

Therapeutic Outcomes of HPV Positive and HPV Negative Oropharyngeal Squamous Cell Carcinomas

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Abstract

Background & Objectives: HPV associated (HPV+) oropharyngeal cancers, compared with HPV non-associated ones (HPV-) have different characters and significantly better outcomes. HPV and cancer characteristics differ among countries and few data is available in Indian population regarding this issue. Thus, we attempted to determine the treatment response and survival rates between HPV+ versus HPV negative oropharyngeal cancers in Indian population. **Methods:** This prospective observational study was conducted from December 2016 - October 2018 in patients with stage III/IV oropharyngeal squamous cell carcinomas (SCC) (n = 65). The patients received induction chemotherapy with Docetaxel, Cisplatin, 5-Fluorouracil × 3 cycles, followed by concurrent chemoradiation 66 Gy as 33 fractions along with cisplatin 40 mg/m² weekly. The primary outcome was treatment response rate, which was defined as per Response Evaluation Criteria in Solid Tumours (RECIST) criteria. Secondary outcomes were clinico-pathological differences between two groups, overall survival (OS), progression free survival (PFS). **Results:** Of the 65 patients included in the study, 17 were HPV positive and 48 patients were HPV negative. Median age in HPV positive arm is 48 years and HPV negative arm is 59 years. HPV positive patients presented with early T stage and advanced nodal (N) stage. Most common histopathology in both arms was moderately differentiated squamous cell carcinomas followed by well differentiated squamous cell carcinomas. HPV+ vs HPV- showed the following, treatment response 82.4% vs 52.1% (p-0.029). 1 year progression free survival (PFS) of 76.5% vs 52.1% in HPV negative arm (p-0.08) & 1 year overall survival was 82.4% vs 70.8% (p-0.353). Grade 3 or 4 toxicities did not

differ significantly between HPV positive and HPV negative arms. **Conclusion:** HPV positive oropharyngeal SCC patients showed significantly better treatment response than HPV negative ones. Progression free survival, overall survival and toxicity profile did not differ significantly between the two groups. Although due to small size, we did not compare data stratified by the cancer characteristics, the data is worthy to further characterize this tumour especially as HPV positive versus HPV negative.

Keywords

Oropharyngeal Squamous Cell Carcinoma, HPV, Chemoradiation, Docetaxel, Cisplatin, 5-Fluorouracil, Treatment Response

1. Introduction

Head and neck squamous cell carcinoma is the third most common malignancy in both sexes across the globe. It is the most common malignancy in Indian males [1]. Oropharyngeal cancers account for approximately 10% of the annual worldwide incidence of head and neck squamous cell carcinomas (HNSCC). Overall incidence of HNSCC has fallen in the last three decades; however, the incidence of oropharyngeal carcinoma, mainly tonsil and base of tongue, has been increasing both in United States and Europe.

The incidence of oropharyngeal cancer differs significantly by geography. In United States of America, the annual incidence of oropharyngeal squamous cell carcinoma is 4.8/100,000. The rate has increased by 28% from 1988 to 2004 largely because of 225% increase in HPV associated oropharyngeal cancer [2] [3] [4].

The rise in developed countries is unique as other mucosal head and neck cancers have decreased over this same time period. The cause of this is the increasing incidence of HPV associated cancers. The incidence in developing countries is lower at approximately 3/100,000.

The Cancer Atlas project by ICMR (Indian Council of Medical Research) has shown the incidence of various cancers in different parts of India [5]. Kerala has one of the highest incidences of HNSCC which constitutes 30% of all cancers in India. HPV prevalence in India ranges from 33.6% in Eastern region to 67% in South, 15% in western India.

About 15% - 20% of all head and neck squamous cell carcinomas are associated with high risk HPV infection. The highest rates of HPV DNA (upto 70%) have been found in oropharyngeal squamous cell carcinomas (OSCC) especially the tonsils followed by base of tongue. HPV 16 is the most common type, detected in 90% - 95% of HPV related OSCC.

