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RESEARCH ARTICLE

IMPACT OF THE PRESENCE OF HPV DNA IN CERVICAL CANCER ON TREATMENT RESPONSE IN PATIENTS RECEIVING RADICAL RADIOTHERAPY – A REGIONAL CANCER CENTRE STUDY

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ABSTRACT

Background: While HPV has evolved as a significant prognosticator in Carcinoma oropharynx it fails to be so in case of Ca Cervix. The existing literature is divided in this topic mainyowing todemograhic-trends, techniques and HPV subtype-specific epidemiology. So considering the load and mortalitiy associated with the disease in our country a study on the local population to assess for role of HPV status in treatment response and toxicity profile was endeavoured

Method: A prospective study was performed on 120 cervical cancer patients meeting inclusion criterion their HPV status was assessed via PCR. Patients were treated with concurrent CTRT in the form of EBRT 50Gy / 2Gy/# / 5 days a week with concurrentweeklyCisplatin 40 mg/m2, followed by brachytherapy.The patients were followed upon regular basis to assess their acute toxicity profile and treatment response

Results: The primary endpoint of DFS at 2 year was analysed. There were 21 recurrences in the HPV Positive arm compared to 3 in the HPV negative arm. (P=0.0122). The treatment response at one month after treatment (RECIST Criterion) was analysed there was residual disease in only 2 of the HPV negative cases(10%) compared to 18 in HPV Positive arm(22.5%) (P<0.05). Toxicity profile in terms of both acute and late had no statistical difference among the groups

Discussion: The study adds evidence to support the fact that HPV has a definite role as a biomarker in the prognostication and treatment outcome of cervical cancer. But the authors equally respect the outcomes which contradicts this study. As our country is perhaps the capital of cervical cancer, more studies on local population is the need of the hour to throw more light into this dilemma

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INTRODUCTION

This decade has witnessed the HPV related oropharyngeal cancers evolving into almost a separate entity and dose de-escalation is HPV positive oropharynx is almost getting ready for prime time, but prognostication of HPV in Cervical cancer is still in its infancy besides a stronger causation. There are plethora of reasons for the same ranging from wide variation in results arising across the globe to large epidemiological variation in HPV subtypes. Hence the literature still stands divided on this topic. Cancer of the cervix is the third most common cancer in India with 1 lakh new cases in 2016, the second most common cancer in women worldwide and the most common cancer cause of death in the developing countries. There are many established factors on which the prognosis of this disease dependent on such as the stage of disease, nodal status, stromal invasion and others.

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Many of these factors are well studied, yet there is huge lacunae in predicting the biological behaviour of this malignancy. Hence the role of evaluating molecular markers such as HPV DNA with respect to disease prognostication and treatment outcome is the need of the hour. The main obstacles in establishing the role of HPV in prognostication is the fact that the literature is divided in this matter. But on a closer scrutiny of these studies it can perhaps be conjured that such variations are a result of not accounting for the epidemiological variations of HPV prevalence across the globe, the variations in subtype specificity, use of a standardized detection assay, variations in the nature of samples used. Though very high prevalence rates were claimed by certain studies which evolved into the concept of absolute necessity, none of them were prospective studies and the lack of reproducibility of such high prevalence in normal clinical studies pointed towards a differential behavior of cervical cancer in terms of presence of HPV. This decade also saw some large sample studies on western population which proved and at the same time some small sample studies equally disproved the role of HPV as a

prognostic marker though from a different geographical regions. Hence a study on local population with an entirely different epidemiological profile could remove some gray areas in this regard pertaining to the role of HPV in our set of patients

MATERIALS AND METHODS

A prospective cohort of 120 patients of cervical cancer positive attending Acharyatulsi RCC, Bikaner OPD was chosen after scrutinizing the inclusion and exclusion criterion, Patient data and clinico-pathological information were collected through personal interview and from case files. HPV DNA subtype assessment was be done with the assistance of Genetics wing of Department of Anatomy SPMC Bikaner by the following method Fresh biopsy specimen were cryopreserved until analysis. DNA Extraction – Genomic DNA was extracted by commercially available QIAGEN USA kit. DNA confirmation – Presence of DNA was confirmed prior to amplification by performing Human interleukin 1B gene specific PCR.HPV Specific Genome amplification – HPV PCR was performed by using HPV specific primers (MY09/MY11) and the positive samples were further subjected to HPV type specific PCR for HPV 16 and 18.which was followed by virus type characterization. Patients were treated with concurrent CTRT in the form of EBRT 50Gy / 2Gy/# / 5 days a week with concurrent weekly Cisplatin 40 mg/m2, followed by brachytherapy 7.5 Gy X 3# with total dose of 85 Gy to point A. patients were followed up on regular intervals to asses toxicity profile and disease status.

RESULTS

Of the 100 patients that were finally available for analysis 80 were found to HPV positive (80%), 60% were positive for HPV 16 and 10 % for HPV 18 and rest 10% other subtypes. With regard to demographic profile, the HPV negative population mostly had a better performance status, lower socioeconomic status, rural background.

