. To study the effects of radio and chemotherapy on squamous epithelial cells
2. To study the rate of recurrence of Squamous cell carcinoma after completion of chemotherapy, Radiotherapy.

MATERIALS AND METHODS

- The Present study was conducted at tertiary level hospital in northern part of India for about 1.5 year duration where facilities of radio and chemotherapy and surgical oncology was present.
- Cases which was already diagnosed of squamous cell carcinoma and underwent radio chemotherapy or both was on follow up and taken for consideration.
- Total No. of 50 cases was taken ranging from 27 yrs. to 70 yrs. age group. Average age was 51.9 yrs. Maximum cases was from 50-59 yrs. age group (18 cases) and minimum was from 20-29 and 30-39 years age group (1 case each). Cases were chosen irrespective of their tumour stage, socio economic status or religious factors.
- Time period between therapy and sample collection was varied from 7 months to 18yrs.
- Time since diagnosis was maximum 18 yrs. with only one case and minimum time was 7 months again with one case. Maximum cases (6 each) were 6 and 10 years time since diagnosis.
- Conventional smear stained with pap stain examined microscopically

Table 1: Showing Cytological findings induced by radiation and chemotherapy in cervical smears.

Cytological findings induced by radiation and chemotherapy in cervical smears. ^[14]
❖ Cytomegaly
❖ Karyomegaly
❖ Normal nuclear-to-cytoplasmic (n:c) ratio
❖ Bizarre cell shape
❖ Binucleation/Multinucleation
❖ Nuclear wrinkling and smudging
❖ Altered nuclear and cytoplasmic staining
❖ Nuclear and cytoplasmic vacuolization
❖ Intracytoplasmic neutrophils

RESULTS

In present study the total No. of cases having various cellular and nuclear changes varied and nucleomegaly was found to be the most common finding in 46 (92%) of cases, next came vacuolisation both cytoplasmic and nuclear however nuclear vacuolisation outnumbered. Nucleomegaly with retained N:C ratio was present in 92% of cases. considerable no. inflammatory smear was noted in 18% cases In present study the total No. of cases having malignant or dysplastic cells varied with age and found to be higher in advancing age groups although in younger age group (20-29) having only one case was found to be positive for malignant/dysplastic cells.

Table 2: Distribution of post radiation/ chemotherapy changes in cytological smears in 50 cases.

Cellular/Nuclear Change/Finding	No. of cases	% age
Increase in cell size		
Vacuolisation	10	20
Nuclear	6	12
Cytoplasmic	1	2
Nucleomegaly	46	92
Binucleation	10	20
Multinucleation	4	8
N:C ratio (Normal)	40	80
N:C ratio (Increased)	10	20
Cellular atrophy or Cellular gigantism	2	4
Dysplastic cells	8	16
Malignant cells	6	12

Table 3: Total No. of cases age wise (n=50)

Distribution of Cases age wise with Dysplastic/ Malignant cells				
Age Group	No. of cases	% age	No. of cases with Dysplastic/ Malignant cells	% age with Dysplastic/ Malignant cells
20-29	1	2	1	100
30-39	1	2	0	0
40-49	17	34	1	5.88
50-59	18	36	2	11.11
60-69	10	20	2	20
70-79	3	6	2	66.66

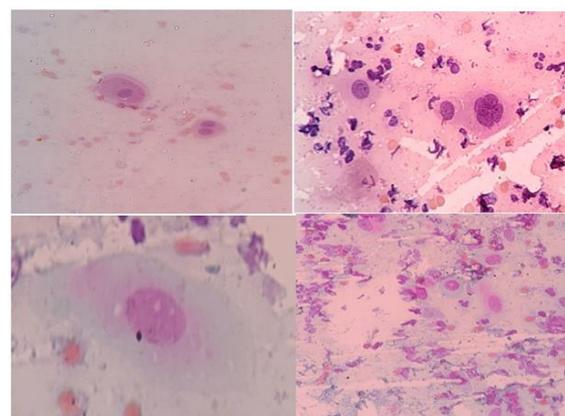


Figure 1: A: Binucleation seen in a squamous epithelial cell in Cervical pap smear (MGG 400X) B: Multinucleation seen in a squamous epithelial cell in Cervical pap smear (MGG 400X) C, D: Nuclear vacuolation seen in a squamous epithelial cell in Cervical pap smear (MGG 400X)