HPV associated oropharyngeal cancers are more likely to occur among men (80% of whom will not have a smoking history), more common among white individuals, diagnosed in individuals who are 5 to 10 years younger than HPV unassociated oropharyngeal cancers, more common with higher socioeconomic

status. HPV associated oropharyngeal cancers are characterized frequently as poorly differentiated, non-keratinizing and basaloid in histopathologically [2].

Early stage oropharyngeal cancers are best managed with single modality therapy (radiation or surgery). Treatment of locally advanced tumours involves multiple modalities, the most common being either concomitant chemotherapy and radiotherapy or surgery followed by adjuvant radiotherapy with or without chemotherapy based on pathologic risk factors.

Patients with HPV associated oropharyngeal cancers have significantly better outcomes compared to HPV unassociated oropharyngeal tumours. Novel approaches to surgical and radiation delivery and the incorporation of molecularly targeted chemotherapeutics are currently the focus of clinical investigation with an intent to maximize the therapeutic index for HPV associated oropharyngeal cancers.

There is growing support for the view that the treatment protocol for oropharyngeal cancer should be modified according to HPV status and that de-escalation of treatment intensity may be a real possibility for patients with HPV positive OPSCC.

2. Relevance of the Study

High rates of HPV association have been found in oropharyngeal squamous cell carcinomas as per the available literature. Patients with HPV positive oropharyngeal cancers have significantly better survival outcomes compared to HPV unassociated cancers. But the studies comparing the treatment outcomes are sparse from India. Sometimes the rate of incidence of HPV infection in Indian population may be low, hence our study may help to address this issue to some extent.

3. Aims and Objectives

Primary Objective

To assess the treatment response in HPV positive and HPV negative oropharyngeal squamous cell carcinoma

Secondary Objective

- 1) Clinicopathological differences between the two arms of study
- 2) Incidence of HPV positive cases in the study
- 3) Progression free survival
- 4) Overall survival

4. Methodology

This is a prospective observational study conducted in Department of Radiotherapy, Government Medical College, Trivandrum from Dec 2016 to Oct 2018. Patients with oropharyngeal cancer (all sub sites-Stage III and IV), squamous cell carcinoma (biopsy proven from primary cancer site) and satisfied the inclusion criteria and who expressed willingness were included in the study. Ethical clear-

ance was obtained prior to the start of the study from Human ethics Committee of the institution.

Inclusion Criteria

- 1) Age more than 18 years and less than 70 years of both sexes
- 2) Biopsy proven (from primary site) cases of squamous cell carcinoma of oropharynx
- 3) Stage III and IV (locally advanced squamous cell cancers)
- 4) Eastern cooperative oncology group (ECOG) performance status of 0 to 2
- 5) Normal blood parameters (CBC, RFT and LFT)
- 6) Chemotherapy and radiation naive patient

Exclusion Criteria

- 1) Patients unwilling for the study and to give written informed consent
- 2) Clinically significant comorbid conditions
- 3) Poor performance status of patients (ECOG 3 and 4)
- 4) Stage I and II
- 5) Medical contraindication for chemotherapy and radiation

Procedure

Sixty Five Patients fulfilling the criteria were enrolled in the study. Written informed consent was obtained from each patient prior to the initiation of treatment. Detailed history was elucidated. The master case file was used for data collection. Being a prospective observational study the data of the patients from the start of evaluation to follow up were recorded from the records. These included the following as per the records.

Detailed physical examination including ENT examination (70 degree endoscopy) and biopsy from primary site were taken. Findings will be recorded in the proforma. HPV p16 immunohistochemistry was done in biopsy specimen block. According to this result, patients receiving the standard treatment are grouped into two-Group A - HPV positive and Group B - HPV negative. Pretreatment investigations done by the treating physician included complete blood count, renal function tests, liver function tests, CT Neck (from skull base to upper mediastinum). The results of these tests were recorded. Baseline performance status according to ECOG score were noted for each patient.