Table 1. Total no of Recurrences at 2 year follow up

HPV Status	Total N	Residual d/s 1st month follow up	Percentage
Negative	20	2	10%
Positive	80	18	22.5%
Overall	100	20	20%

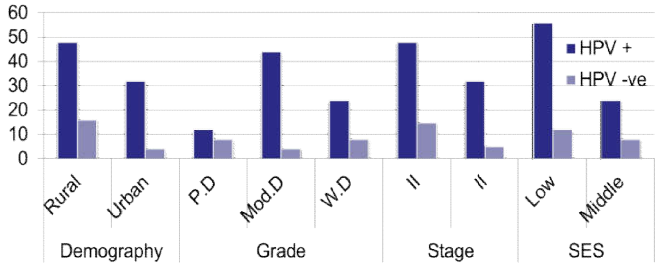

Chart 1. Histo-Demographical profile distribution across HPV status

The histo-pathological profile of HPV negative was mostly low grade early stage lesions, but none of these differences were statistically significant. Toxicity profile in terms of acute effects (Cystistis, Proctitis, Vaginalmucositis, Enteritis) had no statistical difference among the groups. When response at one month after treatment(RECIST Criterion) was analysed there was residual disease in only 2 of the HPV negative cases(10%) compared to 18 in HPV Positive arm(22.5%) and this difference was statistically significant (P<0.05). DFS 2 year was analysed. There were 21 recurrences in the HPV Positive arm compared to 3 in the HPV negative arm. On Kaplan meier survival analysis and applying log-rank test this difference was statistically significant (P=0.0122).

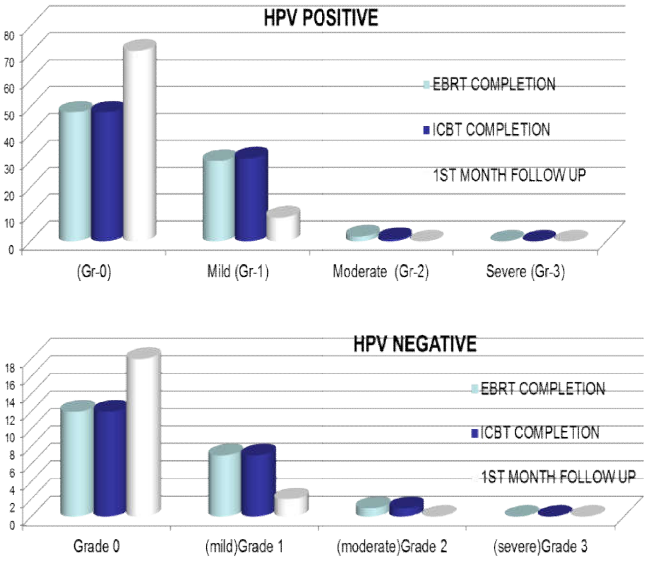

Chart 2. Acute toxicity .profile across the arms

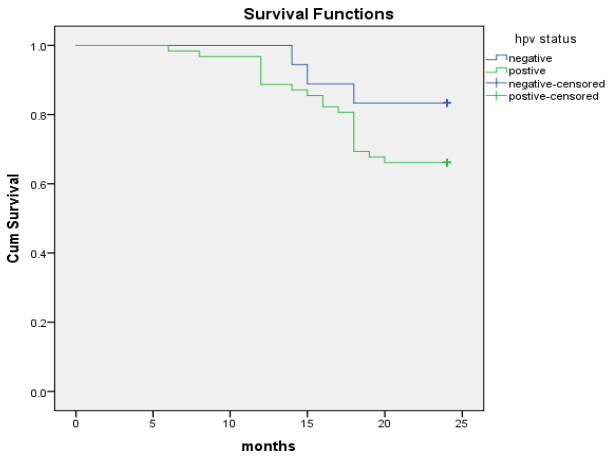

Fig. 3.Kaplan Meier plot of DFS at 2 year

DISCUSSION

The findings of this study is in line with many of the western studies and contradicts some equally. King *et al.,* 1989 was among the first group to assess prognostication potetnital of HPV and found to that there was no significant association which contradicts our findings, but very soon Burger *et al.,* 1996 in their study found HPV 18 to be an independent prognostic factor, in this study HPV 18 arm had a poor prognostic profile but was not powered to see if the difference was significant. But Hakarimoetal[3]in a study from Japan of 50 patients opined that HPV negative group had poorer DFS and O.S, a finding which also contradicts the finding of this study. A 10 year long data study by Pilch *et al.,* 2001 perhaps the largest study on HPV as a potential biomarker observes HPV

16 as a poor prognostic marker, a finding in tune with our study. The reason for such large differences in study outcomes could be due to the epidemiological variations attributing to biological variations in HPV leading to variable treatment outcomes. Our study further confirms the fact that HPV has a definite role as a biomarker in the prognostication and treatment outcome of cervical cancer. As our country is perhaps the capital of cervical cancer, more studies on local population would throw more light into this dilemma. The use of molecular markers HPV DNA and its sub typing could be pivotal in patient stratification with respect to prognosis and identification of high risk group. Once established this might yield way to dose intensification or alternate treatment strategies in this high risk group offering them better treatment outcome.

Conclusion

Study further adds evidence to the philosophy that HPV has a definite role as a biomarker in the prognostication and treatment outcome of cervical cancer. As our country is perhaps the capital of cervical cancer, more studies on local population would throw more light into this dilemma. The use of molecular markers HPV DNA and its sub typing could be pivotal in patient stratification with respect to prognosis and identification of high risk group. Once established this might yield way to dose intensification or alternate treatment strategies in this high risk group offering them better treatment outcome. Our study was a humble but sincere attempt in this regard with limitations not limiting to a short follow up, limited quality assurance modalities and lack of sub type specific stratification. But it definitely fuels the scope for further studies in this regard

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