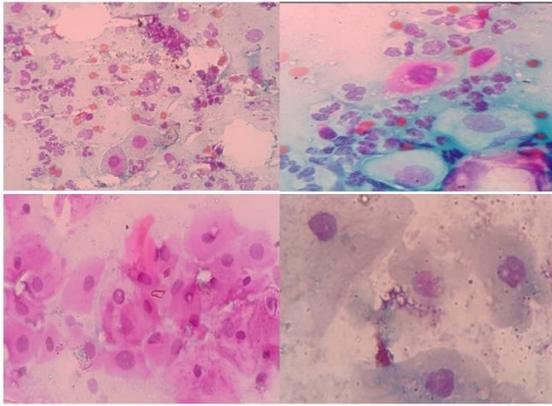


Figure 2: A: Inflammation seen in Cervical pap smear (MGG 400X) B: Cytoplasmic vacuolation seen in a squamous epithelial cell in Cervical pap smear (MGG 400X) C: Nucleomegaly seen in a squamous epithelial cell in Cervical pap smear (MGG 400X) D: Nuclear vacuolation seen in a squamous epithelial cell in Cervical pap smear (MGG 400X)

DISCUSSION

The conventional pap smear test has important role in cervical cancer prevention programs and contributes significantly to follow-up programs for patients undergoing radio-chemotherapy for cervical cancer. It has been noted that radio and chemotherapy can make a wide range of morphologic alterations in neoplastic and non-neoplastic cells in the squamous epithelium. In the present study, cytological follow-up ranged from 7 months minimum to 18 years maximum. Reactive nucleomegaly with retained N:C ratio was found to be most common finding in 46 cases followed by cytoplasmic and nuclear vacuolization in 16 cases, dysplastic and malignant cells was found in 8 cases showing evidence of recurrence.

It was observed that the cases in which radiation-induced morphological cellular alterations were revealed, the period between the end of the treatment and the cytopathologic follow-up varied from seven months to fifteen yrs. The acute effects of radiation and chemo tend to decline gradually. However, bizarre and enlarged cells may continue to show their presence on cytological smears for a period of years after the treatment. Similar finding was noted by Shield PW.^[15]

Zannoni and Vellone (2008) in their study found 46% of smears with benign alterations produced by radiochemotherapy, 20% with atrophy and 9% inflammation. The authors reported that nuclear and cytoplasmic enlargement, multinucleation, cytoplasmic vacuolization, and bizarre cell forms were among the most radiation induced cell morphological changes in the smears studied, corroborating much of the morphological changes found in the present study.^[16]

In another study conducted by Kafil Akhtar in 2016 found nuclear enlargement most frequent change seen in 38 cases (95.0%), followed by vacuolization of the cytoplasm in 32 cases (80%), with fine, regular or large and voluminous vacuoles. Multinucleation was another prominent feature observed in 30 cases (75%). Histiocytic and neutrophilic infiltration of the smears was present in 23 cases (57%). and bizarre forms like tadpole and fibre like cells were noted in 15 cases (37.5%). Recurrence of squamous cell carcinoma was observed in 9 cases (22.5%), with presence of small dark tumor cells and large naked nuclei in the post irradiated cytological smears. This study again found well concordant with present study.^[17]

CONCLUSION

In this study a total of 50 cases were included in the age group of 27-70 years, the average being at 51.9 years. The samples were collected after 7 months to 18 years after collection of therapy. The total no. of cases having malignant or dysplastic cells varied with age and found to be higher in advancing age groups although in younger age group (20-29) having only one case was found to be positive for malignant/dysplastic cells.

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How to cite this article: Kumar N, Bansal A, Kaur M, Kaur NP, Wadhera D. Radiotherapy Induced Changes in the Cervical Pap Smears- A Study of 50 Cases. *Ann. Int. Med. Den. Res.* 2019; 5(4):PT01-PT04.

Source of Support: Nil, **Conflict of Interest:** None declared