The standard treatment followed by majority of the physicians for oropharyngeal squamous cell carcinoma stage III and IV was induction chemotherapy with TPF 3 cycles followed by concurrent chemoradiation. Chemotherapy schedule includes Docetaxel-75 mg/m² on D1, Cisplatin-60 mg/m² on D1, 5-Fluorouracil-750 mg/m² on D1 and D2 every 3 weekly and premedication to avoid allergic reactions. Concurrent chemoradiation is cisplatin 40 mg/m² weekly along with radiation 66 Gy as 33 fractions. Post treatment CT scan are taken after 3 months, 6 months and 1 year. Post treatment clinical examination including ENT evaluation was done 3 monthly for 1st year and then 4 monthly thereafter. Treatment response was assessed using the RECIST criteria and entered into excel sheet. The treatment toxicity will be assessed in both groups using CTC version 4.

Data Analysis

Data analysis was done with the help of Excel 2010 and SPSS 16 statistical software. Student T test for continuous variables, Chi square test for categorical variables and Kaplan-Meier and log rank test for survival analysis.

5. Results

In this prospective observational study, we have enrolled a total of 65 pathologically proved squamous cell carcinoma of oropharynx who satisfied the selection criteria. Among this, 17 patients were HPV positive and 48 patients were HPV negative.

- 1) Baseline characteristics of the patients in this study are depicted in **Table 1**.
- 2) Clinical presentation
- 3) **Table 2** Symptoms of the patient at presentation (**Table 2**).
- 4) Tumour characteristics (**Table 3**).

Table 1. Baseline characteristics of the cases in this study.

Variable	HPV positive (Arm A)	HPV negative (Arm B)
Mean age (yrs)	51.18 +/- 9.1	59.73 +/- 7.0
Median age (yrs)	48	59
Sex		
Male	58.8%	68.7%
Female	41.2%	31.3%
Tobacco use present	58.8%	72.9%
Alcohol use present	58.8%	68.8%
Diabetes Mellitus	29%	25%
Hypertension	41%	42%
Both	12%	12%
ECOG PS		
0	47%	50%
1	35%	33%
2	18%	17%
Socio Economic status		
Below poverty line	88%	83%
Above poverty line	12%	17%

Table 2. Clinical presentation.

Symptoms	HPV Positive N (%)	HPV Negative N (%)	Total N (%)
Dysphagia	9 (53%)	25 (52%)	34 (52%)
Swelling in neck	4 (25%)	10 (21%)	14 (22%)
Swelling in oral Cavity	2 (12%)	6 (13%)	8 (12)
Hoarseness	1 (5%)	4 (8%)	5 (8%)
Others	1 (5%)	3 (6%)	4 (6%)
Total	17 (100%)	48 (100%)	65 (100%)

Table 3. Tumour characteristics of the study population.

Variable	HPV+ (Arm A)	HPV- (Arm B)
Tumour (T)		
T1	23.5%	12.5%
T2	35.3%	25%
T3	29.4%	41.7%
T4	11.7%	20.8%
Node (N)		
N0	5.9%	18.8%
N1	17.6%	43.8%
N2	23.5%	22.9%
N3	52.9%	14.6%
Composite stage		
Stage III	29.4%	56.3%
Stage IV	70.6%	43.8
Sub sites		
Tonsil	52.9%	45.8%
BOT	29.4%	25.0%
Palate	11.8%	16.7%
Vallecula	5.9%	12.5%
Pathological subtypes		
Well differentiated SCC	11.8%	14.6%
Moderately differentiated SCC	47.1%	64.6%
Poorly differentiated SCC	23.5%	18.8%
Basaloid differentiation SCC	11.8%	0
Unknown differentiation SCC	5.9%	2.1%

5) HPV positivity-pattern of staining of P16 (**Table 4**).

6) Treatment response

The response to the planned treatment as per RECIST criteria is shown in **Table 5**.

7) Time to maximum response—Nearly 90% of the responders in both the arms showed the response to treatment in less than 6 month period (**Table 6**).

8) **Toxicities**—The major toxicities are enlisted as a table below (**Table 7**).

9) **Recurrence pattern**—The first failure pattern of the study population during the study period is given in **Table 8**.

