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Randomised Controlled Study To Evaluate The Association Of Human Papilloma Virus With Carcinoma Cervix & To Study The Effect Of External Radiotherapy Along With Brachytherapy On HPV Titre In Carcinoma Cervix.

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Abstract: *Radiotherapy is often the primary treatment modality for inoperable carcinoma cervix. One of the main etiology is Human papilloma virus. The main aim of this study is to evaluate the association of HPV with carcinoma cervix and to analyse the effect of RT. 71 patients of locally advanced carcinoma cervix were included in this study. Pre-treatment cervical biopsies were taken & HPV DNA typing & estimation of titre was done. All patients received EBRT in dose of 4600 CGY/23fr in 4.5 wks to pelvis with Co-60 (780E). This was followed by ICRT in dose of 650 CGY weekly for 3 weeks. After 6 months of completion of RT 38 patients were on follow up in which HPV typing was done & titre was measured by real time PCR in pap smear specimen. Pre RT & Post RT HPV titres were compared. HPV - 16 was associated with 49.3% cases, HPV – 18 with 7% cases & combined – 16 + 18 in 18.3% cases & 25.4%cases were negative for HPV. HPV titres was measured before RT & after 6 months of completion of RT and it has been found that there is decrease in the titre after RT. The HPV titre ranged from 0.00145 to 7090 before RT & from 0.0064 to 71.7 in ng/ml after 6 months of completion of RT with P Value < 0.001. HPV titre is 0 in 7 patients after t/t. RT is the most effective mode of treatment for cervical cancer. A Reduction in HPV titres of their baseline values at the end of RT is also associated with better survival outcomes. HPV plays an important role as a causative agent in the epedimiology of cervical cancer . RT is effective in decreasing the HPV titre .*

Keywords: *Brachytherapy, Cervical Cancer, HPV, ICRT, Squamous cell.*

I. Introduction

The Incidence of cervical cancer varies from country to country and from race to race, globally it is second commonest neoplasm in women[1]. It is the commonest malignancy to affect the female population in developing countries. Cervical cancer is accounting for an estimated 3.4 lacs new cases and 1.6 deaths every year. Uterine cervix is the commonest site to be involved by malignant growth transformation. 90% tumours are squamous cell type, 5% are Adenocarcinoma 1-2% are of clear cell or mesonephric type. The predisposing factors are early marriage[2], intercourse at an early age, history of sexual promiscuity, large number of pregnancies, multiple sexual partners, infestation with tumor papilloma virus, inhaled cigarette smoking, male partner infected with venereal pathogens, poor genital hygiene, compromised immune status.

HPV is a double stranded DNA tumor virus belonging to papovavirus family. There is a strong relationship between Human papilloma virus, CIN & squamous cell carcinoma cervix. (3,4,5,6). Genital tract associated HPV types are. Low Risk : 6,11,40,42,43,44, Intermediate Risk :- 31,33,35,51,52, High Risk :- 16,18,45,56. The molecular basis for oncogenesis in cervical cancer can be explained by regulation & function of two viral oncogenes E6 & E7[7]. These genes possess transforming ability when transfectd into cells lines.

Radiotherapy is the treatment of choice for locally advanced carcinoma cervix. The purpose of this study is to evaluate the association of HPV with carcinoma cervix, to measure HPV titre before and after Radiotherapy and to correlate HPV types with carcinoma cervix, to evaluate the effect of Radiotherapy in eliminating HPV infection in carcinoma cervix and to evaluate clinical, histopathological and cytological correlation of HPV titre with locally advanced carcinoma cervix before and after Radiotherapy.

Important prognostic factors are Tumor Related, host related and Treatment related.Poulami Das et al in a retrospective study of 132 patients showed the association of HPV with ca cervix and effect of radiotherapy in reducing HPV titre, published in indian journal of medical research in year 2015. The present study was designed to study the efficacy and acceptability of the radiotherapy treatment in reducing HPV titre in cancer cervix and to establish a strong relationship of HPV with carcinoma cervix.

II. Material And Methods

This Randomised controlled study was carried out in previously untreated histologically and cytologically proven patients with locally advanced carcinoma of cervix (stage II A to stage IV) Study entry criterias were pts with written consent, age less than 70 years, KPS between 80-100, adequate hematology,

Liver and kidney function, no distant metastasis. Complete medical history, significant family, past and personal history was asked. Complete examination was carried out including general examination, pervaginal, per-rectal and bimanual examination .Complete radiological investigations were done.

71 patients of locally advanced carcinoma cervix were included. In all cases tissue specimen / cervical swab was obtained and DNA extraction was done. All samples were subjected to PCR using consensus-Sequence for HPV-16 & HPV-18 and HPV titres were measured [8]. Every patient was treated with External Beam Radiotherapy to whole pelvis by AP/PA parallel opposed portal in total Dose of 4600 CGy in 23 fractions in 4.5 weeks with CO-60 Theratron (780E) unit at a source to axis distance of 80 cm. EBRT was delivered 5 days a week i.e. from Monday to Friday for 4.5 weeks Followed by 3 sessions of HDR intracavitory Radiotherapy, each a week apart. Thus total duration of treatment was approximately 10 weeks. The HDR ICRT was delivered by central uterine tandem and ovoid applicators, using remote after loading Iriduim – 192 sources described as in the Manchester system [9]. After completion of brachytherapy patients were kept on monthly followup and after 6 months pap smear of 38 patients who were on regular followup was taken and HPV DNA typing and HPV titre estimation with real time PCR (121-122) was done (light cycler 2.0 instrument, Roche) using light cycler fast start DNA master SYBR green I (Roche). The Standard used for RT PCR was P1321 plasmid incorporating E6/E7 gene of HPV-16 (Adgene) consensus sequence for HPV-16 and HPV-18 was used for RT PCR. Response assessment was done according to WHO Criteria for complete response and partial Response.

III. Results And Discussion

In this study the age of patients ranged from 30-65 years. The age at marriage ranged from 12 years to 20 years. Majority of the patients 59% belonged to low socio economic group. 67.6%were in post-menopausal age group. Maximum Patients (64.8%) had 3-5 pregnancies. Majority Patients (59.4%) presented with stage III B of carcinoma cervix. 59.1% patients were having moderately differentiated squamous cell carcinoma cervix. HPV- 16 was associated with 49.3% cases. HPV-18 with 7% cases and HPV 16-18 in 18.3 % cases. While 25.4% cases were negative for HPV with P Value < 0.001 which is coming highly significant. Before Radiotherapy out of 38 patients, (63.2%) patients were having HPV titre in the range of 100-1000 ng/ml & (21%) patients were having titre> 1000ng/ml. After 6 months of completion of radiotherapy treatment (100%) patients were having HPV titre in the range of 0-100ng/ml showing a significant reduction in HPV titre with P value <0.001 which is highly significant.

In 38 patients HPV titre decreased in (47.4)% patients out of which (77.8%) Patients had complete Response & (22.2%) patients had partial Response clinically after 6 months of Radiotherapy. HPV titre became 0 in 7 patients (18.4%) who were having a significant higher titre before radiotherapy and all 7 patients showed complete response clinically. In patients whose HPV titre decreased or become 0 after 6 months and those who were showing complete response clinically the pap smear done also revealed normal epithelium in significant percentage of the patients.

IV. Figures, Tables And Graphs

Fig. 1 **HPV 16**

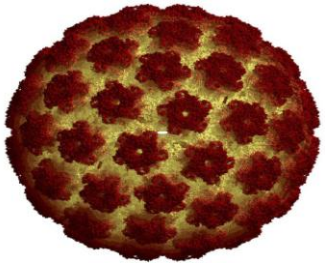


Fig. 2 **HPV Genomic Structure**

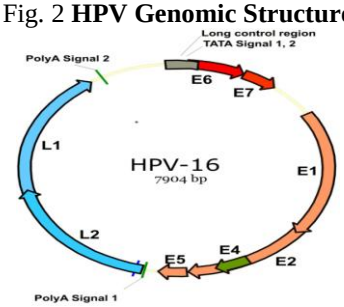


Table : 1 **Association of HPV with Carcinoma Cervix**

Sr.	**HPV Type**	**No of cases+ve**	**%**
1	HPV-16	35	49.3
2	HPV-18	5	7.0
3	HPV-16+18	13	18.3
4	HPV-VE	18	25.4
	Total	71	100