Table 4. HPV staining pattern.

HPV p16 staining	N (out of 17 positives)
70% - 79%	2
80% - 89%	13
90% - 99%	2

Table 5. Treatment response evaluation.

Variable	HPV+	HPV–
Complete response (CR)	35.3%	18.8%
Partial response (PR)	47.1%	33.3%
Stable disease (SD)	5.9%	27.1%
Progressive disease(PD)	11.8%	20.8%
Treatment Response summary		
Objective response (CR+PR)	82.4%	52.1%
No objective response	17.6%	47.9%
P value		0.029

Table 6. Time to maximum response.

	Objective response	HPV Positive N = 14 (responders) N (%)	HPV Negative N = 25 (responders) N (%)
1	<3 months	7 (50%)	11 (44%)
2	3 - 6 months	6 (43%)	11 (44%)
3	>6 months	1 (7%)	3 (12%)

Table 7. Major treatment toxicities.

Toxicity	HPV+	HPV-
Mucositis		
Grade 0	5.9%	6.3%
Grade 1	11.8%	12.5%
Grade 2	41.2%	41.7%
Grade 3	35.3%	33.3%
Grade 4	5.9%	6.3%
Xerostomia		
Grade 1	11.8%	10.4%
Grade 2	52.9%	56.3%
Grade 3	29.4%	25.0%
Grade 4	5.9%	8.3%
Dermatitis		
Grade 0	5.9%	6.3%
Grade 1	11.8%	12.5%
Grade 2	41.2%	41.7%
Grade 3	35.3%	33.3%
Grade 4	5.9%	6.3%

Table 8. Recurrence pattern.

Failure pattern	HPV+	HPV-
Loco-regional failure	23.5%	43.75%
Systemic failure	5.9%	6.25%
Total failure	29.4%	50%

10) Progression free survival

1 year progression free survival rate in HPV positive arm is 76.5% while in HPV negative arm it is 52.1% (p value = 0.08) (**Figure 1**).

11) Overall survival

1 year overall survival in HPV positive arm is 82.4% while in HPV negative arm it is 70.8% (p value-0.353) (**Figure 2**).