Graph: 1 **Showing Association of HPV With Carcinoma Cervix**

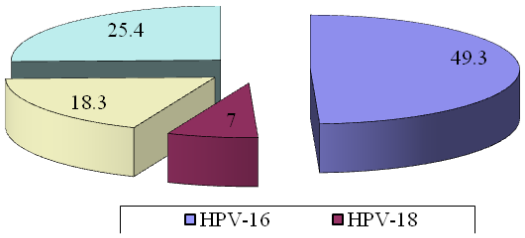


Table : 2 **HPV Titre before and after 6 months of radiotherapy**

Sr. No.	**HPV-Titre (in ng/ml)**	**Before Radiotherapy**		**After 6 months Radiotherapy**	
		No.	**%**	**No.**	**%**
1	0-100	24	63.2	38	100
2	100-1000	6	15.8	-	-
3	>1000	8	21	-	-
	Total	**38**	**100**	**38**	**100**

Graph : 2 **Showing HPV Titre Before Radiotherapy & After 6 Months of Completion of Radiotherapy**

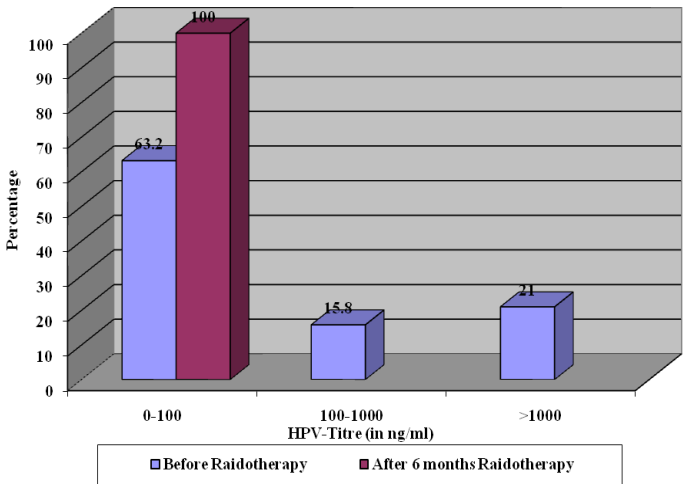
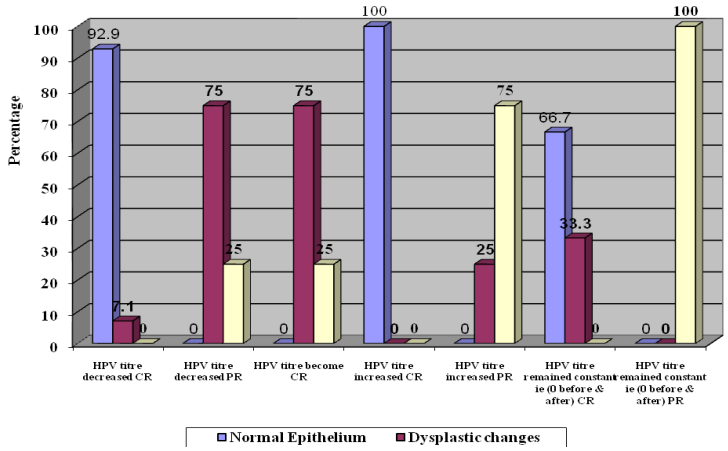


Table : 3 Correlation Of Hpv Titre, Clinical Response And Pap Smear After 6 Months Of Radiotherapy

	Normal Epithelium	Dysplastic changes	Squamous cell ca
HPV titre decreased CR	92.9	7.1	0
HPV titre decreased PR	0	75	25
HPV titre become CR	0	75	25
HPV titre increased CR	100	0	0
HPV titre increased PR	0	25	75
HPV titre remained constant ie (0 before & after) CR	66.7	33.3	0
HPV titre remained constant ie (0 before & after) PR	0	0	100

CR = Complete Response, PR = Partial Response

Graph : 3 **Correlation of HPV Titre, Clinical Response and PAP Smear done after 6 months of completion of Radiotherapy**



V. Conclusion

It is concluded that Radiotherapy is the most effective mode of treatment for cervical cancer. HPV plays an important role as a causative agent in the epidemiology of cervical carcinoma. Radiotherapy is effective in decreasing the HPV titre. A Reduction in these titre of their baseline values at the end of Radiotherapy is also associated with better survival which is statistically significant with P value < 0.001. Long term disease free survival is under assessment.

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