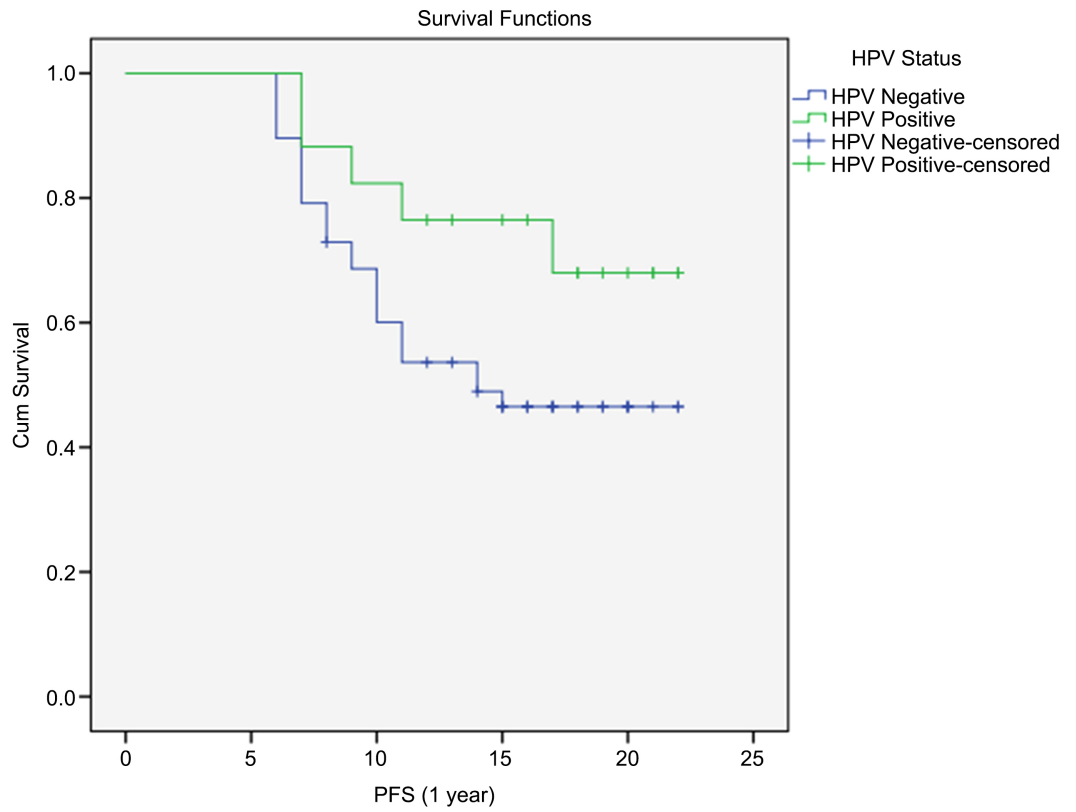


Figure 1. Kaplan Meir curve of progression free survival.

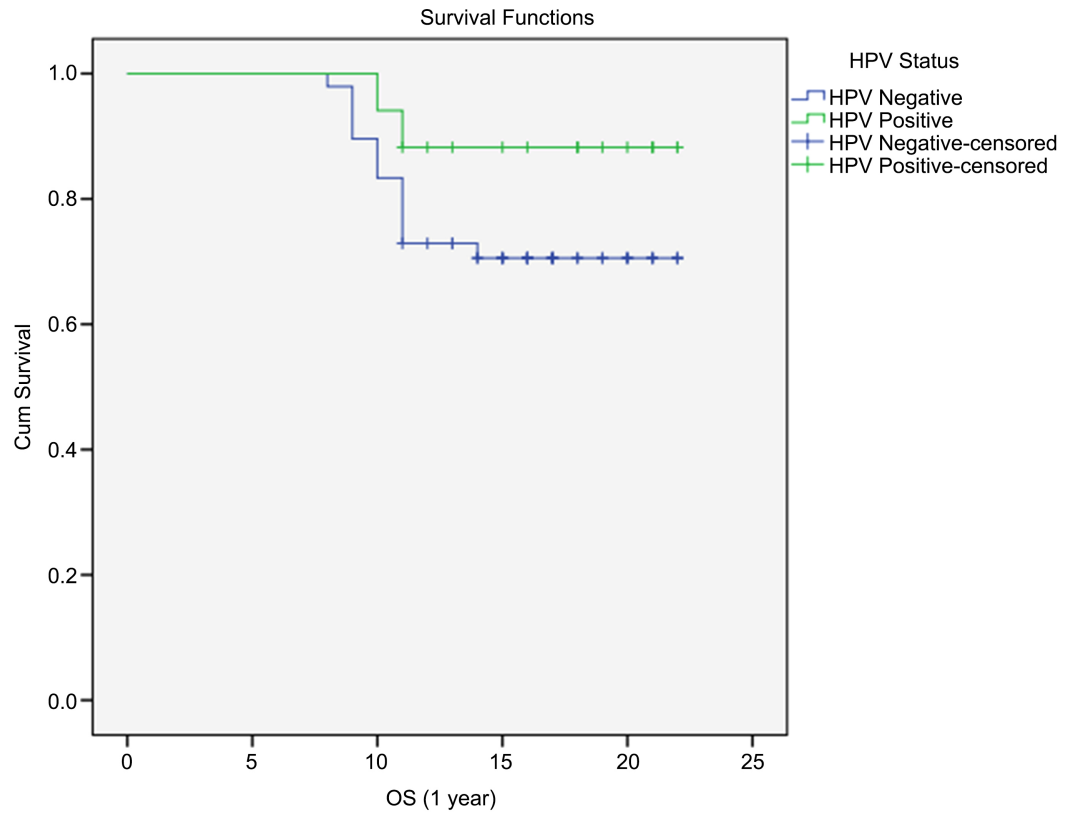


Figure 2. Kaplan Meir curve of overall survival.

6. Discussion

The median age in HPV positive arm was 48 years while in HPV negative arm it was 59 years. This is similar to the findings of the study by Chaturvedi *et al.* in which HPV positive patients tend to be 5 to 10 years younger than HPV negative patients [6]. The male: female ratio in HPV positive arm is less which is correlated by the study by Hemminki *et al.* in which there is an increased risk of HPV associated OPSCC in female patients with a history of HPV associated anogenital cancers [7]. In HPV positive arm only 58.8% were tobacco users while in HPV negative it was 72.9%. In HPV positive arm 58% had the habit of consuming alcohol while in HPV negative arm 68% were alcohol users. These results correlated with the findings of the study by D'Souza *et al.* in which HPV positive patients have less exposure to tobacco and alcohol [8].

With respect to the Tumour (T) status, in HPV positive arm, 59% patients had early T stage (T1 + T2) and 41% were of advanced T stage (T3 + T4). In contrast, HPV negative arm had only less proportion of early T stage (37.5%) and a higher proportion of advanced T stage (67.5%). This finding is again similar to the observations of the study by Huang *et al.*, which have shown that HPV positive tumours are more likely to present with early T stage [9]. In HPV positive arm, 53.9% patients presented with N3 nodal disease while in HPV negative arm 14.6% presented with N3 disease. A study by Goldenberg *et al.* in has shown that HPV positive tumours present with higher N stage [10].

In both arms the most common histology was moderately differentiated SCC. In HPV positive patients poorly differentiated histopathology was seen in 23.5% of patients and basaloid SCC in 11.8% while in HPV negative patients, poorly differentiated was only 18.8% and no basaloid SCC. These findings show similar pattern as in the study by Gillison *et al.* [11], which showed that HPV positive tumours tend to be poorly differentiated and basaloid squamous cell carcinomas.

The incidence of HPV in the cohort is 26%. A study by V Murthy *et al.* shows an incidence of HPV oropharyngeal cancer in India varies from 20% to 38% [12].

In HPV positive arm, the objective treatment response rate is 82% while in HPV negative arm the response rate is 52%. There was statistically significant difference between two groups in case of treatment response (p value—0.029). Study by Fakhry *et al.* the treatment response in HPV positive arm was 84% and in HPV negative arm was 57% [13] [14].

In HPV positive arm the 1 year progression free survival is 76.5% while in HPV negative arm the 1 year progression free survival is 52.1%. But the difference between the two groups was not statistically significant (p value—0.08). This may be due to the small sample size of the study.

In HPV positive arm the 1 year overall survival is 82.4% while in HPV negative arm the 1 year overall survival is 70.8%. But the difference between the two arms was not statistically significant (p value—0.353). Nguyen-Tan *et al.* [15] study showed improved PFS and OS in HPV positive OPSCC. In HPV positive

arm only 30% of patients have recurrences while in HPV negative arm 50% of patients have recurrences. These results correlated with the study by Posner *et al.* [16].

The treatment related toxicities were almost similar in both arms. The percentage of grade 3 and 4 mucositis in HPV positive arm is 35.3% and in HPV negative arm was 31.2%. Grade 3 and 4 dermatitis in HPV positive arm is 41.2% and in HPV negative arm is 39.6%. The results of these toxicities correlated with the study by Kanotra *et al.* [17].

7. Conclusion

The prevalence of HPV in the present study is 26% and the highest prevalence is noted in the tonsillar subsite of oropharynx. In this prospective observational study, we observed that there is a statistically significant difference in treatment response in HPV positive patients compared to HPV negative patients. Though there was no statistically significant difference between two arms in case of progression free survival and overall survival, there was a trend of better PFS and OS towards HPV positive patients. The limitation of our study is that due to small sample size a sub group analysis cannot be made based on the different characteristics. In view of better prognosis of HPV positive patients, several investigators are trying for de-escalation of treatment for HPV positive patients. HPV status in future will definitely play role in decision of treatment planning in oropharyngeal squamous cell carcinoma patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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